To my family and friends

"Learn from yesterday, live for today, hope for tomorrow.
The important thing is never to stop questioning.
Never lose a holy curiosity."

-Albert Einstein-

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Oulu, June 2021 *Henna Rossi*

Abbreviations

AMH	anti-müllerian hormone
AP	adiposity peak
AR	adiposity rebound
ART	assisted reproductive technology
ASRM	American Society for reproductive Medicine
ATC	anatomical therapeutic chemical classification
BMI	body mass index
CA	cancer antigen
CHD	coronary heart disease
COX_2	cyklo-oxygenase-2
CPP	chronic pelvic pain
CRHC	the Care Register for Health Care
DIE	deep-infiltrating endometriosis
EFI	endometriosis fertility index
ESHRE	European Society of Human Reproduction and Embryology
FCP	Finnish Centre for pensions
GnRH-a	gonadotrophin releasing hormone agonists
GWAS	genome-wide association
HC	hip circumference
HRQoL	health related quality of life
IBS	irritable bowel syndrome
ICD	international classification of disease
IGF-1	insulin-like growth factor-1
IL	interleukin
IVF	*in vitro* fertilization
LNG-IUS	levonorgestrel intra uterine system
MaxPTo	maximal pressure pain tolerance
MRI	magnetic resonance imaging
NFBC1966	Northern Finland Birth Cohort 1966
NGF	nerve growth factor
NHSII	Nurses Health Study II
NRS	numerical rating scale
NSAIDs	non-steroidal anti-inflammatory drugs
OMA	ovarian endometriosis
PGE_2	prostaglandin E_2

PPT	pressure pain threshold
PTo	pressure pain tolerance
SII	social institution of Finland
SPRMs	selective progesterone modulators
SUP	superficial/peritoneal endometriosis
TVUS	transvaginal ultrasound
VAS	visual analogue scale
VEGF	vascular endothelial growth factor
WAI	work ability index
WAS	work ability score
WC	waist circumference
WHO	world health organization
WHR	waist to hip-ratio
WPAI	work productivity and activity impairment

Lists of original publications

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Contents

1 Introduction

Endometriosis is a chronic, estrogen-dependent disorder that affects 6–10% of women in their fertile age (Giudice & Kao, 2004; Bulun, Yilmaz, et al., 2019; Zondervan, Becker, & Missmer, 2020). It is defined by endometrium-like tissue outside of the uterine cavity, mainly in the pelvic peritoneum and ovaries (Giudice & Kao, 2004). The etiology of endometriosis remains elusive, but still the theory of retrograde menstruation is widely accepted (Sampson, 1927). Besides retrograde transition of endometrial cells, predisposing factors are necessary to develop endometriosis. Pathogenesis includes increased production of estrogen, progesterone resistance, altered immune responses and inflammation, as well as hereditary predisposition (Bulun, Yilmaz, et al., 2019).

The link between endometriosis and body size and adiposity has been raised by several studies indicating low body mass index (BMI) as a risk factor for endometriosis (Vitonis, Baer, Hankinson, Laufer, & Missmer, 2010; Hediger, Hartnett, & Louis, 2005; Ferrero, Anserini, et al., 2005; Liu & Zhang, 2017). Also, lean habitus and a pear-shaped body is shown to be associated with endometriosis, indicating a possible underlying mechanism in adipose tissue distribution and endometriosis (McCann, Freudenheim, Darrow, Batt, & Zielezny, 1993; Hediger et al., 2005). However, lifetime measurements and resultant data among the general population, including women at late fertile age, are lacking.

The central symptom of endometriosis is pelvic pain. Mechanisms of endometriosis-related pain are multifactorial, including a peripheral mechanism, such as neuroinflammation, and high levels of nerve growth factors and central sensitization due to the chronicity of experienced pain (Coxon, Horne, & Vincent, 2018; Nezhat, Vang, Tanaka, & Nezhat, 2019; Medina & Lebovic, 2009; Morotti et al., 2016). Indeed, case-control studies have shown that women with endometriosis who suffer from chronic pain have an altered pain sensitivity (As-Sanie et al., 2013; Brawn, Morotti, Zondervan, Becker, & Vincent, 2014; Giamberardino, Tana, & Costantini, 2014; Howard, 2009). Earlier studies were restricted to small sample sizes and only considered women at fertile age. However, central sensitization may have a long-term effect on pain perception, and thus endometriosis may have adverse effects on women's life beyond fertile age.

Mechanisms of endometriosis and related pain symptoms have also led to the hypothesis that endometriosis may also be associated with other immunological and pain-causing diseases (Shigesi et al., 2019; Sinaii, Cleary, Ballweg, Nieman, & Stratton, 2002; Nielsen, Jørgensen, Pedersen, Rostgaard, & Frisch, 2011; Adewuyi

et al., 2020, Saidi et al., 2020). Indeed, different comorbidities in affected women have been reported in several studies; however, only few studies have considered overall morbidity instead of showing association between endometriosis and certain diseases (Kvaskoff et al., 2015; Teng et al., 2016; Parazzini, Esposito, Tozzi, Noli, & Bianchi, 2017; Choi et al., 2017).

Pain, as well as other endometriosis-related symptoms, disturb professional performance. Previous literature has indicated that women with endometriosis have poor work ability at fertile age compared to non-endometriosis women (Hansen, Kesmodel, Baldursson, Schultz, & Forman, 2013; Fourquet, Báez, Figueroa, Iriarte, & Flores, 2011; Nnoaham et al., 2011; Sperschneider et al., 2019; Facchin et al., 2019). These studies have been mostly questionnaire-based, and again, mainly rooted in a case-control study setting including only women at fertile age.

Altogether, endometriosis has been shown to have several adverse effects on women's life, especially at fertile age. Studies of the consequences of endometriosis beyond fertile age and at a population-based level are, on the other hand, scarce. This study aimed to assess these aspects in a population-based study setting based on the Northern Finland Birth Cohorts 1966 (NFBC1966), focusing mainly on women at late fertile age.

2 Review of literature

2.1 Definition of endometriosis

Endometriosis is a chronic, benign gynecological disorder that is defined by the presence of endometrial-like tissue outside the uterine cavity (Giudice & Kao, 2004). According to the definition that was first accepted in 1927, the presence of endometrial, epithelial, and stromal cells in ectopic sites is sufficient to make the diagnosis (Sampson, 1927). However, with advances in disease knowledge, there have been radical changes in our view of the disease since the original description (Burney & Giudice, 2012; Vigano et al., 2018; Zondervan et al., 2020).

Clinically, endometriosis forms macroscopically detectible lesions in the abdominal cavity. Typical anatomical locations of endometriotic lesions are the pelvic peritoneum, ovaries, uterosacral ligaments, posterior vaginal fornix, rectovaginal septum, vesicouterine pouch and urinary bladder wall, and rectosigmoid colon. If ectopic endometrial glands and stroma can be found within the myometrium, it is called adenomyosis. Rarely, endometriotic lesions can be found in the pericardium, pleura, and even in the brain (Anders et al., 2020). Following translocation of the endometrial cells into the peritoneal cavity, the endometrial tissue fragments must survive the defenses of the body, attach to a surface, and subsequently invade and modify the target organ in order to finally establish endometriotic lesions. In addition to endometrial cells, a smooth muscle component (myofibroblasts) and fibrosis represent consistent features of all disease forms (Vigano et al., 2018; Zondervan et al., 2020). On the basis of these histological findings and new pathogenetic theories of endometriosis, it has been proposed to redefine endometriosis as a fibrotic condition in which endometrial stroma and epithelium can be identified (Vigano et al., 2018).

2.2 Origin of lesions

The origin of endometriotic lesions is still unknown, but the most widely accepted theory of endometriosis etiology is Sampson's *theory of retrograde menstruation* from 1927 (Sampson, 1927). This theory proposes that viable endometrial tissue is disseminated into the peritoneal cavity via the fallopian tubes during menstruation and is subsequently implanted onto peritoneal tissue or pelvic organs followed by lesion growth.

Among theories proposing a non-uterine origin of endometriosis, *coelomic metaplasia theory* was presented many years ago. This theory involves the transformation of normal peritoneal tissue into ectopic endometrial tissue (Burney & Giudice, 2012). The agents responsible for this transformation remain poorly defined, but endocrine-disrupting chemicals are suspected (Crain et al., 2008). The closely related *induction theory* holds that an endogenous inductive stimulus, such as a hormonal or immunological factor, promotes the differentiation of peritoneum cells to endometrial cells (Merrill, 1966). The *theory of embryonic Müllerian rests*, or müllerianosis, suggests that residual cells from the embryological Müllerian duct alter migration profiles. Normally, these cells form the uterus, tubes, and upper vagina, but in endometriosis they stay in the pelvis and maintain the capacity to develop endometriotic lesions under the influence of estrogen at puberty. The estrogen-induced embryonic theories are supported by epidemiological studies that show a twofold risk of endometriosis in women exposed to diethylstilbestrol in utero (Missmer et al., 2004; Vannuccini et al., 2016).

According to *stem cell theory*, endometrial stem/progenitor cells from the basalis layer of the endometrium can travel to the abdominal cavity during newborn retrograde menstruation, develop into endometriotic lesions already in the newborn period, and activate during menarche due to the influence of estrogen (Cousins, Dorien, & Gargett, 2018). A more recent proposal suggests that extra-uterine stem/progenitor cells originate from bone marrow and may differentiate into endometriotic tissue (Koninckx et al., 2019). Candidate cell lineages include bone marrow mesenchymal stem progenitors and endothelial progenitors. Support for theories of a non-endometrial origin for endometriosis is derived from clinical cases of histologically confirmed endometriosis in patients without endometrium, such as Rokitansky-Kuster-Hauser syndrome individuals who do not develop a uterus (Bulun, Yilmaz, et al., 2019).

The theory of benign metastasis implicates ectopic endometrial implants as the result of the lymphatic or hematogenous dissemination of endometrial cells (Burney & Giudice, 2012). Microvascular studies have demonstrated the flow of the lymph from the uterine body into the ovary, highlighting a possible role for the lymphatic system in the etiology of ovarian endometriosis. Endometriosis within lymph nodes has been documented in 6–7% of women with endometriosis at lymphadenectomy (Jerman, Anderson, Markham, & Hey-Cunningham, 2020). The strongest evidence for the theory of endometriosis being a benign metastasis is derived from reports of histologically confirmed endometriotic lesions occurring in

sites distant from the uterus—in bones, lungs, and the brain (Vigano et al., 2018). Theories on the origin of endometriotic lesions are shown in Figure 1.

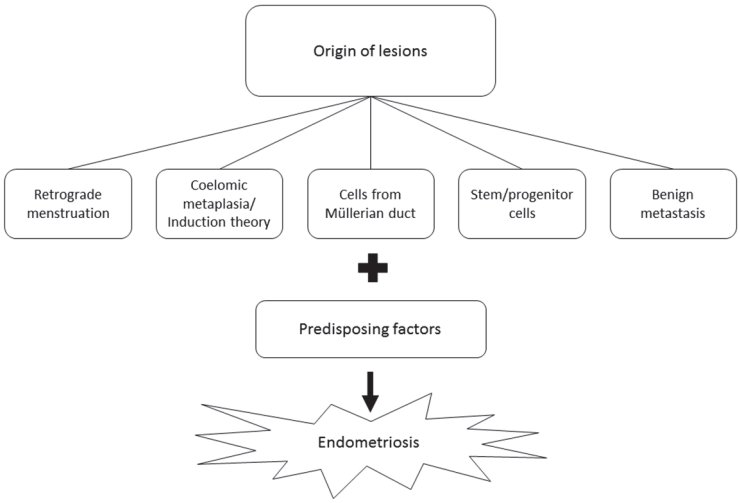

Fig. 1. Theories on the origin of endometriosis.

2.3 Pathogenesis

While the Sampson theory of retrograde menstruation as the origin of endometriosis is generally accepted, it should be noted that only 10% of women are diagnosed with endometriosis, even though almost 90% of healthy women undergo retrograde menstruation. Thus, the disease most likely entails multifactorial pathogenesis, including factors that are necessary for the development of endometriotic implants. Escape from immune clearance, attachment into the peritoneal epithelium, invasion into the epithelium, establishment of local neovascularity, and continued growth and survival are essential for the disease (Burney & Giudice, 2012). Some survival mechanisms seem to be necessary for the initial attachment of endometrial tissue fragments to the ectopic site. Moreover, a defective immune system might fail to clear implants from the abdominal cavity. Once the initial implantation of the endometrial tissue fragment occurs, proliferation and tissue growth may be necessary for the long-term survival of the tissue (Zondervan et al., 2020).

Estradiol is a key factor in the development and growth of endometriotic lesions (Huhtinen, Ståhle, Perheentupa, & Poutanen, 2012). Ovaries are the main source of estradiol from puberty to menopause. In addition to ovaries, aromatase produced by peripheral adipose and skin tissue converts circulating androstenedione to estrogens. Estradiol promotes the proliferation and inhibits apoptosis in the endometrium and thus maintains endometriotic cell survival. The endometrial implants have also intrinsic *aromatase activity*, which causes the conversion of cholesterol to estradiol, leading to large quantities of estradiol formation. Estrogen also has proinflammatory effects, while estradiol stimulates cyklo-oxygenase-2 inhibitor (COX2), leading to overproduction of prostaglandinE_2 (PGE_2) and, further on, to inflammation (Reis, Petraglia, & Taylor, 2013). Eventually, induced estrogen synthesis leads to the growth of the endometrial implants, COX-2 expression, and prostaglandin secretion, which further induces aromatase activity and builds a positive feedback cycle (Figure 2).

Growing evidence suggests a role of *progesterone resistance* in women with endometriosis. Progesterone downregulates estrogen receptors and converts estradiol to estrone, which is a less biologically active form of estrogen (Patel, Rudnicki, Yu, Shu, & Taylor, 2017). Progesterone also modulates apoptosis-related genes and favors induced apoptosis. In women with endometriosis possible progesterone resistance, enhanced estradiol formation and deficient estradiol inactivation results in the accumulation of the estrogen effect and decreased apoptosis, leading to the growth of endometriotic lesions and induced inflammation (Reis et al., 2013).

Angiogenesis and sufficient vascularization are essential in the survival and growth of endometriotic lesions—and indeed, high levels of vascular endothelial growth factor (VEGF) have been detected in the peritoneal fluid of affected women (Kyama et al., 2006). Studies have also shown abnormalities in almost all types of immune cells in the peritoneal fluid, including increased levels of peritoneal neutrophils and macrophages, reduced cytotoxic function of natural killer cells, and aberrant numbers of T and B lymphocytes that aid endometriotic cell growth, maintenance, invasion, and angiogenesis in women with endometriosis (Izumi et al., 2018).

Inflammation is one of the essential processes in endometriosis development. The elevated production of cytokines and prostaglandins and infiltration of immune cells are hallmarks of inflammation (Halme, Hammond, Hulka, Raj, & Talbert, 1984; Bellelis et al., 2019). The endometriotic stromal cells are one of the major

sources of cytokines and prostaglandins. It has been shown that menstrual blood of women with endometriosis more often contains cells that form the basal layer of the endometrium, which causes more trauma and leads to the activation of interleukin-1b (IL-1b) and interleukin 6 (IL-6), induced COX-2 activation, prostaglandin formation, and aromatase expression (Leyendecker, Wildt, & Mall, 2009). Recurrent retrograde menstrual bleeding activates macrophages, which leads to increased production of prostaglandins, cytokines, and growth factors, and to retrograde menstrual blood release of free iron molecules and heme, which causes oxidative stress (Donnez, Binda, Donnez, & Dolmans, 2016). In oxidative stress, reactive oxygen species are formed, maintaining chronic inflammation and damaging surrounding pelvic organs, leading to adhesion formation.

One potential mechanism for developing endometriosis are *alterations in the eutopic endometrium*. Studies have shown that the eutopic endometrium of women with endometriosis differs significantly from that of healthy controls (Aghajanova et al., 2011). Several molecular defects, such as the activation of oncogenic pathways or biosynthetic cascades that favor increased production of estrogen, cytokines, prostaglandins, and metalloproteinases, have been found (Kitawagi et al., 2002; Bulun, Yilmaz, et al., 2019). Moreover, previous studies have revealed progesterone resistance in the eutopic endometrial cells, including stem cells obtained from women with endometriosis (Barragan et al., 2016). In addition, eutopic endometrial cells from women with endometriosis are more resistant to cell-mediated immune attack, having increased proliferative capacity and increased aromatase expression, leading to increased estrogen concentrations. Finally, a pathological presence of nerve tissue has been immunohistochemically identified in the functional layer of eutopic endometrial tissue in women with endometriosis but not in the eutopic endometrium of disease-free women. This may have important implications in understanding the origin of pain in women with endometriosis (Asante & Taylor, 2011).

A simplified pathogenesis cascade is shown in Figure 2.

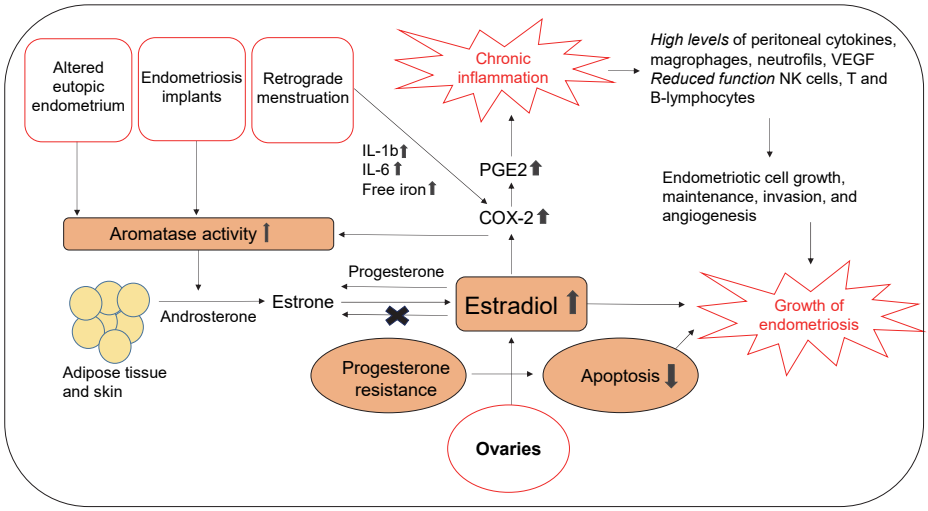

Fig. 2. Simplified pathogenesis cascade of endometriosis.

2.4 Prevalence, genetics and clinical risk factors

2.4.1 Prevalence of endometriosis

The accurate prevalence of endometriosis is unknown because of a lack of reliable, low-cost, non-invasive diagnostic methods. A Finnish TEENMAPS study showed that even 33% of 15–19-year-old girls have suffered severe menstrual pain, suggesting endometriosis (Suvitie, Hallamaa, Matomäki, Mäkinen, & Perheentupa, 2016). Among the general unselected female population, the prevalence of pelvic endometriosis approaches 6–10% (Giudice & Kao, 2004; Tissot et al., 2017). In adult women undergoing laparoscopy for chronic pelvic pain (CPP), endometriosis is detected in one-third of cases and, in women with CPP and infertility, the prevalence is as high as 50% (Howard, 2009). Endometriosis and adenomyosis often coexist in the same patients; adenomyosis prevalence in women with endometriosis ranges between 20–80% (Vannuccini & Petraglia, 2019). However, endometriosis and adenomyosis are considered two different entities because of specific pathogenic pathways and clinical presentation. Furthermore, the prevalence of endometriosis may be influenced by ethnicity. A meta-analysis showed that Black women were less likely to be diagnosed with endometriosis (OR 0.49, 95% CI 0.29–0.83) compared with White women, whereas Asian women

were more likely to have this diagnosis (OR 1.63, 95% CI 1.03–2.58) (Bougie, Yap, Sikora, Flaxman, & Singh, S. 2019).

2.4.2 Genetics of endometriosis

Women with endometriosis have been suggested to have an inheritable predisposition to the disease. Indeed, it has been shown that women have a sevenfold higher risk for endometriosis if their mother or sisters have severe endometriosis (Simpson & Bischoff, 2002), and the overall heritability has been estimated to be at around 50% (Saha et al., 2015; Borghese, Zondervan, Abrao, Chapron, & Vaiman, 2017). In addition, familiar cases of endometriosis have an earlier onset of symptoms and they are more severe compared with non-familiar cases. Common genetic variation covers approximately 26% of the risk. Genome-wide association studies have found almost 30 significant loci and the adjacent genes. However, it is still unclear how these significant loci contribute to the pathogenesis of endometriosis, i.e., cell adhesion and proliferation, angiogenesis, inflammation, and hormonal pathways (Zondervan et al., 2020). Besides specific loci, several endometriosis-related somatic mutations in genes (i.e., ARID1A, KATZ, LAMA5, KRAS, PIK3CA, FGFR2) have been identified in both endometriotic lesions and the eutopic endometrium (Rahmioglu et al., 2015).

2.4.3 Clinical risk factors of endometriosis

Menstrual cycle characteristics, such as early age at menarche, short menstrual cycle length, and heavy menstrual bleeding, which reflects the frequency of exposure to menstruation or the volume of menstrual reflux, are documented to increase the risk of endometriosis. A meta-analysis of 18 studies showed a 55% probability of woman with endometriosis having earlier menarche than those without endometriosis (Nnoaham, Webster, Kumbang, Kennedy, & Zondervan, 2012).

Several lifestyle factors have been shown to contribute to the risk of endometriosis, although the results remain somewhat controversial (Hemmings et al., 2004; McLeod & Retzloff, 2010; Saha, Kuja-Halkola et al., 2017; Hemmert et al., 2019). In some studies, smoking, high vegetable and fruit consumption, and regular physical exercise have been shown to be preventive factors, while high amounts of red meat and fat in the diet seem to increase the risk (McLeod & Retzloff, 2010; Bravi et al., 2014).

2.5 Endometriosis and body size

The mechanism and pathophysiology of endometriosis seem to be multifactorial, including genetic, molecular, environmental, and lifestyle components, all of which have effects on individuals' body size. In human studies, altered expression of metabolism-related hormones, such as leptin, in peritoneal fluid, serum, and inside endometrioma have been reported in women with endometriosis (Matarese et al., 2000; Wu, Chuang, Chen, Lin, & Tsai, 2002; Alviggi et al., 2009; Concalves et al., 2015). Leptin is well known to modulate food intake and appetite control (Crovesy & Rosado, 2019) and thus might be a common factor in endometriosis and body size. Another potential and common mechanism for endometriosis and body size could involve insulin-like growth factor 1 (IGF-1), which exerts anabolic effects and modulates glucose metabolism (Hamed, El-Sherbeny, & El-Din, 2019). Evidence suggests that high IGF-1 levels in plasma and peritoneal fluid are associated with a higher risk of endometriosis (Mu, Hankinson, Schernhammer, Pollak, & Missmer, 2015). Besides these factors, women with a higher ratio of estrogen to androgen have been found to have a lower waist-to-hip ratio (WHR), which may lead to an association between endometriosis and lean habitus (Zondervan et al., 2018).

The relationship between body composition and endometriosis has been established in several epidemiological studies. Body size in childhood and adolescence in women with endometriosis have, however, reported conflicting results. Nurses' Health Study II reported a lower incidence of endometriosis in females with a larger body size at ages 5 and 10 years, whereas a study by Nagel suggested that being underweight at age 16, but also overweight at age 10, was associated with a higher risk for the disease (Vitonis et al., 2010; Nagle et al., 2009).

In adulthood, taller height and leaner habitus have been reported to be associated with the risk of endometriosis (McCann et al., 1993; Hediger et al., 2005; Ferrero, Anserini, et al., 2005; Farland et al., 2017). A meta-analysis by Liu and Zhang (2017) showed that a higher BMI may be associated with a lower risk of endometriosis (Liu & Zhang, 2017). Also, a pear-shaped body figure and distribution of adipose tissue below the waist characterized by a low WHR have been shown to be associated with endometriosis (McCann et al., 1993; Hediger et al., 2005; Backonja, Buck Louis, & Lauver, 2016; Backonja et al., 2017). However, these studies did not consider differences between the subtypes of endometriosis.

2.6 Severity and subtypes of endometriosis

2.6.1 Classification

The classification of endometriosis has remained controversial and challenging due to the variable manifestations of the disease but also due to the diagnostic methods, all of which have their limitations. The best-known classification system for endometriosis is the revised American Society for Reproductive Medicine (r-ASRM) classification from 1997. The r-ASRM classifies endometriosis into four stages, from minimal to severe, according to laparoscopic findings of the disease, i.e., location and depth of lesions and density of adhesions (ASRM, 1996). In addition to r-ASRM, Enzian and Endometriosis Fertility Index (EFI) classification systems are in use (Lee, Koo, & Lee, 2021). However, all of these systems have attracted criticism because of the poor correlation with disease stages and symptoms as well as a lack of predictive prognostic value (Haas, Shebl, Shamiyeh, & Oppelt, P 2013; Andres, Borrelli, & Abrão, 2018). Thus, the classification that is more commonly used today is based on the location and depth of the endometriotic lesions, which better consider the heterogeneity of the disease: superficial/peritoneal endometriosis (SUP), ovarian endometrioma (OMA), and deep-infiltrating endometriosis (DIE) (Zondernvan et al., 2018).

2.6.2 Superficial/peritoneal endometriosis (SUP)

In superficial/peritoneal endometriosis (SUP), endometriotic implants are detected on the surface of the pelvic peritoneum and ovaries, and lesions are superficial (< 5 mm depth). The laparoscopic appearances of peritoneal lesions are red, black, or white nodules depending on the age of the lesions (Figure 3a) (Giudice & Kao, 2004). The size of the lesions varies from a few millimeters to several centimeters. Besides macroscopic lesions, microscopic lesions are also possible and in blind biopsies of normal-looking peritoneum, endometriosis is detected in 6–15% of symptomatic patients (Khan et al., 2014). A Finnish nationwide register study showed that 40% of women with endometriosis had peritoneal disease at their first surgery and SUP is often diagnosed at a younger age than other types of endometriosis (Saavalainen, Tikka, But, Gissler, Haukka, Tiitinen, … Heikinheimo, 2018). However, it is not clear whether peritoneal endometriosis is a progressive state toward more severe types of endometriosis, own endometriosis entity or even a physiological phenomenon occurring intermittently in all women and resolving

spontaneously (Gordts, Koninckx, & Brosens, 2017). The laparoscopic appearance of peritoneal endometriosis is shown in Figure 3a.

2.6.3 Ovarian endometriosis (OMA)

The typical finding for ovarian endometriosis (OMA) is one or more cysts in the ovary lined by endometrioid mucosa, i.e., endometrioma. Cysts vary in size and can be bilateral and adherent to pelvic organs or the side wall. It is typical that both ovaries with endometrioma are adherent to each other but also to the back wall of the uterus. This phenomenon is called "the kissing ovaries." Endometrioma contain old blood, and they appear as dark "chocolate cysts" in laparoscopy (Figure 3b). A Finnish study group has shown that among women with surgically confirmed endometriosis, 46% had OMA, and this was the most common subtype of endometriosis (Saavalainen, Tikka, But, Gissler, Haukka, Tiitinen, … Heikinheimo, 2018). OMA is easier to detect by clinical and ultrasound examination than other subtypes, which may result in a high prevalence of OMA.

2.6.4 Deep-infiltrating endometriosis (DIE)

Deep-infiltrating endometriosis (DIE) is defined as the deep invasion (> 5 mm) of endometriosis nodules. The DIE nodulus may be located in uterosacral ligaments (52.7%), the bowel (22.7%), the vagina (16.7%), the bladder (6.3%), or the ureters (2.3%) (Chapron et al., 2012). These nodules are a solid, complex mass comprising endometriotic, adipose, and fibromuscular tissue (Figure 3b). In a Finnish study, among surgically confirmed cases, DIE was present in 8.2% of cases (Saavalainen, Tikka, But, Gissler, Haukka, Tiitinen, … Heikinheimo, 2018). As DIE causes severe adhesions and distorted anatomy, affected women have the most severe symptoms, and the treatment is usually complex and requires advanced professional skills, often a multidisciplinary team (Setälä, Kössi, Silventoinen, & Mäkinen, 2011). About 50% of women with DIE also have concomitant OMA (Chapron et al., 2009). The laparoscopic appearance of SUP, OMA and DIE is shown in Figure 3.

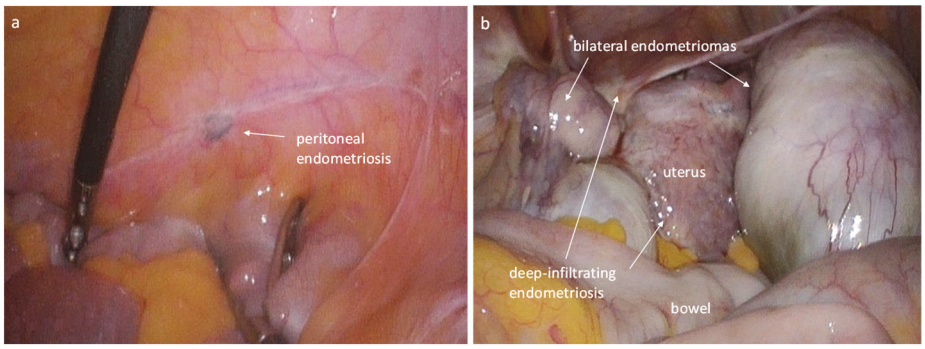

Fig. 3. Laparoscopic appearance of a) superficial/peritoneal endometriosis (SUP) and b) ovarian (OMA) and deep-infiltrating endometriosis (DIE). Permission from the patient to publish.

Altogether, endometriosis is a complex disease. Whether different subtypes share a common origin or if these three subtypes include separate entities caused by different mechanisms, and whether there is progression from superficial subtype to ovarian or deep-infiltrating disease remains unknown (Nisolle & Donnez, 1997; Nisolle, 2002; Bulun, Yilmaz, et al., 2009). However, all subtypes share common histologic features of presence of eutopic endometrial stroma or ephitelial cells, bleeding and inflammation.

2.7 Clinical manifestation of endometriosis

Clinical manifestations of endometriosis vary drastically among affected women. Approximately one-third of women with endometriosis are asymptomatic and, in these cases, diagnosis usually occurs due to a clinician's attention during evaluation for infertility or during pelvic surgery (Tissot et al., 2017). It is typical that the severity of the disease is poorly correlated with the severity of the symptoms. Cyclic and chronic pelvic pain is the most common symptom of endometriosis. Two-thirds of women with endometriosis have pain symptoms, which are often unspecific and may overlap with symptoms of other pain-causing/pelvic area diseases, such as lower back pain or irritable bowel syndrome (IBS) (Rolla, 2019; Culley et al., 2013). In practice this may lead to long diagnostic delay, which in the literature has been shown to be between 6–10 years (Hadfield, Mardon, Barlow, & Kennedy, 1996; Arruda, Petta, Abrão, & Benetti-Pinto 2003; Staal, van der Zanden, & Nap, 2016). Other symptoms include dysmenorrhea, dyspareunia, dyschezia, irregular bleeding, lower back pain, hematuria and dysuria, and fatigue (Figure 4)

(Culley et al., 2013). In rare cases of endometriosis of the lungs and brain, the disease may present with hemoptysis and seizures (Andres et al., 2020). Mostly, women with endometriosis report the onset of symptoms during adolescence, which tend to diminish after menopause.

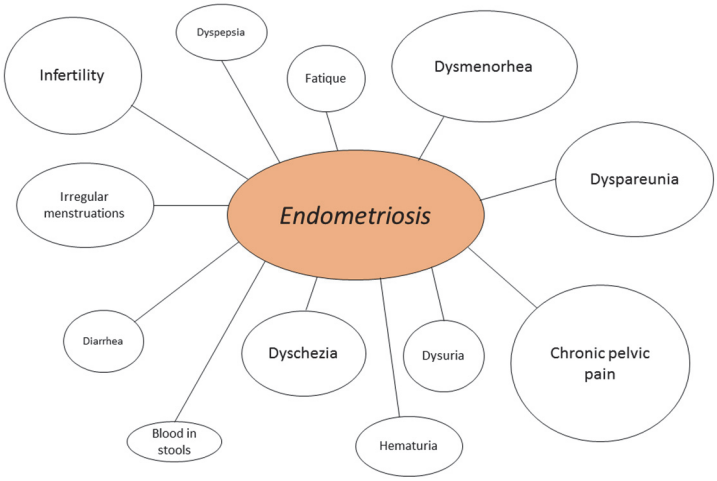

Fig. 4. Symptoms of endometriosis.

2.7.1 Dysmenorrhea and dyspareunia

Commonly, endometriosis-related pain appears as cyclic menstrual pain, dysmenorrhea, usually starting a couple of years after menarche in adolescence (secondary dysmenorrhea) or in early adulthood (Sachedina & Todd, 2020). It has been estimated that a large number of patients who are suffering from dysmenorrhea have undiagnosed endometriosis (Zannoni, Forno, Paradisi, & Seracchioli, 2016). According to the opinion of the American College of Obstetricians and Gynecologists (ACOG), endometriosis should be considered among patients with persistent, clinically significant dysmenorrhea despite treatment with hormonal agents and non-steroidal anti-inflammatory drugs, particularly if no other etiology for CPP or secondary dysmenorrhea has been identified based on history, physical examination, and pelvic ultrasonography (ACOG, 2018).

In addition to dysmenorrhea, one-half of women with endometriosis suffer from dyspareunia (Yong, 2017). Endometriosis-related dyspareunia is defined as deep dyspareunia, which may also be associated with co-morbid urethral, bladder, or pelvic floor pain and tenderness independent of endometriosis-related factors (Orr et al., 2018).

Other differential diagnoses of dyspareunia include some other gynecological disorders, such as vulvodynia and vaginismus, which causes pain mainly in the vaginal vestibulum during intercourse (Heim, 2001).

2.7.2 Chronic pelvic pain (CPP)

Pain is the leading symptom of endometriosis. The pathophysiology and mechanism of endometriosis-associated pain involves inflammatory and hormonal alterations and changes in brain signaling pathways; pain may be nociceptive, neuropathic, or a combination of these. Emotional, cognitive, and behavioral components are also present (Coxon et al., 2018; Fauconnier & Chapron, 2005). CPP is defined as constant pain in the lower abdomen or pelvis for at least six months that does not occur with menstruation, intercourse, or pregnancy (RCOG, 2018). Endometriosis is a leading cause of CPP, but it should be noted that at least one-third of adult women with CPP have no organic cause for pain (Daniels & Khan, 2010).

The pain in endometriosis is mostly due to elevated levels of prostaglandins, interleukins, cytokines, and other inflammatory cells attracted to ectopic endometrial-like tissue, which can then activate nerve fibers (peripheral mechanism) (Nezhat et al., 2019). Moreover, peritoneal fluid in women with endometriosis contains high levels of nerve growth factors that promote neurogenesis, and the ratio of sensory nerve fibers and nerve density is significantly increased in endometriotic lesions (Medina & Lebovic, 2009; Forster et al., 2019). A direct association between an increased number of endometriosis-associated nerve fibers in endometriotic lesions and significantly greater menstrual pain has also been observed (Coxon et al., 2018). Interestingly, it has been suggested that ovarian endometriotic lesions may be less innervated than lesions elsewhere in the pelvis, which might indicate that patients with ovarian endometriosis feel less pain than women with other subtypes of the disease (Liutkevičienė, Mečėjus, Žilovič, & Bumbulienė, 2019). On the other hand, women with deep endometriosis (rectovaginal septum) experience more pain and the nerve fibers are situated closer to the lesion.

Chronic pain causes central sensitization, which is another mechanism that promotes endometriosis-associated pain. Specific peripheral receptors (nociceptors) detect noxious stimuli, and the message travels to the brain through the spinal cord (nociception) where the conscious experience of pain is generated. If pain exists for a prolonged time, the patient becomes highly sensitive to subsequent painful stimuli because of neuroplastic changes in descending pathways that modulate pain perception (Aredo, Heyrana, Karp, Shah, & Stratton, 2017). Women with endometriosis can experience pain as a result of inability to engage descending inhibition pathways. Many areas of the brain are activated during the perception of pain, forming a dynamic network of brain regions, which varies between individuals and reflects the complexity of the pain experience (Morotti et al., 2016). Also, changes in brain functions and structures may be detected in women with endometriosis and chronic pain. It has been shown that women with endometriosis and pain symptoms have greater resting connectivity of the anterior insula with other brain regions and have higher levels of excitatory neurotransmitters in the anterior insula, which is associated with the connectivity between the anterior insula and the medial prefrontal cortex (As-Sanie et al., 2016). These findings suggest that hyperalgesia may develop especially in these women. Further on, As-Sanie et al. (2012) showed that both women with endometriosis-associated pelvic pain and women with pelvic pain, but without endometriosis, had decreased grey matter volume in brain regions involved in pain perception, suggesting that it is the presence of pain, not endometriosis independently, that is associated with these structural changes (As-Sanie et al., 2012). Endometriosis-related pain cascade is shown in Figure 5.

Valid methods of assessing the severity and intensity of pain are essential for clinical management and research purposes. The self-report visual analog scale (VAS) and numerical rating scale (NRS) are the most frequently used and best-adapted tools for endometriosis pain measurement (Bourdel et al., 2015). Studies regarding pain threshold and pain tolerance mainly use pressure pain measurements, which have been shown to have high reliability (Waller, Straker, O'Sullivan, Sterling, & Smith, 2015).

As a conclusion, studies have shown increased pain sensitivity among women with endometriosis, with or without CPP, in response to mechanical stimuli (As-Sanie et al., 2013). Pain-threshold studies have suggested hyperalgesia at extra-pelvic sites, most likely due to peripheral and/or central sensitization mechanisms in affected women (Brawn et al., 2014; Giamberardino et al., 2014; Howard, 2009;

Morotti et al., 2016). However, these studies are limited by small sample size, case-control study set, and focus only on women at fertile age.

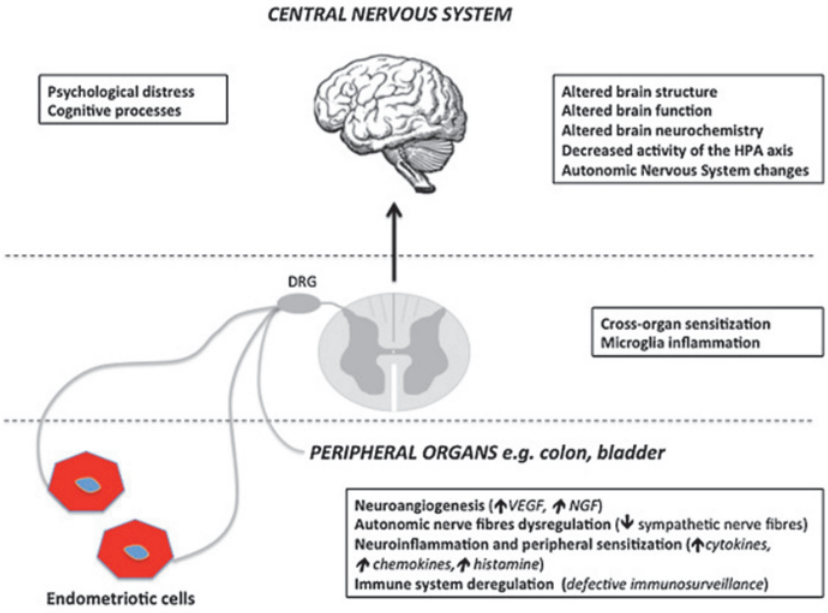

Fig. 5. Endometriosis related pain cascade (figure from Morotti 2016, permission to reuse).

2.7.3 Infertility

The prevalence of endometriosis in women with infertility is reported to be between 25% and 50%. On the other hand, 30–50% of women with endometriosis have concomitant infertility (Evans et al., 2017). Infertility in endometriosis is proposed to be caused by multiple mechanisms, including underlying anatomical distortions (adhesions, changes in ovarian and tubal anatomy), endocrine abnormalities (progesterone resistance, increased estrogenic milieu), and immunological disturbances (chronic inflammation, altered cytokine profile) (Tanbo & Fedorcsak, 2017; Macer & Taylor, 2012; de Ziegler, Borghese, & Chapron, 2010).https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5794019/ - R8 Studies have shown that women with endometriosis have a decreased ovarian reserve predicted by lower levels of anti-müllerian hormone (AMH) (Pedachenko, Anagnostis,

Shemelko, Tukhtarian, & Alabbas, 2020). Also, surgical treatment of endometriosis may have an adverse effect on ovarian reserve. Excess production of inflammatory mediators can result in suboptimal function and damage to oocytes and sperm along with decreased endometrial receptivity (Tanbo & Fedorcsak, 2017). Further on, inflammation impairs tubal function and decreases tubal motility, which can impair gamete transportation. At the endometrial level, increasing evidence supports the assertion that endometriosis also impairs eutopic endometrium function and causes implantation failure (Lessey & Kim, 2017). It should be noted that adenomyosis, which often coexisting with endometriosis and having effects on endometrial function, has been shown to lead to a lower clinical pregnancy rate and live-birth rate compared with women with endometriosis alone (Vannuccini & Petraglia, 2019). However, the mechanism of cellular or molecular signaling from the lesion to the uterus is unknown.

Surgical treatment of endometriosis-associated infertility focuses on improving fertility by removing ectopic endometrial implants and restoring normal pelvic anatomy. However, *in vitro* fertilization (IVF) is the most effective treatment for endometriosis-associated infertility (de Ziegler et al., 2019). A recent report on the Society of assisted reproductive technology (ART) data showed that the average delivery rate per retrieval of implants from patients undergoing IVF was 39.1% for women with endometriosis compared to 33.2% for women with all causes of infertility (Senapati, Sammel, Morse, & Barnhart, 2016). A systematic review concluded that women with endometrioma undergoing ART treatment had similar reproductive outcomes as women without endometriosis. Moreover, surgical preoperative treatment of endometrioma did not alter the outcome of ART treatment compared with those who did not receive surgical intervention (Hamdan, Dunselman, Li, & Cheong, 2015). In summary, endometriosis-associated infertility should be taken into account in patient consultation individually considering patient`s age, parity, desire for ART and subtype and location of endometriosis.

2.8 Diagnosis of endometriosis

2.8.1 Symptoms and clinical examination

Commonly, patients` clinical history leads to suspicion of endometriosis. Although endometriosis-related symptoms begin typically in adolescence, the diagnostic delay might be several years. Previous studies have estimated the delay to be 7–10

years (Hudelist et al., 2012; Ghai, Jan, Shakir, Haines, & Kent, 2020). Factors causing the delay of diagnosis, and at the same time the prolongation of symptoms and adequate treatment, were shown to be false diagnosis and normalization of endometriosis-related symptoms (Hudelist et al., 2012). Furthermore, endometriosis patients usually seek medical attention several times before receiving the diagnosis of endometriosis, which places a burden on health care and generates additional social costs (Epstein et al., 2017; Surrey et al., 2018).

First-line diagnostics include interviews and patients' clinical history with particular emphasis on endometriosis-related symptoms: dysmenorrhea, dyspareunia, dysuria, dyschezia, and CPP. Gynecological examination is usually painful in affected women, especially deep pain in the upper vagina and in the lower pelvic cavity. A pelvic examination should be performed to assess the characteristics of the uterus and adnexa, including their tenderness and pain when moving them (Bazot & Daraï, 2017). A painful retrocervical nodulus can be found in palpation. During the speculum examination, the focus should be on the posterior vaginal fornix to look for possible retraction and dark endometriosis nodules (Bazot & Daraï, 2017).

2.8.2 Diagnostic surgery

Surgery, mainly laparoscopy, and histopathological diagnosis still remain the gold standard for definitive diagnosis of endometriosis (Rolla, 2019; Leonardi et al., 2020). However, the procedure must be weighed against the risks of surgical and anesthesia intervention and high treatment costs. If surgery is needed, preoperative planning of the diagnostic and possible excision of the endometriosis implants and the extent of surgery should be planned in advance (Leonardi et al., 2020). However, nowadays, knowledge about the disease and advanced non-invasive diagnostic tools offer a valid, specific, and sensitive diagnostic method for endometriosis.

2.8.3 Transvaginal ultrasound (TVUS) and magnetic resonance imaging (MRI)

Transvaginal ultrasound (TVUS) combined with clinical examination is the first-line diagnostic tool given its easy availability and cost-effectiveness. TVUS has high sensitivity (87–99%) and specificity (92–99%) to detect OMA (Guerriero et al., 2018). In experienced hands, it can also detect DIE, but it fails to detect peritoneal lesions. Endometrioma is usually a unilocular cyst, rarely multilocular,

with ground glass content (Figure 6a). TVUS is also reliable to distinguish between OMA and malignant ovarian tumors. According to the international ovarian tumor analysis study, the misclassification rate between OMA and malignancy was only 0.9% (Van Holsbeke et al., 2010). Three-dimensional TVUS has shown an equal sensitivity and specificity compared to two-dimensional TVUS; however, the advantages of three-dimensional TVUS are improved anatomical detection and depiction of the size and volume of ovarian lesions (Grasso et al., 2010).

Diagnosis of DIE requires more experienced ultrasound skills. DIE lesions appear as hypo- or iso-echoic solid nodules, which may vary in size and have smooth or irregular contours, or as hypoechoic thickening of the wall of the bowel, vagina, bladder, or peritoneal cavity (Figure 6b).

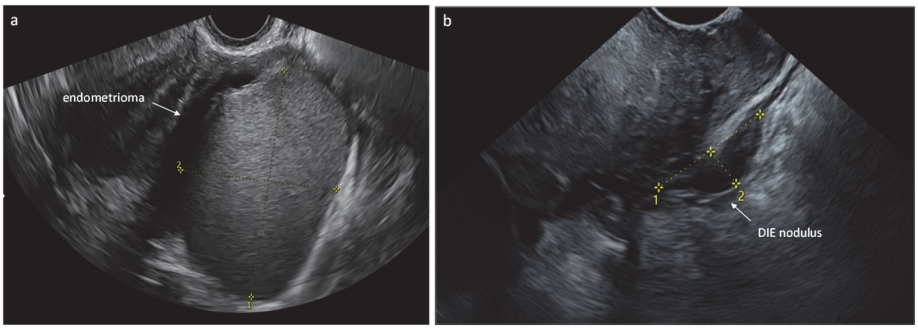

Fig. 6. Transvaginal ultrasound image of a) ovarian endometrioma (OMA) and b) deep-infiltrating endometriosis (DIE) nodulus. Permission from the patient to publish.

The real-time dynamic TVUS examination of adhesions and pouch of Douglas obliteration, using the "sliding sign" technique, seems to be useful in the identification of women at increased risk for bowel or rectovaginal endometriosis (Exacoustos, Zupi, & Piccione, 2017). The sensitivity and specificity of a negative sliding sign has been reported to be 85% and 96% in DIE (Hudelist et al., 2011).

As for planning surgery, the sensitivity and specificity of the TVUS for detecting the location of DIE might not be adequate enough, and thus magnetic resonance imaging (MRI) should be considered. Furthermore, bowel lesions could be located high in the sigmoid and TVUS does not reach its level. A recent review article stated that regardless of DIE location, for all TVUS techniques, the pooled sensitivity and specificity were 79% and 94%, respectively, while MRI had a 94% sensitivity and 77% specificity for pelvic endometriosis diagnosis (Bazot & Daraï, 2017). For rectosigmoid endometriosis, the sensitivity and specificity of MRI were

as high as 92% and 96%, respectively (Bazot & Daraï, 2017). However, the results of a meta-analysis demonstrated similar diagnostic performance of TVUS and MRI in the detection of DIE, confirming the role of TVUS as a cost-effective first-line technique (Guerriero et al., 2018). As a conclusion, MRI has a higher specificity than TVUS in the diagnosis of DIE with rectovaginal location and should be considered when planning surgical treatment of DIE.

2.8.4 Blood biomarkers

Even after the evaluation of hundreds of biomarkers for their use in the diagnosis of endometriosis, none have been validated as suitable for detecting endometriosis. Cancer antigen (CA) 12-5 is a well-established biomarker for detecting epithelial ovarian cancer and endometriosis (Chen et al., 2019). Even though the sensitivity of the elevated level of CA 12-5 is only 52% and it fails to detect the peritoneal type of endometriosis (Nisenblat et al., 2016), it remains the most recommended marker for suspicion of the disease, especially OMA. It should be noted that several other conditions such as infections raises S-CA12-5 levels, and hormonal and surgical treatment of endometriosis, on the other hand, may lower the levels of CA 12-5 (Hirsch et al., 2016; Petta et al., 2009; Margatho, Mota Carvalho, Eloy, & Bahamondes, 2018). Other biomarkers, such as CA 19-9, CA 72-4, and HE-4, have more value for differentiating endometriosis from other pathologies (Imai, Horibe, Takagi, Takagi, & Tamaya, 1998; Huhtinen et al., 2009; Mckinnon, Mueller, Nirgianakis, & Bersinger, 2015). Altogether, a Cochrane review from the year 2016 evaluated 122 blood biomarkers and found that none of them consistently met the criteria for diagnostic testing. A subset of blood biomarkers could be useful either for detecting pelvic endometriosis or for differentiating OMA from other benign ovarian masses, but insufficient evidence has been drawn to derive any meaningful conclusions (Nisenblat et al., 2016).

2.8.5 Self-reported endometriosis diagnosis

Self-reported diagnosis of endometriosis has only recently been described in the literature, and its validity and reliability have been reported by few studies (Saha, Marions, & Tornvall, 2017; Shafrir et al., 2021). For research purposes, endometriosis diagnosis has mainly been based on surgically confirmed cases. However, up to one-third of women with endometriosis are asymptomatic, and thus case-control studies using surgically confirmed cases or cases collected only from

hospital-based registers represent possibly more severe and symptomatic cases, leading to selection bias toward the more symptomatic population. Thus, population-based studies, which consider all cases of endometriosis as comprehensively as possible, are needed to compile studies with high specificity.
Self-reported diagnosis of endometriosis has raised the question of its validity. A Swedish cohort study of 26 898 female twins aged 20–60 years showed that self-reported data on endometriosis are moderately accurate and may be useful in studies when register data are not available (Saha, Marions, et al., 2017). More recently, self-reported diagnoses were also considered in four international cohorts. This study showed that self-reported endometriosis diagnosis was fairly accurate, showing > 70% confirmation from the clinical and surgical records (Shafrir et al., 2021). Altogether, combining medically confirmed endometriosis cases with self-reported endometriosis cases leads to a high specificity of cases. The sensitivity of this combined diagnosis method, on the other hand, is more difficult to evaluate.

2.9 Treatment of endometriosis

Treatment of endometriosis should be planned individually. Treatment choices are based on several factors, including age and patient preference, reproductive hopes and plans, subtype of the disease, intensity of symptoms, incidence of adverse effects and risks involved, and contraindications for treatment.

2.9.1 Hormonal therapy

While endometriosis is an estrogen-dependent disease and the constant supply of estrogen is crucial for the development, growth, and persistence of endometriotic lesions, the main principle of hormonal therapy is to lower estrogen levels or reduce their action. Hormonal therapies that rely on the suppression of the ovaries and endometriotic tissues include *combined oral contraceptives, progesterone-only contraceptives, gonadotropin-releasing hormone agonists (GnRH-a), selective progesterone receptor modulators (SPRM), aromatase inhibitors, and danazol.*

Combined oral contraceptives are the most commonly used first-line hormonal therapy for endometriosis by the negative inhibition of gonadotrophins and thus ovarian estrogen synthesis. Also, extrinsic estrogen and progesterone combination promotes the differentiation and decidualization of endometrial cells instead of the proliferation of the endometriotic tissue and slows the progression of the disease

(Rafique & Decherney, 2017). Continuous dosing is preferred as it prevents menstruation and the bleeding of endometriotic lesions.

Progesterone has multiple mechanisms of action in restricting endometriosis, thus supporting the central role for progestin derivates as treatment options in endometriosis. Progesterone induces decidualization of the endometrium, inhibits estrogen-induced mitosis and proliferation, alters estrogen receptors, and inhibits angiogenesis and expression of matrix metalloproteinase, which are needed for the growth of endometriotic implants (Aghajanova et al., 2011). Progestins have the advantage of several routes of administration (oral, injectable, implant, or intra-uterine device), better tolerability, fewer side effects, and minimal contraindications, achieving better treatment compliance than combined contraceptives. Especially the 52-mg levonorgestrel intrauterine system (LNG-IUS), which is a T-shaped device that releases 20 ug of hormone per day over a seven-year period. Multiple studies have demonstrated the efficacy of LNG-IUS in women with endometriosis (Grandi, Farulla, Sileo, & Facchinetti, 2018; Carvalho, Margatho, Cursino, Benetti-Pinto, & Bahamondes, 2018; Samy et al., 2021). Some women suffering endometriosis, however, do not seem to benefit from progestin treatment, most likely due to possible progesterone resistance (Aghajanova et al., 2011; Barragan et al., 2016).

Continuous administration of *GnRH-a* leads to hypoestrogenism by inhibiting gonadotrophin release and subsequent suppression of folliculogenesis and ovarian estrogen production, hence reducing endometriotic implants. However, GnRH-a treatment is approved for only up to six months due to side effects secondary to hypoestrogenism, like bone loss, vaginal atrophy, hot flashes, and adverse metabolic outcomes. Add-back therapy with estrogen-containing pills provides symptomatic relief and decreases the rate of bone loss and may thus be considered in cases in which longer-term treatment with GnRH-a is needed (Bedaiwy, Allaire, & Alfaraj, 2017).

SPRMs cause selective inhibition of endometrial growth without the side effects of hypoestrogenism. Mifepristone and ulipristal acetate are the two SPRMs that are most commonly studied. In animal models, treatment with ulipristal acetate has been shown to result in atrophy of the endometrium, suppression of estrogen-dependent endometrial growth, and decreased expression of COX-2 (Fu et al., 2017; Bressler, Bernardi, Snyder, Wei, & Bulun, 2017). However, mifepristone is used in medical abortion, which limits its clinical use in the treatment of endometriosis, while ulipristal has been shown to have hepatotoxic effects and was thus withdrawn from the Finnish market in 2019.

Studies have shown that aromatase activity is over-expressed in endometriosis. *Aromatase inhibitors* block estrogen synthesis both in the periphery and in the ovaries. Thus, aromatase inhibitors prevent the progression of endometriosis and have been shown to decrease endometriosis-associated pain, improve quality of life, and decrease the size of endometriotic lesions. Similarly, with GnRH-a, aromatase inhibitors lead to hypoestrogenism and related adverse effects, and thus the use of aromatase inhibitors should be limited up to six months unless add-back therapy is combined (Garzon et al., 2020).

Danazol, a derivative of 17 alpha-ethinyl–testosterone, is an androgenic agent that inhibits luteinizing hormone surge and decreases ovarian steroidogenesis by direct inhibition of the ovarian enzymes. It has been shown to be effective in controlling endometriosis-associated pain, but it may cause several adverse side-effects, like acne, hirsutism, deepening of voice, weight gain, muscle cramps, liver dysfunction, and an abnormal lipid profile (Selak, Farquhar, Prentice, & Singla, 2000).

Even though hormonal therapy is the first-line choice for treatment of endometriosis, it is a suppressive rather than a curative treatment. Recurrences are common and often rapid when hormonal therapy is discontinued. Thus, women with endometriosis should be advised of the chronic nature of the disease and advised to receive long-term hormonal treatment until the end of their fertile age and always in between periods of desired pregnancies.

2.9.2 Surgical treatment

If conservative treatment is inadequate, surgery is recommended for the treatment of endometriosis. In some cases of large OMA, surgery is needed as a first-line treatment. Laparoscopy is the preferred approach for its benefits with less postoperative pain, shorter hospital stay, faster recovery, less bleeding, and better cosmetic aspects compared to open surgery (Kho et al., 2018). Surgical treatment should focus on the complete removal of all endometriotic lesions. However, much of the recurrence of endometriosis is related to poor first surgery quality or incomplete removal of all lesions. A recent meta-analysis showed that operative laparoscopy improves overall pain at six months compared with diagnostic laparoscopy, and it is recommended if medical therapy does not achieve an optimal response (Leonardi et al., 2020). Regarding pregnancy rates, the meta-analysis showed that operative laparoscopy yields only small improvement, or no difference

compared with diagnostic laparoscopy (RR 1.29; 95% CI 0.99–1.92) (Leonardi et al., 2020).

The type and localization of endometriosis are central when planning and evaluating surgical treatment. According to ESHRE guidelines for operative treatment of endometriosis, SUP lesions should be excised whenever and wherever possible (Dunselman et al., 2014). Surgery for OMA is an issue that needs attention, since ovarian reserve is affected by surgery. It should be noted, however, that the ovarian damage is, at least partly, due to the endometrioma itself and not only due to the surgical procedure (Seyhan, Ata, & Uncu, 2015). Common opinion differs regarding the size of the endometrioma, the age of the patient, and the future desire for pregnancies, and thus treatment of OMA should be planned individually.

Treatment of DIE is challenging. Medical treatment has been found to be ineffective or temporary, while surgery requires expertise and, in many cases, interdisciplinary surgical teams, including gastrointestinal surgeons and urologists. The complication rate of DIE surgery is high, and the outcomes can be severe, like late bowel and ureteral perforation and fistulas. However, the results of rectovaginal surgery are mostly good. More than 85% of women are pain-free after surgical treatment at 12 months and overall recurrence rate ranges from 2% to 43.5%. The risk factors for recurrence of colon DIE are young age, repeated surgery, high BMI, and incomplete surgery (Minelli et al., 2009, Bassi et al., 2011).

To conclude, the quality of surgery is an important aspect for a successful surgical treatment outcome in endometriosis. Recurrence of the disease and pain symptoms after surgery are high (36% 3 years; 46% 7 years, Abott et al., 2003; Shakiba, Bena, McGill, Minger, & Falcone, 2008), and thus postoperative hormonal treatment is recommended when pregnancy is not desired (Roman et al., 2018). IVF treatment should be considered for women with endometriosis and infertility soon after surgery. In an observational study of 825 women with endometriosis-associated infertility, Barri, Coroleu, Tur, Barri-Soldevila, and Rodríguez (2010) concluded that for the women with endometriosis who are treated with IVF after surgery, the likelihood of achieving pregnancy is as good as for other women conceiving though IVF for other indications (Barri et al., 2010).

2.9.3 Pain killers

All symptomatic endometriosis patients should have a treatment plan for their pain. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used first-line agents in the management of endometriosis-related pain. NSAIDs work

by blocking the COX enzymes, which are crucial for the production of inflammatory mediators. Several studies have shown that ectopic endometrial tissues have a higher concentration of COX 2 receptors (Leyendecker et al., 2009). Furthermore, selective COX 2 inhibitors have been shown to inhibit the growth of endometrial tissue (Dogan et al., 2004). Thus, COX 2 inhibitors might be more efficient for endometriosis-related pain than other NSAIDs. Combining paracetamol with NSAIDs is generally used as a first-line treatment for dysmenorrhea and pain symptoms.

Chronic, severe pain has traditionally been treated with opioid therapy. Regular or high dose use of opioids may lead to addiction and abuse of these drugs. Women with endometriosis have higher probabilities of prolonged use of opioids (Lamvu et al., 2019), and addiction aspects should thus be considered when using opioids in the treatment of endometriosis-related pain.

The neuropathic and centralized component of endometriosis-related pain has raised interest in the use of neuromodulators (gabapentin, pregabalin, amitriptyline, and duloxetine) in affected women with CPP, while neuromodulators are the first-line treatments for neuropathic chronic pain by lowering the pain threshold. A Cochrane review of the management of CPP showed that gabapentin had a more favorable VAS score than amytriptyline (Cheong, Smotra, & Williams, 2014). However, side effects limit the long-term use of these analgesics.

2.9.4 Other treatment and therapeutics

Sacral neuromodulation has been used in the treatment of pelvic floor disorders and CPP. Some clinical studies have shown that sacral neuromodulation provides significant relief of pain symptoms as well as defecation and urinary symptoms in women with severe endometriosis (Lavonius, Suvitie, Varpe, & Huhtinen, 2017; Agnello, Vottero, & Bertapelle, 2020; Zegrea et al., 2020).

A recent Cochrane review demonstrated that dietary supplementation with vitamin B6, vitamin B1, vitamin E, Mg, and omega-3 fatty acids (fish oil) involves analgesic and anti-inflammatory properties in women with endometriosis and could have some effect for the treatment of dysmenorrhea (Pattanittum et al., 2016). In a meta-analysis regarding acupuncture, a significant benefit in pain reduction was shown as compared with placebo, whereas the benefits of other complementary treatments were inconclusive (Mira, Buen, Borges, Yela, & Benetti-Pinto, 2018).

2.10 Comorbidities and co-manifestations related to endometriosis

2.10.1 Gynecological comorbidities

It has been suggested that endometriosis and uterine leiomyomas have similarities in their etiology. Both of these diseases are steroid hormone-dependent and act similarly under the influence of estrogen (Kim, Kurita, & Bulun, 2013). Women with endometriosis had a significantly higher likelihood of leiomyoma diagnosis than women without endometriosis (summary relative risk RR 2.17, 95% CI 1.48–3.19) (Gallagher et al., 2019). A Finnish study showed an association between symptomatic endometriosis and symptomatic uterine leiomyomas, and 26% of patients with symptomatic endometriosis also had fibroids (Uimari, Järvelä, & Ryynänen, 2011). Other studies have yielded similar results, and a diagnosis of concomitant endometriosis in women with leiomyoma should be considered, in particular in patients with subfertility and pain. Women with endometriosis have been shown to have a higher prevalence of chronic endometritis (Cicinelli et al., 2017). Some studies have also suggested a link between polycystic ovary syndrome (PCOS) and endometriosis (Hart & Doherty, 2015; Glintborg, Hass Rubin, Nybo, Abrahamsen, & Andersen, 2015). Although both of these conditions are steroid hormone-related, the anovulatory state and oligo-amenorrhea, common in PCOS, would restrict the distribution and growth of endometriosis lesions. However, a genetic link cannot be ruled out. In any case, the rate of endometriosis in PCOS and vice versa is higher than for other women due to more frequent and thorough gynecological check-ups for women suffering from infertility. The association of endometriosis and adenomyosis has already been discussed earlier.

2.10.2 Immunological diseases

Abnormalities in the immune system have been suggested to explain the implantation of ectopic endometrial tissues into the peritoneal cavity and pelvic organs (Izumi, 2018; Zhang, De Carolis, Man, & Wang, 2018). Thus, an association between endometriosis and autoimmune diseases has been proposed. In a systematic review and meta-analysis, endometriosis was reported to be associated with a range of autoimmune diseases, including systematic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis, autoimmune thyroid disorder, coeliac disease, multiple sclerosis, inflammatory bowel disease, and Addison’s disease (Shigesi et al., 2019). However, a Danish register-based study was not able to find

increased risks of multiple sclerosis, systematic lupus erythematosus, and Sjögren`s syndrome in women with endometriosis (Nielsen et al., 2011).

Cytokines and chemokines regulate the immune responses and control immune functions (Borish & Steinke, 2003). Several studies have shown a significantly higher risk for allergic rhinitis (OR 23.32, 95% CI 9.42–57.73), eczema (RR 4.59, $p = 0.029$), and food sensitivities (RR 3.21, $p = 0.035$) among women with endometriosis (Matalliotakis, Cakmak, Matalliotakis, Kappou, & Arici, 2012; Lamb & Nichols, 1986). Altogether, the possible comorbidity between autoimmune diseases and allergies and endometriosis supports the hypothesis of altered immune surveillance in the pathogenesis of endometriosis.

2.10.3 Pain-causing diseases

CPP is a key symptom of endometriosis. Many pain conditions tend to co-occur (Affaitati, Costantini, Tana, Cipollone, & Giamberardino, 2020), and considering the mechanisms behind chronic pain, an association between endometriosis and other pain-causing diseases can be expected.

Several studies have shown an association between endometriosis and migraine (Tietjen, Conway, Utley, Gunning, & Herial 2006; Jenabi & Khazaei, 2020; Adewuyi et al., 2020). In a meta-analysis, Janebi and Khazaei (2020) showed a significant association between endometriosis and the risk of migraine (OR = 1.56, 95% CI 1.21–1.90) (Jenabi & Khazaei, 2020). Adewuyi et al. (2020) examined the relationship between endometriosis and migraine using a genome-wide association study (GWAS) data and found a significant concordance of single nucleotide polymorphism risk effects across endometriosis and migraine in interleukin-1 receptor binding, focal adhesion-PI3K-Akt-mTOR-signaling, and MAPK and TNF-α signaling (Adewuyi et al., 2020). Thus, endometriosis and migraine are suggested to have also shared genetically controlled biological mechanisms underlying the co-occurrence.

A recent meta-analysis of endometriosis and IBS showed that women with endometriosis seem to have a twofold or threefold risk of also fulfilling the criteria for IBS (Saidi, Sharma, & Ohlsson, 2020). The relative risk estimate of the four studies included in the meta-analysis was 2.39 (95% CI 1.83–3.11), but it is uncertain whether there is a true comorbidity between endometriosis and IBS, or whether the gastrointestinal symptomatology in endometriosis depends on a shared symptomatology of both diseases with visceral hypersensitivity (Saidi et al., 2020).

Also, the risk for developing a painful bladder syndrome and interstitial cystitis has been shown to be increased among women with endometriosis (Wu et al., 2018).

Studies of the association between musculoskeletal disorders and endometriosis are lacking. Lower back dorsopathies may be considered as overlapping pain conditions with endometriosis-related pelvic pain, and inadequate diagnosis may lead to a diagnostic delay of endometriosis. Fibromyalgia is a chronic condition of diffuse musculoskeletal pain accompanied by a number of non-specific symptoms in the absence of any objective organic cause. A large Swedish register-based study found that the incidence rate ratios for fibromyalgia was 2.83 (95% CI 1.96–4.08) among women with endometriosis (Pardo et al., 2019). In another study, the prevalence of fibromyalgia was higher among women with DIE, but not in other subtypes of endometriosis (Coloma et al., 2019). While DIE is known to cause more severe pain symptoms as compared with other types of endometriosis, this finding supports an association between endometriosis and other pain disorders.

2.10.4 Cancers

Although endometriosis is considered a benign disease, it, and particularly OMA, may increase the risk of developing malignancies. OMA has been shown to be associated with ovarian malignancies, including ovarian clear cell carcinoma, endometrioid carcinoma, and rare seromucinous tumors, but the underlying mechanism has remained elusive (Samartzis et al., 2020). It has been stated that somatic mutations in epithelial tumor suppressor genes (PIK3CA, PTEN, KRAS, ARID1A) or massively high concentrations of estrogen lead to the accumulation of mutations and malignant transformation (Samartzis, Noske, Dedes, Fink, & Imesch, 2013; Bulun, Wan, & Matei, 2019). In cases of OMA, the accumulated products of inflammation, a high estrogenic environment, oxidative stress, and hemorrhage increase the likelihood of carcinogenic transformation (Bulun, Wan, et al., 2019). A meta-analysis stated that endometriosis is associated with a 1.2–1.8-fold increased risk of ovarian cancer (Kim, Kim, Chung, & Song, 2014). In some studies, the risk associations for clear cell and endometrioid carcinoma have been shown to be as high as threefold (Rossing, Cushing-Haugen, Wicklund, Doherty, & Weiss, 2008). A Finnish register-based study showed that OMA was associated with increased risk of ovarian cancer (OR 1.78), especially endometrioid and clear cell carcinomas. However, no association was found between ovarian cancer and SUP or DIE (Saavalainen, L., Lassus, H., But, A., Tiitinen, A., Härkki, P., Gissler, M., …

Heikinheimo, O. 2018). In conclusion, endometriosis-associated ovarian cancer seems to be a distinct clinical entity; patients are younger, diagnosed in earlier stages, have lower grade lesions, and have a better survival rate than in ovarian malignancies overall.

Breast cancer and endometriosis are both hormone-dependent conditions and share common risk factors and reproductive characteristics. Still, evidence for a possible relationship between endometriosis and breast cancer is conflicting. A recent meta-analysis showed a slightly increased risk of breast cancer in women with a diagnosis of endometriosis (SRR 1.04, 95% CI 1.00–1.09) (Kvaskoff et al., 2021), whereas other studies observed a reduction in the risk of breast cancer (Matta et al., 2013; Pontikaki, Sifakis, & Spandidos, 2016). Recently, a Finnish research group extensively investigated the link between endometriosis and cancer in a cohort of 49 933 Finnish women. They found that the overall risk of breast cancer was similar in women with or without endometriosis; however, the risk of breast cancer at a young age was increased: 20–29 years SIR 4.44; 95% CI 2.22–7.94, and 30–39 years SIR 1.28; 95% CI 1.03–1.57 (Saavalainen et al., 2019). The association were obvious only in OMA, not for other subtypes of endometriosis (Saavalainen et al., 2019).

Some studies have also shown a correlation of endometriosis with other types of cancers, such as non-Hodgkin's lymphoma, melanoma, kidney cancer, and endocrine cancers (Somigliana et al., 2013). Regarding non-gynecological cancers, a recent Finnish register study showed that endometriosis was associated with an increased risk of thyroid cancer (SIR 1.43, 95% CI 1.23–1.64) and basal cell carcinoma (SIR 1.18, 95% CI 1.10–1.25), but not with other non-gynecological malignancies (Saavalainen, Lassus, But, Tiitinen, Härkki, Gissler, … Pukkala 2018).

2.10.5 Mental distress

Women with endometriosis have shown an increased risk of being diagnosed with depressive-, anxiety-, and stress-related disorders, alcohol/drug dependence, and attention-deficit hyperactivity disorder compared with the general population (Gao et al., 2020; Facchin et al., 2015). A meta-analysis of 24 studies showed higher levels of depression among women with endometriosis compared to controls, and women with endometriosis and chronic pain had significantly higher levels of depression compared to those without pain (Gambadauro, Carli, & Hadlaczky,

2019; Warzecha et al., 2020). Also, mouse model studies have revealed that mice with endometriosis were more depressed, anxious, and sensitive to pain compared to sham controls, which underscores the effect of endometriosis on the brain and mood disorders (Li et al., 2018; Facchin et al., 2017). Accordingly, the association between endometriosis and depressive symptoms is mainly determined by chronic pain, but it may also be modulated by individual vulnerabilities. Thus, short diagnostic delay and adequate treatment of endometriosis-related symptoms, early psychological intervention, and multidisciplinary treatment are warranted to reduce the risk of developing mental disorders, and it would help affected women to find more effective strategies to cope with the disease and its implications.

2.10.6 Metabolic factors and cardiovascular diseases

Chronic inflammation in women with endometriosis has raised the question of whether women with endometriosis have increased risk of cardiovascular diseases, since inflammation is the leading mechanism in the development and progression of atherosclerosis. In the Nurses Health Study II (NHS II), women with surgically confirmed endometriosis had a relative risk of 1.25 (95% CI 1.21–1.30) for developing hypercholesterolemia compared to women without the disease. Furthermore, they had an almost twofold risk of myocardial infarction (RR = 1.52), angiographically confirmed angina (RR = 1.91), coronary artery bypass graft surgery or coronary angioplasty procedure or stent (RR = 1.35), or any coronary heart disease (CHD) end points combined (RR = 1.62), independent of potential confounders. Part of the association was found to be accounted for by endometriosis surgical treatments, such as hysterectomy, which reduces ovarian blood flow, and oophorectomy, which causes ovarian failure and subsequent deficiency of endogenous estrogens (Mu, Rich-Edwards, Rimm, Spiegelman, & Missmer, 2016). Regarding this finding, women with endometriosis need guidance on risk awareness for the possible increased risk for CHD. It should be noted that obesity, especially central obesity, is associated with cardiometabolic diseases, while women with endometriosis have been suggested to be leaner, and thus body shape might be a protective factor against metabolic syndromes.

2.11 Effects on quality of life, socio-economic status, and working ability

Given the chronic nature of endometriosis and its symptoms, their impact on affected women's social life is obvious, causing a significant burden on their quality of life. Endometriosis-specific health-related quality of life *(HRQoL)* questionnaires are specifically developed, validated, and recommended as a research tool for HRQoL in women with endometriosis (Aubry, Panel, Thiollier, Huchon, & Fauconnier, 2017). Another questionnaire is the Endometriosis Health Profile (EHP-30), which has been shown to be a valid instrument for clinical purposes (Khong, Lam, & Luscombe, 2010). Analysis of cross-sectional data of 236 women with endometriosis showed that a negative coping response to a pain experience (e.g., magnification, rumination, and feelings of helplessness) was associated with a worse quality of life score (McPeak et al., 2018). This association was independent of other psychological comorbidities, pelvic pain scores, other pain conditions, and social-behavioral and demographic variables. The review article by Koliba, Kužel, and Fanta (2017) showed that pharmacological as well as surgical treatment significantly improved the quality of life of patients with endometriosis (Koliba et al., 2017). Moreover, a follow-up study by Fagervold, Jenssen, Hummelshoj, and Moen (2009) showed that one-half of the women with endometriosis reported endometriosis having had some negative impact on their lives even 15 years after being diagnosed (Fagervold et al., 2009).

Dyspareunia and subfertility are factors that may potentially affect relationship and marital status. Due to the negative impact of endometriosis on sexual functions, affected women may be anxious and worry about initiating a new relationship. Studies have shown that incapacitating pain and dyspareunia have a negative impact on sex life (Forquet et al., 2010). The majority of women who experience dyspareunia subsequently avoid or limit sexual intercourse (Denny, 2004), and this has been shown to have a negative impact on their relationships and may contribute to relationship breakups (Denny, 2004). A 15-year follow-up study showed that 51% of women felt that endometriosis had a negative effect on their relationship, 15.4% reported serious problems in their relationships, and 7.7% had suffered a broken relationship. Furthermore, they found a significant correlation between dyspareunia and a negative influence on relationships, but the correlation between infertility and the negative influence on relationships was not significant (Fagervold et al., 2009).

In addition to relationship status, numerous symptoms related to endometriosis negatively affect women's educational and professional performance. Severe dysmenorrhea causes absenteeism from school and thus complicates schoolwork (Banikarim, Chacko, & Kelder, 2000; Suvitie et al., 2016; Parker, Sneddon, & Arbon, 2010). A couple of studies have explored educational levels among women with endometriosis, but the results are somewhat inconclusive (Gilmour, Huntington, & Wilson, 2008; Fagervold et al., 2009), although even 40% of women with endometriosis have reported impaired career development (Sperschneider et al., 2019).

A more common study area is endometriosis-related ability to work. Endometriosis-related work ability studies are based mostly on self-reported Work Productivity and Activity Impairment questionnaires (WPAIs), in which the impact of disease or symptoms are measured as hours of missed work (absenteeism), perceived impairment of work tasks (presenteeism), perceived loss in productivity levels (work productivity loss), and impairment of a patient's daily life activities (activity impairment). The Work Ability Index (WAI) questionnaire was developed in 1980 at the Finnish Institute of Occupational Health and is commonly used worldwide. Furthermore, a Finnish study evaluated the reliability of using only the first item of the WAI and concluded that this single-item Work Ability Score (WAS) was a reliable alternative to the WAI score (Jääskeläinen et al., 2016). A previously mentioned study by Sperschneider (2019) showed 50% of women with endometriosis had experienced decreased ability to work due to health-related aspects (Sperschneider et al., 2019). In terms of absenteeism, earlier studies have reported that individuals with endometriosis miss an average of 6–11 hours of work per week, and 19.3 days of work per year (Fourquet et al., 2010, 2011; Nnoaham et al., 2011; Soliman et al., 2017) because of health-related aspects. Reduced working ability in women with endometriosis causes indirect costs, and it has been estimated that about 66% to 75% of the total costs of endometriosis arise from reduced ability to work (Gao et al., 2006; Klein et al., 2014; Soliman, Yang, Du, Kelley, & Winkel, 2016; Surrey, Soliman, Trenz, Blauer-Peterson, & Sluis, 2020).

2.12 Register-based research

There is a long tradition of keeping medical and health registers in Finland (Gissler & Haukka, 2004). The main purposes of health registers are to collect reliable information about diseases and to assess the quality of treatment and costs related to healthcare (Sund, 2012). Secondly, register data have been used widely for

research purposes. Register-based research provides a valuable opportunity to conduct large, representative, general population-based research with minimal selection bias. The data obtained from the registers can be considered more reliable than self-reported questionnaire data. Cross-linking registers offer a vast scale of variables to consider exposures or co-variates. The quality and reliability of the Finnish Health Care register has been shown to be high and thus provides good opportunities for utilizing data in medical research (Gissler & Haukka, 2004; Sund, 2012). In terms of register-based study limitations, the validity of the study population is more difficult to assess, and sometimes conclusions about causality cannot be drawn due to the observational study-set. In Northern Finland, two large live birth cohorts were established in 1966 and 1986, and data were collected through follow-up questionnaires and visits as well as by linking several administrative registers. Register data from these cohorts have been widely used in health research.

3 Aims of Studies I–IV

The aim of this study was to explore the association between endometriosis and (1) body size from birth to late fertile age, (2) pain perception, (3) comorbidities, and (4) work ability in women with endometriosis at late fertile age in the Northern Finland Birth Cohorts 1966 (NFBC1966).

Low BMI has been identified as a risk factor for endometriosis. However, multiple life-course stages and measurement-based data are lacking, and the association between body size and endometriosis subtypes is unknown.

Dysmenorrhea and CPP are leading symptoms of endometriosis. Although endometriosis affects fertile-aged women, long-term chronic pain may lead to hyperalgesia due to peripheral or central sensitization mechanisms. Thus, altered pain perception can be hypothesized and this may cause harm at work, leisure time, and sleep, which affects quality of life.

Common mechanisms of endometriosis and some non-gynecological diseases raise the question of whether there is an association between them. Furthermore, some symptoms of endometriosis are non-specific and overlapping with other pain-causing diseases, leading to possible diagnostic delay. Affected women often have several contacts with health services before being diagnosed with endometriosis, resulting in high health care costs, delay of accurate treatment, and the prolonging of endometriosis-related symptoms.

Numerous endometriosis-related symptoms, such as chronic pain and fatigue, may also have a negative impact on women's work ability, career development, and professional performance, especially considering that the most symptomatic time period coincides with early career and active working life.

1. The first objective was to assess the association between endometriosis and body size development and adipose tissue distribution from birth to age 46.
2. The second objective was to determine whether women with endometriosis experience altered pressure-pain sensitivity and adverse pain symptoms at age 46.
3. The third objective was to investigate the associations between endometriosis and non-gynecological comorbidities.
4. The fourth objective was to examine work ability at 46 years of age, and life-long participation in working life up until 52 years of age, among women with endometriosis.

4 Materials and methods

This study was based on the NFBC1966, which is a large, prospective, population-based, longitudinal birth cohort. Originally, the cohort was established to investigate the life-courses of various health-related conditions, but it has since been used widely for general health research purposes. All individuals with an expected term in 1966 in the two northernmost provinces of Finland (Oulu and Lapland) were included in this birth cohort, and finally it consists of 96.3% of all expected births (12 231 births, 5 889 females). Enrolment to this cohort study began at the 24th gestational week and, so far, the cohort population has been followed cross-sectionally at birth and at ages 1, 14, 31, and 46. Postal questionnaires were sent at ages 14, 31, and 46, and clinical examinations were performed at ages 31 and 46.

4.1 Identification of women with endometriosis in the Northern Finland Birth Cohorts 1966 (NFBC1966) data

4.1.1 Self-reported endometriosis

At 46 years, a postal questionnaire was sent to 5 123 (87.0% of female population) women. The response rate to 46 years questionnaire was 72% (n = 3 706). The questionnaire included the following question: “Have you ever been diagnosed with endometriosis by a physician?”, and if the answer was yes, followed by a multiple-choice question whether the diagnosis was based on gynecologic examination, ultrasound or laparoscopy/surgery, and what was the age of first diagnosis of endometriosis. An answer of “yes” resulted in the women with endometriosis population (n = 284 women, 8% of the total female population) and an answer of “no” resulted in the population of women without endometriosis (n = 3 390 women). Among the self-reported endometriosis cases, n = 151 (53%) reported having surgical confirmation of endometriosis, n = 107 (38%) reported having been diagnosed by using ultrasound, and n = 26 (9%) reported having been diagnosed in a gynecological examination. The validity of self-reported endometriosis was verified through the patient records available at Oulu University Hospital. Of the 284 women with endometriosis, patient records for 92 (32.4%) were found. Thirty-seven women (13%) did not give permission to access their patient records. According to the patient records available, 71/92 women (77.2%)

were diagnosed with endometriosis in a gynecology inpatient or outpatient clinic. Of these diagnoses, 90.1% were established in surgery (laparoscopy/laparotomy). Fifteen women did not have a diagnosis of endometriosis in hospital patient records, and six were classified as unclear cases. In these cases, it was possible that the diagnosis of endometriosis was established later in another hospital after moving away from the area (groups "no endometriosis" and "unclear cases") or in private clinics.

4.1.2 Register-based diagnosis from the Care Register for Health Care (CRHC)

In addition to self-report cases, in projects I and III-IV, endometriosis cases were identified through the Care Register for Health Care (CRHC) in order to achieve as comprehensive a sample of women with endometriosis as possible. In the Finnish health care system, ICD codes are used primarily for clinical diagnosis purposes, and secondly for municipal billing purposes. The ICD codes are set by the clinical doctor in charge of discharging the patient, and the codes are chosen based on their clinical relevance for each hospital visit. Studies have shown that more than 95% of discharges can be identified from the CRHC, and positive predictive values have been found to be between 75% and 99% (Sund, 2012). Thus, CRHC diagnoses are considered accurate and reliable.

The NFBC1966 population was linked to the CRHC, which includes all international classifications of disease (ICD) codes and dates for each inpatient hospital visit since 1968. In this study, the collection point for CRHC diagnoses of endometriosis was 2012, which is the same time point as the collection of self-reported endometriosis. Disease codes for endometriosis, ICD-9: 617.1–617.9 and ICD-10: N80.1–N80.9, were used for case identification. Earlier-used ICD-8 codes have been converted to ICD-9 codes and thus were included. The age at first diagnosis was collected, too. Further on, endometriosis was classified according to ICD codes into three subtypes: peritoneal endometriosis (N80.2, N80.3), ovarian endometriosis (N80.1) and DIE (N80.4, N80.5, N80.6). In this study, sole N80.0 (adenomyosis) codes were not included since its different clinical presentation and adenomyosis were not part of the NFBC questionnaire set.

Finally, the total endometriosis population in projects I and III–IV consisted of 349 women (self-reported n = 284 and/or register-based cases n = 224), which is 9% of the whole study population. As for endometriosis subtypes, 59 (26%)

peritoneal endometriosis, 118 (53%) ovarian endometriosis, and 37 (17%) DIE were identified. Women who did not have an ICD code for endometriosis and who replied “no” to the self-reported endometriosis question were considered to not have endometriosis (n = 3 499). The flow chart of the study population and the verification of self-reported diagnosis of endometriosis are shown in Figure 7.

4.1.3 Ethical considerations

By law in Finland, health register data for research purposes are strictly regulated to ensure participants’ right to privacy. According to legislation on social and health care services, informed consent from is needed for the use of health or social welfare data in scientific research. In this study, all participants took part on a voluntary basis and signed an informed consent document. Personal identification numbers were replaced by project IDs from the dataset to ensure participants’ privacy and confidentiality. Permission to use the CRHC register data and linkage it to NFBC1966 data was obtained. The data were analyzed via a secured telecommunication link. Finally, the study followed the principles of the Declaration of Helsinki, and the Ethics Committee of Northern Ostrobothnia Hospital District approved the research.

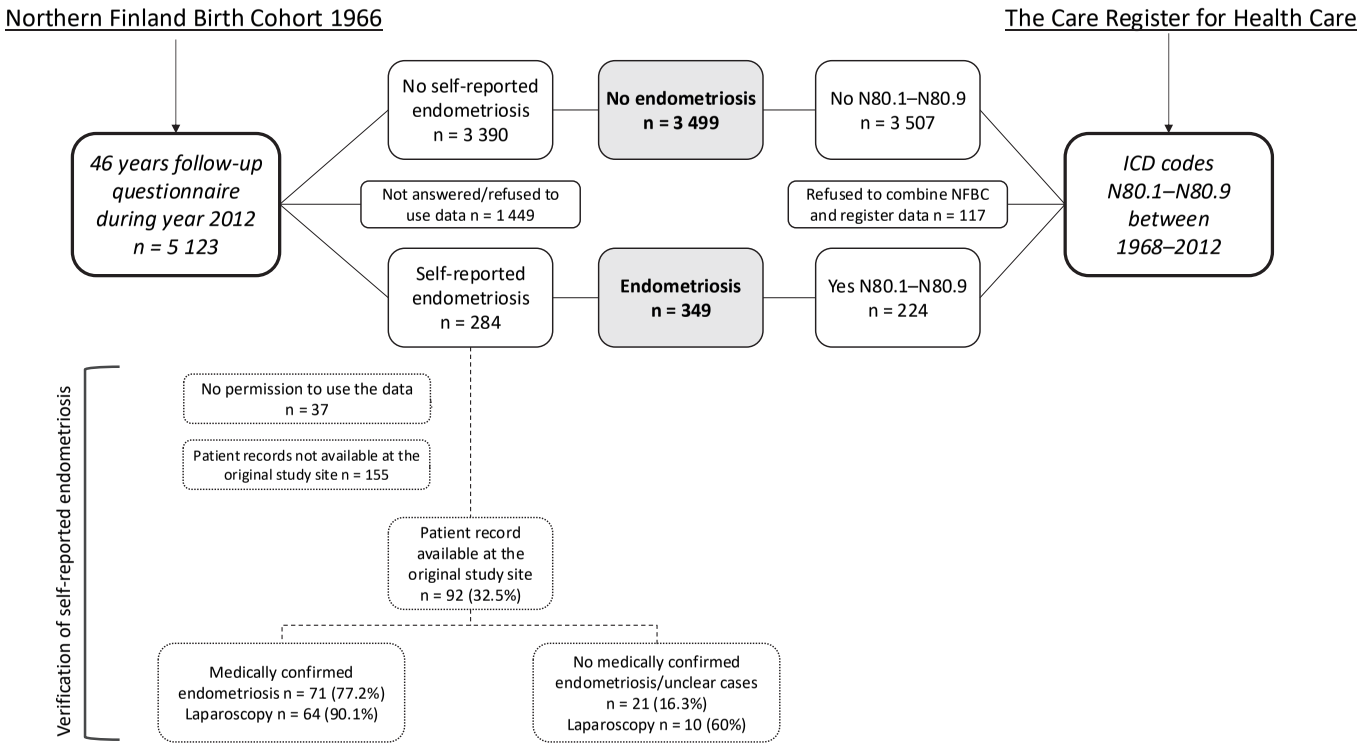

Fig. 7. Flowchart of the study population and verification of self-reported diagnosis of endometriosis according to the patient records available at Oulu University hospital.

4.2 Methods

4.2.1 Body size, adiposity and body shape measurements (Study I)

Maternal pregnancy data and childhood body weight data were collected at welfare clinics until age 6 and at schools between ages 6–17 as part of the national child-health screening program. Between ages 17–20, measured BMIs were collected in the context of the general health care system. The long-term BMI behavior between ages 2 to 20 was assessed longitudinally by using group-based modeling. The modeling identified clusters or subpopulations following the same pattern of change or behavior over time. The model clustered women in four different groups with a similar trend in their BMI behavior between ages 2 to 20. In addition, at age 14, the parents of the study subjects reported individuals' weight and height in the postal questionnaires. Childhood adiposity was analyzed by determining the timing of adiposity peak (maximum weight during this period, around 9 months, AP) and adiposity rebound point (nadir of the BMI curve, usually around 5 years, AR).

Adulthood body size and body shape measurements were collected cross-sectionally during NFBC1966 follow-up visits at ages 31 and 46. Weight and height were measured in the clinical examinations, and BMI was calculated as the ratio of weight (kg) to height squared (m^2). Body shape was analyzed by measuring waist circumference (WC, cm) and hip circumference (HC, cm) and calculating the WHR.

4.2.2 Pain perception (Study II)

Pressure pain threshold (PPT) and maximal pressure pain tolerance (maxPTo) were tested by using a 10-mm contact head, which was applied perpendicularly to the skin. The pressure was increased at a constant rate of 50 kPa, and participants were advised to mention the point at which it felt uncomfortable (PPT). As the pressure was increased, the participants were advised to mention when they could no longer tolerate the pressure (maxPTo). The PPT and maxPTo measurements were taken at four anatomical sites: (1) shoulder, (2) tibia, (3) wrist, and (4) lower back. Of the peripheral sites, primarily the right side was used. The highest value of the two measurements was used in the analysis to avoid overestimating the pain threshold or tolerance. In addition, mean PPT and maxPTo values at the four measured locations were calculated and used in the analyses.

The number of pain sites was derived from the questionnaire data, in which the prevalence of musculoskeletal pain during the previous 12-month period was determined by asking the following questions: "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. If pain had occurred, the following question on the frequency of pain was asked: "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) from 0 (no pain / no disability) to 10 (extremely severe or disabling pain).

4.2.3 Non-gynecological comorbidities (Study III)

Participants' ICD codes and the first date on which diagnosis was made were collected from the CRHC from 1968 to 2016. ICD codes were divided into main categories and further subcategories according to the World Health Organization (WHO) classification. Certain subsets of ICD codes according to the literature and the results of the main category were selected for detailed analysis.

According to the Finnish health care system, allergies and autoimmune diseases are diagnosed and treated in outpatient health care and thus cannot be detected from the CRHC. Therefore, self-reported life-time allergic, infectious, and autoimmune symptoms were collected from a 46-year questionnaire to extend the disease/morbidity data. Furthermore, continuous medication usage was asked of participants at age 46, and medication usage was divided into different groups according to the WHO Anatomical Therapeutic Chemical Classification (ATC) system.

4.2.4 Work ability, unemployment, disability, and retirement (Study IV)

Self-rated work ability was determined at age 46 by using two items of the WAI questionnaire. First, a work ability score (WAS 0–10) was determined, and respondents' work ability was classified into good (8–10) or poor (0–7) work ability. Data on self-reported health-related absenteeism from work were collected by asking: "How many whole days have you been absent from work due to your health

within the last 12 months?" Answers were divided into 0–9 days and 10 or more days. At age 46, participants were also asked: "Have you considered retiring before normal retirement age due to medical or any other health reasons?"

Disability and unemployment days were collected between ages 46–48 from the Social Insurance Institution of Finland (SII) and the Finnish Centre for Pensions (FCP) registers. Individually determined two-year follow-up periods (730 days) started from the day after the women completed the WAI questionnaire. The days with "disability" as one of the codes were considered as a code in the final coding.

Early retirement data were collected from the FCP and SII registers between ages 16–52 for each individual who had ever been granted a pension of any type, either full-time or partial. For these individuals, data were collected about the date on which the pension decision had been made as an indicator of long-term disability, as well as the diagnoses warranting the pension decision.

4.3 Confounding variables

NFBC66 questionnaires at ages 31 and 46 included several co-variates, which were considered as confounders. Covariates were collected from 31-year questionnaire data when exploring 31 years of exposure and from 46-year questionnaire data when exploring 46 years of exposure. Besides follow-up studies, maternal covariates were collected from hospital and welfare records. Confounding variables and studies in which they were used are shown in Table 1.

4.4 Statistical methods

The statistical analyses were performed using IBM SPSS Statistics software version 22 for Windows (SPSS, Inc., 1989, 2013, IBM Corp). The results of characteristics are reported as numbers or means with percentages of respondents (%) and standard deviation (SD). Differences in continuous variables were analyzed using the independent samples t-test or the Mann–Whitney U test, and the chi-square test was used to analyze differences in categorical parameters. A two-sided p-value < 0.05 was considered statistically significant. The association between study groups was analyzed with a binary logistic regression model. Appropriate confounding factors were included in the multivariate analysis models. The results are reported as odds ratios (ORs) with 95% confidence intervals (CIs).

Table 1. Confounding variables of each study.

Covariate	Reported	Used method	Notions	Used in study
Mother`s weight gain during pregnancy	kg	Hospital and welfare records		I
Mother`s smoking status during pregnancy	yes/no	Hospital and welfare records		I
Gestational age at birth	gestational weeks	Hospital and welfare records	Categorized: very preterm, 33 + 6; preterm, 34 + 0 to 36 + 6; at term, 37 + 0	I
Age at menarche	years	Self-reported age at menarche		I
Contraceptive use	yes / no	"Have you ever used any hormonal contraception (yes / no)?"	Additionally, in study II: "Are you currently using hormonal contraception?"	I–IV
Infertility	yes / no	"Have you ever suffered from infertility?"		
Parity	Study I n / mean, Study I–IV categorized	"How many deliveries you have had?"	Measurements at timepoint 31 parity at age 31 were used, otherwise parity at age 46	I–IV
Widespread pain	yes / no	Self-reported pain sites past 12 months: 1–3 no, 4–8 yes		IV
Body mass index (BMI)	kg/m^2	Measured weight: digital scale (kg), height: stadiometer (cm)	Study II–III: If measurement was no available, replaced with self-reported data	II, III, IV
Smoking	current / former / non-smoker	"Have you ever smoked / Do you currently smoke?"	Women were considered smokers if smoking at least once per week.	I–IV
Alcohol use	g/day	"Do you use alcohol, and if so, what kind, how often and how much?"	Categorized: 1) abstainer, 2) light (< 20 g/l), 3) moderate or heavy use	I–IV

Covariate	Reported	Used method	Notions	Used in study
Physical activity	MET[1] min/week: metabolic equivalent of task score	"Intensity and duration of light and brisk physical activity?"	Study I: At age 31 and 46 years Study III–IV: Categorized	I, III–IV
Education	years / categorized	Classified into three groups according to the number of education years: ≤ 9, 9–12 and > 12 years		I-IV
Occupational status		Classified into three groups according to self-reported occupation: White collar, Blue Collar, Entrepreneur		IV
Relationship status	partnership	Self-report data. Consisted of those who were married or cohabitating		I–IV
Working history	continuous / discontinuous	"Which of the following options best describe your work history?"	Continuous (working always, or mostly via permanent or long work contracts); discontinuous (long and short contracts with occasional unemployment periods, mainly short work contracts, mostly unemployed, mostly supported working or never in paid employment)	IV
Baseline employment	disability / employed / unemployed	Social Insurance Institution of Finland and the Finnish Centre for Pensions registers		IV
Depression	HSCL-25[2] ≥ 1.55	HSCL score for anxiety symptoms ≥ 1.55 was considered to indicate depressive symptoms		II

Covariate	Reported	Used method	Notions	Used in study
Anxiety	HSCL-25 ≥ 1.55	HSCL score for anxiety symptoms ≥ 1.75 was considered to indicate anxiety symptoms.		II

Questionnaire/Self-reported data at ages 31 or 46 if otherwise not mentioned. [1] metabolic equivalent of task score, [2] Hopkins symptom checklist

4.4.1 Specific statistical methods in Study I

R-Studio version 3.3.2 was used for longitudinal modeling and derivation of BMI, and group-based trajectory modeling from the Proc Traj procedure in SAS software version 9.4 (SAS Institute Inc, Cary, North Carolina) was used.

To exclude possible outliers, 2SD threshold was used as a sensitivity analysis in the logistic regression calculation in WC, HC, and WHR measurements. Bonferroni correction was conducted to reduce the risk of Type I Error: a p-value $< 0.05/4$ (< 0.0125) denoted statistical significance. A Sobel test was used to assess possible mediation between endometriosis and confounders.

4.4.2 Specific statistical methods in Study II

A Tobit regression model was used to evaluate independent associations between endometriosis and PPT and maxPTo. Modes were adjusted for several confounders.

4.4.3 Specific statistical methods in Study III

Benjamini-Hochberg correction was conducted to reduce the risk of Type I Error. Kaplan-Meier survival analysis and the Mantel-Cox estimate was used to estimate the number and age of cumulative ICD codes among women with or without endometriosis until 2016.

4.4.4 Specific statistical methods in Study IV

Poisson regression analyses were used to calculate the incidence rate ratios (IRRs) and their 95% CIs, in both unadjusted and adjusted models. Kaplan-Meier survival analysis with the Mantel-Cox estimate was used to estimate the lifetime emergence of disability pensions among women with or without endometriosis until 2018.

The summary of study characteristics (study population, outcome measurements, and main results) of each study are shown in Table 2.

Table 2. Characteristics and results of studies I–IV.

Study Characteristics	Study I	Study II	Study III	Study IV
Study population	Endometriosis: Self-reported endometriosis "yes" or in CRHC[1] data N80.1–N80.9 n = 348; Controls: self-reported endometriosis "no" and no CRHC[1] data on N80.1–N80.9, n = 3 487	Endometriosis: self-reported endometriosis "yes", n = 284; Controls: self-reported endometriosis "no" n = 3390	Endometriosis: Self-reported endometriosis "yes" or in CRHC[1] data N80.1–N80.9 n = 349; Controls: self-reported endometriosis "no" and no CRHC[1] data on N80.1–N80.9, n = 3 499	Endometriosis: Self-reported endometriosis "yes" or in CRHC[1] data N80.1–N80.9 n = 348; Controls: self-reported endometriosis "no" and no CRHC[1] data on N80.1–N80.9, n = 3 487
Outcome measurements	Measured weight, height and BMI[2] longitudinally between early infancy and up till 20 years, adiposity peak and adiposity rebound in childhood. Measured weight, height, waist and hip circumference cross-sectionally at ages 31 and 46.	At age 46 years: Pain threshold and pain tolerance measurements. Questionnaire data on pain troublesomeness and number of pain sites.	ICD[3] disease codes from CRHC[1] register between years 1968–2016. Self-reported autoimmune, allergic and infectious symptoms at age 46.	Questionnaire on work ability index at age 46. Disability and unemployment days from SII[4] and FCP[5] registers between ages 46–48 years. Retirement decision from FCP[5] register until age 52.
Main results	Endometriosis and body size have an inverse association at reproductive age, but not in childhood. At late fertile age, peritoneal endometriosis, but not other subtypes, associated leaner body size.	Endometriosis was associated with 5% lowered pressure-pain sensitivity at late fertile age. The pain was more troublesome and widespread.	Endometriosis associated with higher overall morbidity, especially diagnosis of non-specific symptoms, mood disorders, pain diseases and respiratory diseases and self-reported allergic, infectious and autoimmune symptoms.	Endometriosis associated with poor work ability and sick leaves but not unemployment in late forties. Women with endometriosis did not have increased rate of early disability retirements up till 52 years.

[1] The care register for health care, [2] Body mass index, [3] International classification of disease, [4] Social insurance institution, [5] Finnish Centre for Pensions

5 Results and discussion

5.1 Characteristics of the study population

Characteristics of the study population are shown in Table 3. Women with endometriosis had used contraception and suffered from infertility more often, and their parity was lower than in women without endometriosis. No statistically significant differences were observed between the groups in terms of health-related or lifestyle factors between the study groups (Table 3).

Table 3. Characteristics of the NFBC 1966 study population in women with and without endometriosis.

Character	No endometriosis n = 3 499 % (n)	Endometriosis n = 349 % (n)	p-value
Mother`s pre-pregnancy weight (kg)	56.8 (15.1)	56.9 (14.7)	0.856
Mother`s pregnancy weight gain (kg)	11.9 (4.0)	12.1 (4.2)	0.654
Mothers smoking at the end of pregnancy	4.6 (161)	4.9 (17)	0.966
Gestational age at birth			
Very preterm birth (< 34 weeks)	4.0 (14)	2.9 (10)	
Preterm birth (34–37 weeks)	3.8 (132)	4.5 (1579)	0.360
Birth at term (> 37weeks)	91.7 (3198)	93.1 (324)	
SGA (small for gestational age	8.4 (277)	8.2 (27)	0.882
LGA (large for gestational age)	11.3 (371)	7.9 (26)	0.064
Age at menarche (years)	12.9 (1.2)	12.6 (1.2)	0.898
BMI at menarche (kg/m^2)	18.5 (2.7)	18.3 (2.3)	0.577
Age at the time of first endometriosis diagnosis (years)	NA	31.6 (7.3)	NA
Hormonal contraceptive use (ever)	**89.3 (2981)**	**93.5 (315)**	**0.014**
Infertility	**13.0 (454)**	**31.0 (108)**	**< 0.001**
Parity			
none	**9.7 (303)**	**13.8 (42)**	
1–2	**54.5 (1696)**	**57.0 (174)**	**0.017**
3 or more	**35.7 (1111)**	**29.2 (89)**	
Alcohol consumption			
Abstainer	11.4 (383)	13.5 (46)	
Low-risk drinker	80.7 (2707)	80.6 (274)	0.250
At risk drinker	7.9 (264)	5.9 (20)	

Character	No endometriosis n = 3 499 % (n)	Endometriosis n = 349 % (n)	p-value
Smoking			
Never	56.0 (1861)	59.8 (199)	
Former / Occasional	26.6 (885)	21.3 (71)	0.107
Active	17.3 (575)	18.9 (63)	
Physical activity: MET min/week			
Low	22.2 (746)	19.2 (65)	
Moderate	41.0 (1376)	44.2 (150)	0.351
High	36.7 (1232)	36.6 (124)	
Education level			
Basic	6.2 (209)	4.4 (15)	
Secondary	63.8 (2143)	61.2 (207)	0.143
Tertiary	30.0 (1006)	34.3 (116)	
Occupational status			
White collar	37.5 (1233)	40.2 (132)	0.252
Blue collar	46.9 (1543)	44.2 (145)	
Entrepreneur	8.7 (286)	10.7 (35)	
Other	6.9 (266)	4.9 (16)	
Relationship status			
Lives in relationship	76.8 (2574)	79.3 (268)	0.310
Habitation			
Urban	65.3 (2246)	67.7 (235)	
Rural	34.7 (1192)	32.3 (112)	0.371
Working history			
Continuous	70.6 (2314)	73.3 (242)	
Discontinuous	29.4 (963)	26.7 (88)	0.300

Data are % (n) or mean (SD) of population unless stated otherwise. Significance tests for continuous variables were performed by using the independent samples t-test or the Mann–Whitney U test, as appropriate. P-value < 0.05 was considered significant. Differences in numbers vary in different analyses as a result of some missing data. P-values arise from significance tests for comparison between women with and without endometriosis. Adulthood data are collected at age 46 years.

The mean age of endometriosis diagnosis was 31.6 (SD 7.3) years. Accumulating age of the first diagnosis of endometriosis gained from the CRHC is shown in Figure 8. While earlier studies have shown a 7–10-year delay of diagnosis of endometriosis (Hudelist et al., 2012; Ghai, Jan, Shakir, Haines, & Kent, 2020), the results of this analysis supports a diagnostic delay, although the onset of symptoms was unknown in the present study.

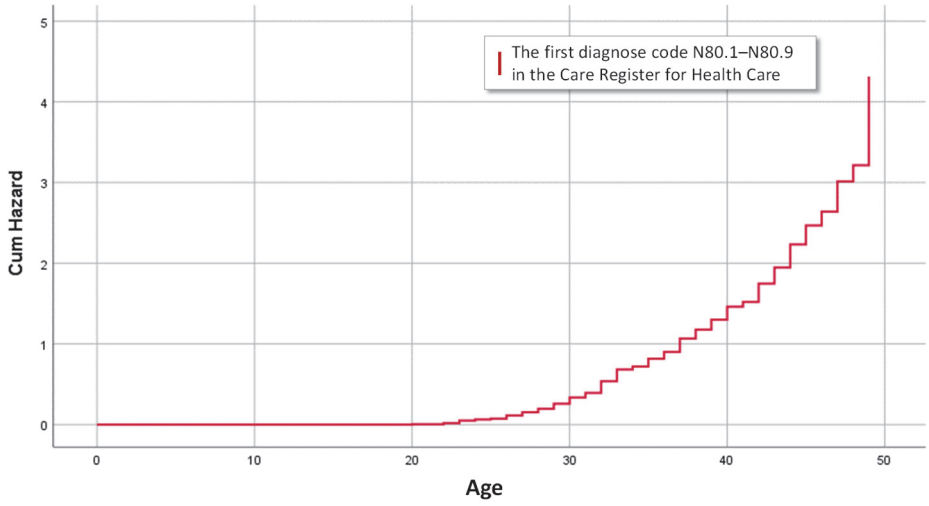

Fig. 8. Accumulating numbers of CRHC diagnosis for endometriosis.

5.2 Associations between life-long body measurements and endometriosis

The main finding of Study I was that endometriosis and body size have an inverse association during reproductive age, but not in childhood. Interestingly, at age 46, there was an inverse association between endometriosis and body size only in women with peritoneal endometriosis. Whether this relates to a different disease mechanism for this subtype, also linking to body weight development, warrants further investigations.

5.2.1 Body weight measurements

The study concluded that women with endometriosis had similar weight development from birth to age 20 than women without endometriosis; there were no significantly different trends in the growth trajectory analysis between the study groups.

At age 31, women with endometriosis exhibited lower mean weight (63.4 kg ± 9.8 vs. 65.5 kg ± 13.0), lower weight gain from age 14 to 31 (12.0 kg ± 8.2 vs. 13.6 kg ± 9.3), and lower BMI (22.9 kg/m^2 ± 4.2 vs. 23.6 kg/m^2 ± 3.5) than women without endometriosis. Multivariate analysis revealed an independent inverse

association between endometriosis and weight (OR 0.98, 95% CI 0.97–1.00), weight gain between ages 14–31 (OR 0.98, 95% CI 0.96–0.99), and BMI (OR 0.94, 95% CI 0.90–0.98). As a conclusion, at age 31 lower weight and lower BMI were associated with endometriosis; the odds for endometriosis were on average 2% lower for every kilogram of weight and 6% lower for every BMI unit. The subtype of endometriosis was not associated with lighter body size.

Even though women with endometriosis were significantly lighter at their reproductive age, at late fertile age these differences disappeared. However, in the subtype analysis, peritoneal endometriosis, but not other subtypes, was still associated with lighter body size at late fertile age (weight; OR 0.95, 95% CI 0.92–0.98, weight gain 14–46 years OR 0.97, 95% CI 0.94–1.00; BMI OR 0.91, 95% CI 0.84–0.98). As a conclusion, the odds for peritoneal endometriosis were on average 5% lower for every kilogram increase in weight, and even 9% lower for every unit increase of BMI.

Figure 9 shows (a) mean BMIs at ages 14, 31, and 46 in women without endometriosis, all endometriosis, and peritoneal endometriosis, and (b) the association between BMI and endometriosis subtypes at ages 31 and 46.

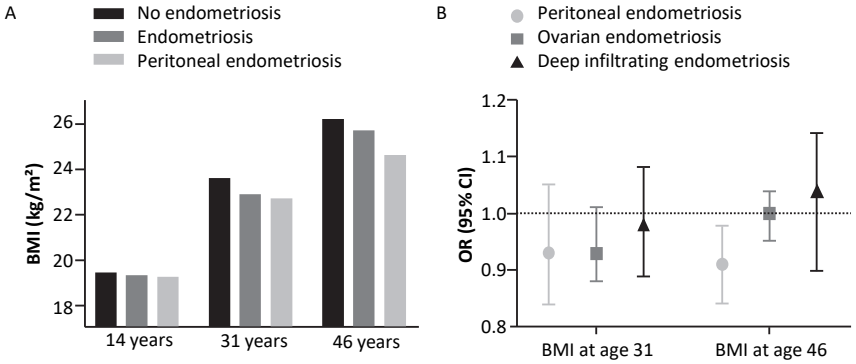

Fig. 9. a) mean BMI at ages 14, 31 and 46 in women without endometriosis (black), women with endometriosis (dark gray) and women with peritoneal endometriosis (light gray), b) association of BMI at ages 31 and 46 in different subtypes of endometriosis.

5.2.2 Adiposity and body shape measurements

In terms of childhood body adiposity, age at adiposity peak and adiposity rebound were equal in women with or without endometriosis (AP 0.8 ± 0.1 years vs. 0.8 ± 0.1 years; AR 5.6 ± 1.0 years vs. 5.7 ± 0.9 years).

At age 31, women with endometriosis had leaner body shape than women without endometriosis; a smaller waist circumference (76.3 ± 9.3 vs. 78.9 ± 12.0) and a lower WHR (0.79 ± 0.07 vs. 0.81 ± 0.08). In multivariate analysis, an inverse association between endometriosis and body shape measurements was significant in WC; on average, 2% lower odds of endometriosis for every centimeter increase in WC (OR 0.98, 95% CI 0.97–1.00) were found. In terms of WC and WHR measurements, a significant association disappeared in subtype analysis, which may be due to the small size of the study groups.

At age 46, interestingly, only women with peritoneal endometriosis had a significantly different body shape compared to women without endometriosis; women with peritoneal endometriosis had significantly smaller WC (82.1 ± 12.2 vs. 87.3 ± 13.1) and WHR (0.83 vs. 0.87). Furthermore, in multivariate analysis, an inverse association with body shape was observed with peritoneal endometriosis; the average odds of endometriosis were 4% lower for every centimeter increase in WC (OR 0.96, 95% CI 0.93–0.99) and even 63% lower for every 0.1 unit increase of WHR (OR 0.37, 95% CI 0.21–0.64).

Figure 10 shows (a) mean WC at ages 31 and 46 in women without endometriosis, women with endometriosis, and women with peritoneal endometriosis, and the association between WC and subtypes of endometriosis at ages 31 and 46.

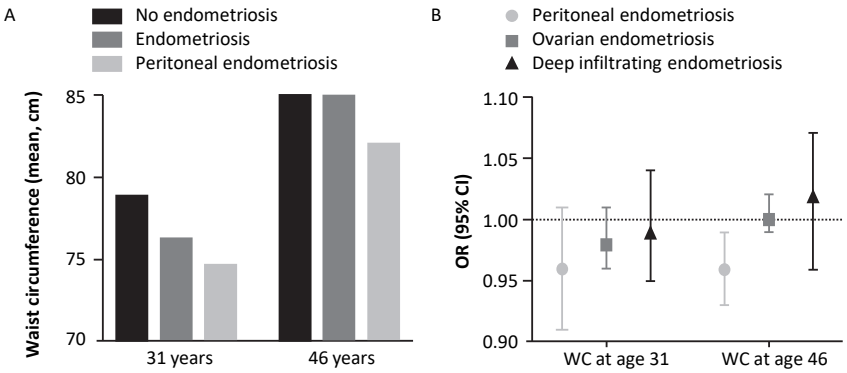

Fig. 10. a) mean WC at ages 31 and 46 in women without endometriosis (black), women with endometriosis (dark gray) and women with peritoneal endometriosis (light gray), and b) association between WC and subtypes of endometriosis at ages 31 and 46.

5.2.3 Association between body size and endometriosis in the context of existing literature

The relationship between small body size, pear-shaped body figure, and endometriosis has been established in earlier studies, and lean body figure has been suggested to be a risk factor for endometriosis (Vitonis et al., 2010; Nagle et al., 2009; Hediger et al., 2005; Ferrero, Anserini, et al., 2005; Farland et al., 2017; Zondervan et al., 2020). This association has been suggested to appear in early life (Vitonis et al., 2010; Nagle et al., 2009), which, in this study, however, could not be confirmed. It should be noted that earlier studies on body size at childhood were based mainly on cross-sectional, self-reported and retrospective body figure illustrations; whereas in this study, data at childhood and in adolescence were longitudinal and obtained from objective measurements. However, another large register-based study with measured weight and height data between ages 7–13 showed that lean and tall girls are more often diagnosed with endometriosis. The location of endometriosis did not affect the results (Aarestrup et al., 2020). Similar to the present study, they found no association between birth weight and endometriosis. Regardless of the controversial finding of an association between endometriosis and childhood body size, some existing data suggests that indicators of endometriosis risk may already be apparent before puberty.

While an association between childhood body size and endometriosis remains inconclusive, this study supports previous data on the association between endometriosis and leaner habitus in adulthood (McCann et al., 1993; Hediger et al., 2005; Ferrero, Anserini, et al., 2005). A meta-analysis of 11 studies showed that the relative risk of endometriosis was 0.67 for each 5 kg/m^2 increase in current BMI (Liu & Zhang, 2017). Data on the association between endometriosis and body size beyond fertile age are lacking. The present study showed an inverse association between endometriosis and body size at reproductive age—but at late fertile age, the association seems to disappear when analyzing endometriosis as a whole entity. These results could be explained by the natural course of endometriosis: Endometriosis is silent during childhood; the disease is most active during reproductive years, after which it tends to become inactive by menopause. Interestingly, the present study showed a significant association between lean body size and peritoneal endometriosis still at late fertile age. This is somewhat surprising given the data arising from the previous literature. Earlier studies have shown that an inverse association between BMI and endometriosis is stronger in women with infertility (Shah, Correia, Vitonis, & Missmer, 2013), in those with

advanced disease (stages III or IV) (Yi et al., 2009), and in those with DIE (Lafay et al., 2012), showing a possible stronger inverse association in women with severe endometriosis. This study, instead, demonstrated a persistent and strongest inverse association between body size and peritoneal endometriosis, while the peritoneal subtype was generally defined as mild endometriosis. This association at late fertile age indicates a possible independent role of peritoneal endometriosis in weight development, which should be considered in further studies.

5.3 Pain perception in women with endometriosis at late fertile age (Study II)

The results of the Study II showed that women with endometriosis had a lower musculoskeletal pain threshold and a lower maximal pain tolerance compared to women without a history of endometriosis. Moreover, women with endometriosis reported an increased number of pain sites and more troublesome pain perception still at age 46.

5.3.1 Pressure pain threshold (PPT) and maximal pressure pain tolerance (maxPTo)

The results of pressure pain measurements revealed that women with a history of endometriosis had 5.5% lower PPT and 5.3% lower maxPTo than women without a history of endometriosis. The PPT was on average 34.0 kPa lower (-5.3% [-1.1, -9.5], $p < 0.05$); and after adjusting with several confounders, the PPT remained 35.4 kPa (-5.5%) lower in women with endometriosis ($p < 0.01$). Also, maxPTo was on average -48.2 kPa lower (-5.1% [-2.2, -8.1]) among women with endometriosis ($p < 0.001$), and the difference was significant even after adjusting for BMI, anxiety, and depressive symptoms, as well as smoking and contraceptive use (mean -50.1 kPa, -5.3%, $p < 0.001$). Altogether, endometriosis was associated with a significant decreases in both the PPT and the maxPTo showing an independent role of endometriosis in the association with decreased pain sensitivity still at age 46. Furthermore, endometriosis, independently, was the strongest contributor to decrease the pain sensitivity (Figure 11). Figure 11 shows the effect of different contributors to (a) PPT and (b) maxPTo at age 46.

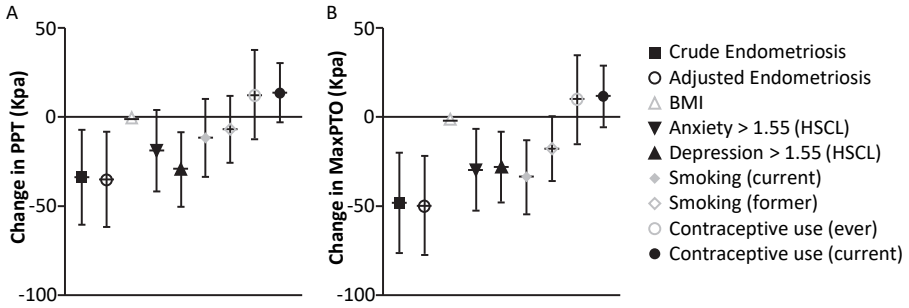

Fig. 11. The effect of different contributors to a) pressure pain threshold (PPT) and b) maximal pain tolerance (MaxPTo). The horizontal reference line reflects the whole study population. Written permission to reuse.

5.3.2 Pain sites, pain intensity and pain troublesomeness in women with endometriosis

Besides lower pain perception, women with endometriosis also reported more widespread pain compared to women without endometriosis (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%, $p < 0.001$). Furthermore, women with endometriosis reported more troublesome pain at work, during leisure time, and at sleep ($p = 0.01$, $p = 0.02$, $p = 0.04$, respectively); but in multivariate analysis, considering the effect of smoking, BMI, depression, anxiety, and contraceptive use, the association with endometriosis and pain troublesomeness was significant only during work ($p = 0.04$), not during leisure time and sleep ($p = 0.05$, $p = 0.06$). A significant association was also found between overall pain intensity and endometriosis ($p = 0.03$).

5.3.3 The association between pain perception and endometriosis in the context of existing literature

The finding of altered pain perception is in line with the previous literature. Several studies have shown lowered pressure-pain sensitivity and threshold in women with endometriosis. As-Sanie et al. (2013) reported in a cross-sectional analysis that women with endometriosis and CPP had significantly lower pressure-pain sensitivity in non-pelvic sites than women without endometriosis, but the difference

was not significant in women with endometriosis but without CPP. Moreover, Issa et al. (2012) showed lower pain thresholds, indicating visceral hypersensitivity, among women with endometriosis compared with controls in a rectal balloon dilation test, whereas Bajaj, Bajaj, Madsen, and Arendt-Nielsen (2003) showed lower pain thresholds and larger pain areas among women with endometriosis after an intramuscular saline injection into the muscle of the hand. In a larger study by Nunes, Ferreira, and Bahamondes (2015), the PPT at 20 different body sites, measured with a visual analog scale (VAS), reported that fertile-aged women with endometriosis had a lower pain threshold in the greater trochanter and abdomen compared with controls. In terms of pain tolerance, van Aken et al. (2018) showed in an experimental study that, similar to the present study, women with endometriosis had lower pain tolerance, independent of pain intensity or stage of endometriosis. It should be noted that, in the present study, lifetime use of contraceptives appeared to be associated with unchanged pain threshold and tolerance. This gives rise to a hypothesis that hormonal therapy may be protective in preventing altered pain responses in women with endometriosis, possibly due to reduced dysmenorrhea episodes and the prevention of the chronicity of pain, especially if hormonal contraceptives have been used continuously. Furthermore, this emphasizes the importance of appropriate and sufficient treatment of endometriosis for preventing altered pain perception, chronic pain, and long-term adverse effects in women with endometriosis.

Altogether, even though a vast body of data exists on altered pain perception in women with endometriosis, earlier studies were limited to case-control datasets and small sample sizes. Furthermore, earlier studies were focused on fertile-aged women. Results of lower pain threshold and tolerance, and more widespread and bothersome pain, in this study, however, arose from a population-based dataset and a focus on women with a history of endometriosis at their late fertile age. As a limitation, clinical significance of 5% decreases in pain threshold and maximal pain tolerance in women with endometriosis remains uncertain, although self-reported more widespread and troublesome pain in women with endometriosis supports its relevance in clinical setting also. In conclusion, altered pain perception until late fertile age indicates that endometriosis may have long-term consequences related to pain receptivity beyond reproductive years.

5.4 Endometriosis-related comorbidities (Study III)

The Study III showed that endometriosis was associated with increased overall morbidity until age 50. The odds of having any non-gynecological hospital-based diagnosis were on average more than twofold in women with endometriosis compared to women without endometriosis (OR 2.37, 95% CI 1.03–5.44). This finding was supported by the results that women with endometriosis reported higher medication usage (OR 1.59, 95% CI 1.07–2.37) at age 46. The association between endometriosis and any non-gynecological diagnosis up until 50 years or continuous use of medication at 46 years among women with endometriosis is shown in Figure 12.

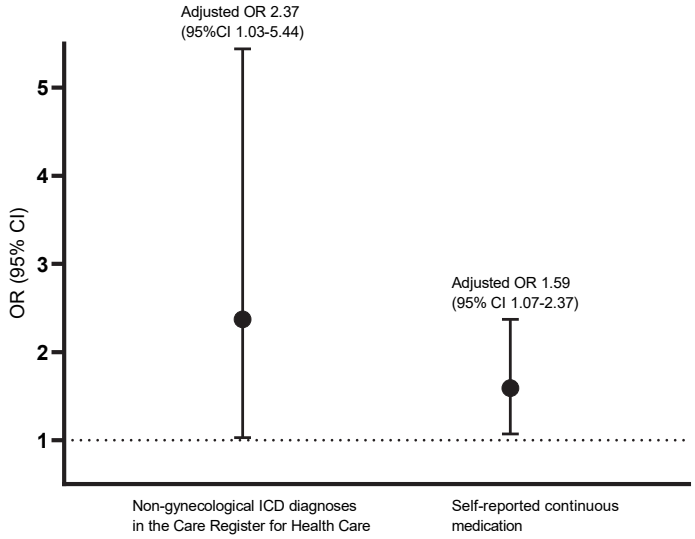

Fig. 12. The association between endometriosis and any non-gynecological diagnosis and continuous use of medication indicating increased overall morbidity in women with endometriosis.

5.4.1 Allergic, infectious and autoimmune symptoms

Endometriosis was associated with several allergic and autoimmune symptoms and recurrent infections. In terms of self-reported allergic symptoms, a significant association was found between endometriosis and asthma (OR 1.51, 95% CI 1.10–2.15), emphysema/chronic bronchitis (OR 1.72, 95% CI 1.01–2.95), allergic

eczema (OR 1.39, 95% CI 1.07–1.81), and allergic eye symptoms (OR 1.54, 95% CI 1.61–2.04). As self-reported infections, endometriosis was associated with recurrent respiratory infections (OR 1.36, 95% CI 1.04–1.77). Furthermore, women with endometriosis reported having almost twofold greater odds for hospitalization required respiratory infections than women without endometriosis (OR 1.75, 95% CI 1.14–2.67). The finding of an association between endometriosis and self-reported respiratory infections was shown to be constant with CRHC data in which women with endometriosis showed a trend toward a risk for diagnoses of acute upper respiratory infections and a significant association between endometriosis and respiratory disorders (OR 1.46, 95% CI 1.06–2.00), which is likely to be explained by the higher incidence of respiratory infections, asthma, etc. In addition to respiratory infections, endometriosis was shown to be associated with CRHC diagnoses of other infectious diseases (OR 1.65, 95% CI 1.14–2.40). Also, symptoms related to autoimmune diseases (i.e., dry mouth, dry eyes) were more prevalent in affected women.

5.4.2 Pain-causing diseases

Women with endometriosis had average twofold greater odds for migraine (OR 2.11, 95% CI 1.34–3.33). Besides migraine, women with endometriosis had a significantly higher rate of diagnosis of musculoskeletal system diagnoses (53.0% vs. 44.0%, $p = 0.005$), and the association between endometriosis and diagnosis of dorsopathies was significant (OR 1.56, 95% CI 1.16–2.10). Women with endometriosis were shown to have more IBS (3.7% vs. 1.8%, $p = 0.023$) than women without endometriosis, but the association disappeared in a multivariate analysis showing that the association was driven by confounders, not by endometriosis independently (OR 1.89, 95% CI 0.91–3.93). These data also support the findings of Study II showing altered pain response in women with endometriosis.

5.4.3 Other diseases and symptoms

Diagnosis of neoplasms and endometriosis showed a significant association (OR 1.66, 95% CI 1.20–2.30); but in more specific analysis, this association was explained by gynecological benign neoplasms, i.e., uterine leiomyomas and uncertain ovarian neoplasms, not non-gynecological neoplasms. Further on, endometriosis was associated with mood disorders (OR 1.86, 95% CI 1.20–2.88)

and digestive system diagnoses (OR 1.42, 95% CI 1.04–1.95). Lastly, diagnosis of non-specific symptoms and signs was associated with endometriosis (OR 2.57, 95% CI 1.81–3.65), and odds for diagnosis of abdominal and pelvic pain were over fourfold greater among women with endometriosis (OR 4.33, 95% CI 3.13–6.00). Furthermore, accumulating age of diagnoses "symptoms, signs, and abnormal clinical and laboratory findings (R00–R99)", and especially "abdominal and pelvic pain (R10)", was earlier in women with than without endometriosis (R00-R99, p=0.042; R10, p=0.001). This finding suggests that women with endometriosis have several contacts to health care due to endometriosis-related symptoms, like unspecific abdominal pain, and possible misdiagnosis of endometriosis, leading to possible diagnostic delay.

5.4.4 Association between comorbidities and endometriosis in the context of existing literature

Endometriosis seems to associate increased overall morbidity. Present study showed a significant association between endometriosis and allergic and autoimmune symptoms and asthma. This association has been reported also in earlier studies (Matalliotakis et al., 2012; Lamb & Nichols, 1986). The association between endometriosis and asthma, however, has conflicting results in the previous literature. In a systematic review, Sinai et al. (2002) found that the prevalence of asthma among women with endometriosis in the United States was 12% compared to 5% for the general female population. However, Ferrero, Petrera et al. (2005) found no association when investigating asthma prevalence in women with endometriosis compared to controls (4.9%, 95% CI 3.1–7.3 and 5.3%, 95% CI 3.4–8.0, respectively). As for autoimmune diseases, two population-based studies, a Danish register study and Nurses' Health Study II, reported a higher risk of several autoimmune diseases, i.e., systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis, and multiple sclerosis, in women with endometriosis (Harris et al., 2016; Nielsen et al., 2011). No association between endometriosis and these diseases in the CRHC data was found in the current study, but this might be due to the Finnish health care system, in which milder diagnoses, like Sjögren`s syndrome, are made in primary health care centers/outpatient clinics and thus may not emerge from hospital-based data. However, self-report data showed a significant association between self-reported allergies (OR 1.39–1.72), infections (OR 1.36–1.92), and autoimmune symptoms (OR 1.27–2.11) and endometriosis. Further on, in the CRHC data, infectious diagnoses were more prevalent in women with

endometriosis than in women without endometriosis, confirming the association between endometriosis and susceptibility to infection.

While the association between allergies, autoimmune symptoms, and endometriosis seem to be somewhat obvious, a shared pathomechanism of these conditions could lead to comorbidity. Furthermore, a shared genetic mechanism behind allergies and endometriosis has been considered. Rahmioglu et al. (2014) showed that carriers of the C allele of the acid phosphatase locus 1 (ACP1) polymorphism have a role in allergic manifestations with a concomitant risk for endometriosis. In terms of autoimmune disease, higher levels of estrogens have been shown to act as immune stimulants, promoting specific immunological events in different types of autoimmune diseases. These pathomechanisms may also explain the association between endometriosis and infections, which was shown to be significant in this study.

Considering the mechanisms behind chronic pain, the association between endometriosis and pain-causing diseases can be expected. Prolonged experience of pain may lead to central sensitization, increased hyperalgesia, and, further on, an altered musculoskeletal pain response in women with endometriosis. The association between endometriosis and migraine and fibromyalgia was also reported in earlier literature, but there are no data on the association between endometriosis and musculoskeletal diseases, especially dorsopathies, which in this study was shown to be statistically significant (OR 1.56, 95% CI 1.16–2.10).

This study could not find an association between endometriosis and malignancies. However, the data size, lack of link to cancer registers, and end of follow-up at the age of 50 may lead to an underestimation of this association. Earlier literature, however, found an association between ovarian endometriosis and ovarian cancer, especially endometrioid and clear cell carcinomas. The Finnish registry study by Saavalainen et al. (2018) showed that ovarian endometriosis was associated with an increased risk of ovarian cancer (standardized incidence ratio 1.76, 95% CI 1.47–2.08) (Saavalainen, Lassus, But, Tiitinen, Härkki, Gissler … Heikinheimo 2018). The same research group revealed that women with surgically confirmed endometriosis had a similar risk for breast cancer than the general population, but the risk of breast cancer at a young age was increased (Saavalainen et al., 2019). Furthermore, the group also reported an association between endometriosis and thyroid and basal cell carcinoma (Saavalainen, Lassus, But, Tiitinen, Härkki, Gissler … Pukkala 2018). Altogether, the association between ovarian endometriosis and ovarian cancer seems to be obvious, but the association with other malignancies is not clear.

Women with endometriosis had an almost twofold greater odds for mood disorders. Part of the psychological distress may be due to chronic pain and infertility. This finding is in line with previous literature, in which women with endometriosis were shown to have an increased risk of depression, anxiety and stress-related disorders, alcohol/drug dependence, and attention-deficit hyperactivity disorder compared with the general population (Gao et al., 2020).

As a conclusion, endometriosis had a significant association with several non-gynecological comorbidities. Two review articles were published earlier. These reviews concluded that women with endometriosis were reported to have a higher risk of ovarian and breast cancers, cutaneous melanoma, asthma, and some autoimmune and cardiovascular diseases (Kvaskoff et al., 2015), diabetes mellitus, cardiovascular disease, chronic liver disease, and rheumatoid arthritis (Teng et al., 2016). Some of these findings were replicated in the present study, and a significant association was found between endometriosis and infections, migraine, mood disorders, respiratory and digestive system diseases, and non-specific symptoms.

5.5 Endometriosis and working ability (Study IV)

The main finding of the Study IV was that endometriosis was associated with poor work ability and higher rates of sickness-based absenteeism at late fertile age. However, women with endometriosis had fewer unemployment days at late fertile age, and endometriosis did not increase the risk for early retirement up until the age of 52.

5.5.1 Self-reported work ability

At late fertile age, the association between self-rated poor work ability and endometriosis was significant in multivariate analysis considering endometriosis-related, health-related and working life-related covariates (OR 1.47, 95% CI 1.06–2.04), even if the unadjusted model and the model considering only widespread pain as confounding factor could not find a significant association. Odds for poor work ability in different adjusting modes are shown in Figure 13a. These results lead to a hypothesis that there are, however, differences between study groups in work-related health and socioeconomic factors even if the baseline characteristics of the study population did not reveal the difference. At age 46, women with endometriosis were reported to be absent for 10 or more days from work during the past 12 months more often compared to women without endometriosis (33.5% vs.

25.4%; p = 0.001); this association between endometriosis and over 10 days of absenteeism was significant, even when considering all confounding factors (OR 1.53, 95% CI 1.05–2.23) (Figure 13b). The association between (a) poor work ability and (b) absenteeism and endometriosis in different adjusting models is shown in Figure 13.

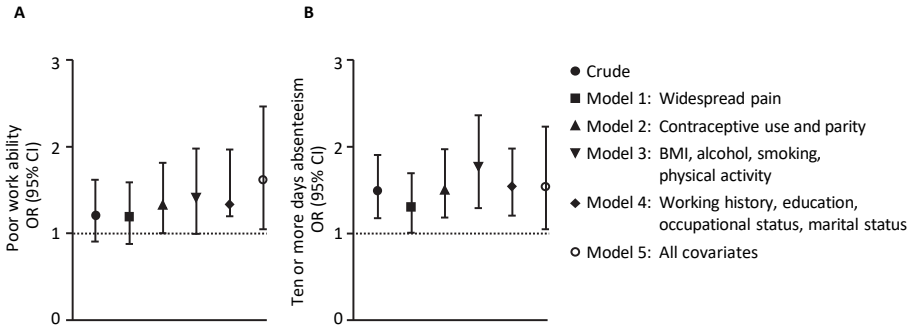

Fig. 13. Association between endometriosis and a) poor work ability b) 10 or more days absenteeism in different multivariate models.

5.5.2 Register-based disability and unemployment

Besides self-reported data, the register-based data showed higher incidence rates for disability days in women with endometriosis at late fertile age. In a two-year follow-up analysis between ages 46 and 48, women with endometriosis had 10 more disability days (55.5 vs. 45.5, p = 0.030) in comparison to women without endometriosis (Figure 14a). In the Poisson regression models, women with endometriosis presented a higher incidence rate for disability days, and the association remained significant after adjusting for baseline employment as well as for endometriosis-related, health-related, working-related covariates (IRR 1.35, 95% CI 1.31–1.38). Surprisingly, in terms of unemployment days, women with endometriosis had 20 fewer unemployment days (40.6 vs. 59.2 days, p = 0.013) during the two-year follow-up period (Figure 14b). The incidence rates remained significantly lower in each individual model and in the final model considering all covariates; IRR for unemployment 0.88 (95% CI 0.86–0.91). It should be noted that it is possible that women with endometriosis, who are better employed, will have better access to occupational health care services and be diagnosed with endometriosis.

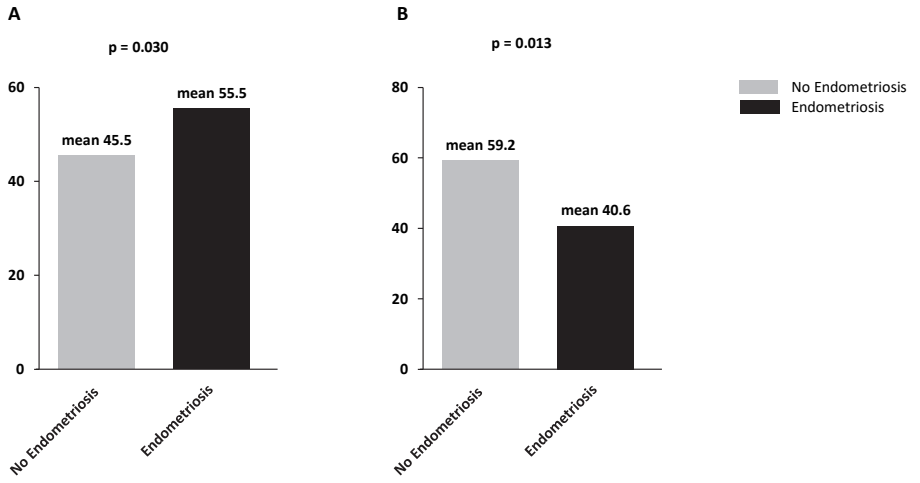

Fig. 14. Register-based a) disability and b) unemployment days in women with or without endometriosis between ages 46–48.

5.5.3 Register-based early retirement

In terms of disability retirement until midlife, women with endometriosis had not been granted disability pension until age 52 more often compared to women without endometriosis (n_{endo} = 18, 5.2% vs. $n_{no\text{-}endo}$ = 153, 4.4%, p = 0.515). The most common diagnoses warranting disability pensions were mental and behavioral disorders, as well as diseases of the musculoskeletal system and connective tissue. Further on, according to questionnaire data, women with endometriosis did not report any earlier retirement intentions compared to non-endometriosis controls (48.0% vs. 44.6%, p = 0.232).

5.5.4 The association between work ability and endometriosis in the context of existing literature

The results of the present study showed an association between endometriosis and poor work ability and sickness-related absenteeism still at late fertile age, which is in line with the previous literature, although previous data consider mainly women of their entire reproductive age. In a cross-sectional study of 193 endometriotic women, these women missed an average of 7.41 hours of work per week when

symptoms were at their worst (Fourquet et al., 2011). Another study showed that women with endometriosis lost an average of 10.8 hours of work weekly, but this was mainly due to presenteeism at work, as opposed to absenteeism (Nnoaham et al., 2011). Moreover, a study by Sperschneider et al. (2009) showed that symptomatic women with endometriosis had a two- to sixfold risk for absenteeism compared to women without endometriosis. It should be noted that although earlier studies were rooted mainly in case-control datasets and focused on women at their reproductive age, the current data were driven by the general population and were focused on work ability in women with endometriosis at late fertile age.

There is substantial evidence that fertile-aged women with endometriosis suffer from poor working ability; employment, however, is less studied and register-based studies are lacking. In a case-control study of 298 endometriotic patients, Facchin et al. (2019) showed that women with endometriosis were less likely to be employed compared to women without the disease; but in a subgroup analysis of asymptomatic endometriosis compared to controls, no significant differences between the study groups were found. Surprisingly, the present study found lower incidence rates for unemployment days in women with endometriosis compared to women without endometriosis at late fertile age. Women with endometriosis had lower parity and suffered from infertility more often than women without endometriosis. This led to fewer maternity-related long absences from working life and possibly better career development. Due to these aspects, women with endometriosis may be more committed to working life than women without endometriosis. On the other hand, women with endometriosis might also feel uncertain about changing employers due to morbidity and upcoming disability days, and thus personal choices and career decisions may affect professional experience.

Only one earlier study has explored the incidence of retirement among women with endometriosis. In the United States, Estes, Soliman, Yang, Wang and Freimark (2020) showed, via a retrospective pair-matched cohort of 6 851 women with endometriosis, no significant differences in early retirement between the controls. Similarly, the current study found no differences in the number of early retirement decision between women with or without endometriosis; however, it should be considered that the follow-up extended to only 52 years of age, and no data since then are available. Yet, since the symptoms of endometriosis typically disappear with menopause, any increase in pre-term disability retirement because of endometriosis should be seen during the fertile years. No evidence was found for this in the lifelong analysis up to age 52 in this study. Considering the natural course

of the disease, it is also unlikely that endometriosis as an independent factor would cause disability retirement later on.

According to this register-based study of disability and unemployment days and disability retirement, it could be concluded that even though endometriosis has an adverse effect on working life by causing absenteeism and poor work ability, there are no major risks of dropping out of working life into unemployment or early retirement due to endometriosis beyond reproductive age.

6 Strengths and limitations

These studies have several strengths. First, the results arose from large, population-based data with a homogeneous female population and minimal variation of ethnicity. Endometriosis cases were identified in both self-reported data and medically confirmed hospital register cases, achieving the most comprehensive study groups with high specificity, as the identified women presented with a typical endometriosis profile in regard to pain experience, infertility, parity, and contraceptive use. This dataset offers a good opportunity to consider several confounding factors in multivariate analysis. Furthermore, the study had an opportunity to conduct a subgroup analysis on different subtypes of endometriosis (peritoneal, ovarian, deep-infiltrating), even though the low number of cases limited the reliability of the subgroup analyses. Pain perception and body size data were based on objectively measured data instead of self-reported data only. Cohort data were linked to several reliable national registers when assessing comorbidity and attachment to working life, reducing the bias of misclassification that may occur when using self-reported data only.

As for limitations, lack of surgically and histologically confirmed diagnoses of endometriosis may be considered as a limitation, although combining self-report and medically confirmed cases can be considered a strength. 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. Excluding adenomyosis from the cases may affect the accuracy of study groups and results. It was not possible to assess the reliable severity of endometriosis and its effect on the results of this study. Data on the onset and severity of symptoms cannot be considered, and information on surgical treatment and its effect on results are lacking. A certain degree of selection bias for the study groups cannot be ruled out, although the participation rate of the total NFBC1966 population was high and the drop-out rate was similar between the study groups. Register data extended only until 50–52 years of age and thus did not fully cover comorbidity, disability, employment, and retirement later in life. Given the homogenous ethnic background and the unique nature of the Finnish health care and retirement system, the results may not be generally applicable, and no conclusions can be made regarding possible ethnic aspects and variation. Finally, although this study found significant correlations between endometriosis and adulthood body size, altered pain perception, some comorbidities, and poorer working ability, the causation or clinical significance of these correlations could not be established.

7 Conclusion and clinical implications

The present population-based study showed an association between low body weight, lean body shape and endometriosis in adulthood but not in childhood or adolescence. The persistent association between lean body size and peritoneal endometriosis until late fertile age may indicate significant differences in pathomechanisms between endometriosis subtypes, suggesting the importance of the classification of endometriosis types in future research. To elucidate the common mechanism between a lean body shape and peritoneal endometriosis, future studies should explore the causality between adiposity and endometriosis.

Secondly, this study showed an altered musculoskeletal pain response and increased self-reported pain sensitivity and troublesomeness among women with a history of endometriosis still at late fertile age. These results indicate that endometriosis may have long-term consequences related to pain receptivity. Long diagnostic delay and prolonged pain sensations predispose an altered pain sensitization among women with endometriosis. According to this finding, the identification of endometriosis behind several overlapping symptoms and the adequate treatment of endometriosis-related pain are crucial to providing appropriate treatment and avoiding long-term health consequences in affected women.

Thirdly, this study suggests that women with endometriosis have significantly higher risk of several chronic non-gynecological diseases and symptoms, especially immunological and allergic symptoms, infectious diseases, respiratory diseases, pain diseases, and unspecific symptoms and signs. A deeper understanding of these associations is needed, as doing so may provide new leads into the causes or consequences of endometriosis. For example, if autoimmunity is present in the pathogenesis of developing endometriosis, immunomodulatory therapy for autoimmune diseases might then be used as a potential treatment choice, such as immuno-modulators. This aspect needs further studies. Women with endometriosis should be given more attention in the health care system since they not only have endometriosis-related health issues but are also at risk for several other medical conditions.

Fourthly, regarding work ability, endometriosis seems to be associated with poor work ability and sick leave still at late fertile age. However, employment visions and attachment to working life after fertile age seem to be equal in women with endometriosis compared to the general female population. In patient counseling, it is crucial to provide this information to women with endometriosis,

who might have an occupational crisis during fertile age and are skeptical whether they will meet the challenges in working life throughout the professional career.

To conclude this population-based study of body size, pain perception, comorbidities and work ability in women with endometriosis, there is a strong evidence that endometriosis has several adverse effects on women's life during reproductive years, but also at late fertile age. Early identification of endometriosis behind menstrual pain, but also somewhat unspecific symptoms, is crucial to avoiding a long diagnostic delay. Moreover, adequate and effective treatment modalities utilizing a multidisciplinary team are important to improving long-term health for women with endometriosis but also to controlling the economic burden related to the disease.

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ORIGINAL RESEARCH ARTICLE

Body size during adulthood, but not in childhood, associates with endometriosis, specifically in the peritoneal subtype—population-based life-course data from birth to late fertile age

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Abstract

Introduction: Endometriosis is a common gynecological condition causing chronic pain and infertility. Only limited data exist on body size during childhood and adolescence in affected women. A leaner body shape has been associated with endometriosis in adults. However, longitudinal follow-up data from birth to adulthood are lacking. The aim of this study was to assess the association between body size and endometriosis from birth to age 46 years. We also performed in-depth analysis of the endometriosis subtypes.

Material and Methods: This was a population-based study including 96% of the children born in Northern Finland in 1966. Endometriosis case identification was based on (a) the World Health Organization's International Statistical Classification of Diseases code documentation from national hospital discharge registers and (b) self-reported diagnosis. A total of 348 women with endometriosis (203 in subtype analysis) and 3487 women without endometriosis were identified. Pregnancy, birth, and growth data up to adolescence were collected from welfare clinical records. Follow-up data of the Northern Finland Birth Cohort 1966 were collected at ages 14, 31, and 46 years through postal questionnaires and clinical examinations and included height, weight, and waist and hip circumference measurements. The associations between endometriosis and body size were assessed using logistic regression models.

Results: Body sizes in childhood and adolescence were comparable between women developing endometriosis and those not developing endometriosis. On average, the risk for endometriosis was 2% lower for every kilogram of weight (odds ratio [OR] 0.98, 95% CI 0.97-1.00) and 6% lower for every body mass index unit (OR 0.94, 95% CI 0.90-0.99) at age 31. By age 46, a lower risk for peritoneal endometriosis was observed with greater weight (OR 0.95, 95% CI 0.92-0.98), weight gain from age 14

Abbreviations: BMI, body mass index; HC, hip circumference; ICD, International Classification of Diseases; IGF-1, insulin-like growth factor 1; NFBC1966, Northern Finland Birth Cohort 1966; OR, odds ratio; SD, standard deviation; WC, waist circumference; WHR, waist-hip ratio.

Outi Uimari and Terhi T. Piltonen contributed equally.

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to age 46 years (OR 0.97, 95% CI 0.93-1.00), body mass index (OR 0.90, 95% CI 0.82-0.98), waist circumference (OR 0.95, 95% CI 0.92-0.99), and waist-hip ratio (OR 0.41, 95% CI 0.21-0.78).

Conclusions: This study provides further evidence of the associations between endometriosis and body size and adiposity, specifically in women with peritoneal endometriosis. The associations are evident in adulthood but not in childhood or adolescence.

KEYWORDS
adiposity, body mass index, body size, body weight, endometriosis, subtype, waist, waist-hip ratio

1 | INTRODUCTION

Endometriosis is a common chronic gynecological condition causing pelvic pain and infertility.[1] Its etiology is multifactorial, including genetic, environmental, and lifestyle components.[2] Endometriosis is characterized by the presence of functional endometrial tissue outside the uterus, most commonly on the peritoneal wall and ovaries. As in the eutopic endometrium, the proliferation of ectopic endometriosis lesions is promoted by the action of estrogen;[1] so the onset of symptoms usually occurs post menarche during the reproductive years.[3] The pathophysiology of endometriosis is complex, including steroidogenic linkage and abnormalities in immune response, angiogenesis, inflammation, and apoptosis. All these factors may lead to adhesion and the growth of ectopic lesions.[2]

The link between endometriosis and weight and adiposity has been the subject of several studies. Findings indicate that early life factors such as prematurity and low birthweight may be associated with the disease.[4] Interestingly, however, body size in childhood and from early to late adulthood seems to be inversely associated with endometriosis.[5,6] Moreover, a body fat distribution characterized by a low waist-hip ratio (WHR) has more often been observed in affected women,[6,7] which is also supported by genetic studies.[8] These results, however, have been obtained from multiple study populations and with no distinction between endometriosis subtypes. Their reliability may further be limited due to small sample sizes and/or the use of self-reported endometriosis diagnosis and body size measurement data, which may be subject to recall bias. The possible inverse association between endometriosis and body size has yet to be confirmed in a larger study setting including multiple life-course stages.

The aim of this study was to explore the association between endometriosis and its subtypes (peritoneal, ovarian, and deep infiltrating endometriosis) and body size development at several life-course stages from birth to adolescence to adulthood. The analysis was based on data of 5889 females, which included (a) longitudinal data on weight and height from birth to age 20 years and (b) cross-sectional data on weight and height at menarche and at ages 14, 31, and 46 years and waist and hip circumference data at ages 31 and 46 years.

Key message

This population-based birth cohort study showed that endometriosis, specifically peritoneal subtype, associates with leaner habitus in adulthood only.

2 | MATERIAL AND METHODS

This study was based on the Northern Finland Birth Cohort 1966 (NFBC1966). It was a prospective birth cohort study consisting of 96.3% of all expected births during 1966 in Northern Finland (12 055 mothers, 12 058 live-born children, 5889 females, all Finnish Caucasian). Enrollment in the cohort began during the 24th gestational week, and birth, childhood, and adolescence growth measurements were collected by professionals through the Finnish health system. Specific time-points for the NFBC1966 data collection were planned about 15 years apart at ages 14, 31, and 46 years via postal questionnaires and clinical examinations. All data were collected by trained study nurses and doctors according to unified protocols. All individuals included in this study provided informed consent for the NFBC1966 study and for the use of their register-level data.

2.1 | Identification of women with endometriosis

Women with endometriosis were identified from the NFBC1966 population using two different data sources. First, self-reported cases were identified from the 46-year follow-up study. In the health questionnaire, women were asked to report whether they had been diagnosed with endometriosis ("Have you ever been diagnosed with endometriosis by a clinical doctor?"). The self-reported endometriosis diagnosis has been validated previously.[9] Second, the NFBC1966 population was linked to the national outpatient and inpatient hospital discharge register (available from 1968 to 2012). The hospital discharge register is considered a reliable data source and has been widely used in scientific studies.[10] It includes World Health Organization International Classification of Diseases (ICD) code

standards for each hospital visit. In Finland, these codes are entered by clinical doctors. The ICD-9 and ICD-10 codes for endometriosis (617.1-617.9 and N80.1-N80.9, respectively; ICD-8 codes were converted to ICD-9) were used for medically confirmed case identification. These cases were categorized into the following endometriosis subtypes: peritoneal endometriosis (617.2, 617.3, N80.2, and N80.3), ovarian endometriosis (617.1 and N80.1), and deep infiltrating endometriosis (617.4, 617.5, 617.8, N80.4, N80.5, and N80.8). Some diagnosis overlap was observed. In these cases, peritoneal diagnosis was accepted only if the individual had no diagnosis of ovarian or deep infiltrating endometriosis. Cases of overlapping ovarian and deep infiltrating endometriosis diagnoses were classified as deep infiltrating endometriosis. There were also 21 diagnoses of unspecified/scar endometriosis (N80.9, N80.6), which were not included in the subtype analysis. Women who did not have an ICD code for endometriosis and replied "no" to the self-reported endometriosis question were considered to be women without endometriosis. A flow chart of the study population is shown in Figure 1.

2.2 | Pregnancy and birth data

Birthweight data of the cohort individuals were collected from the hospital and welfare records. Individuals whose birthweight was below the 10th centile with respect to their gestational age were considered small for gestational age, whereas those whose birthweight was above the 90th centile were considered large for gestational age.

2.3 | Growth data in childhood and adolescence

Childhood weight and height from early infancy until 6 years of age were measured by nurses at welfare clinics and from age 7 to age 17 years in school as part of the national child health screening program, which is free and available to all children born in Finland (coverage: 99% of the population). Between ages 17 and 20 years, body mass indices (BMIs) were measured in the context of the general healthcare system. The BMIs at age 14 years were calculated from height and weight measures reported by the parents. Women reported their age at menarche in the 46-year postal questionnaire, and the corresponding BMIs were calculated from the fitted BMI growth curves.[11,12] The childhood growth data were divided into two age periods: from 2 weeks to 18 months (infancy) and from 18 months to 13 years (childhood).[12] The longitudinal BMI linear mixed-effects model was fitted using the logarithmically transformed BMI as the outcome, and the predicted timing of adiposity peak (maximum weight during this period, around 9 months) and adiposity rebound point (nadir of the BMI curve, usually around 5 years) were calculated using estimated fixed and random coefficients.

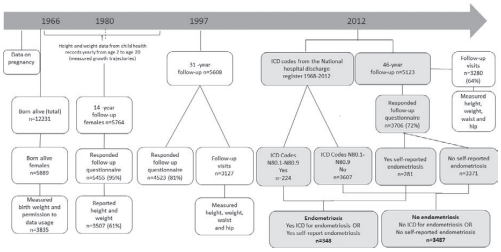

FIGURE 1 Flowchart of the data collection and study population. The population of women with endometriosis and women without endometriosis formed in the Northern Finland Birth Cohort 1966 for the present study are marked in grey. ICD, International Classification of Diseases

The long-term BMI patterns of the cohort individuals between ages 2 and 20 years were assessed with group-based modeling using Nagin's approach.[11] The model identifies clusters or subpopulations exhibiting the same patterns of change or behavior over time. For modeling purposes, 16 age windows were created. Ages 17 to 20 years were grouped together to increase the number of measurements for this window. BMIs (expressed as weight in kg/height in m^2 for each age window) and BMI z-scores were internally calculated. Multiples and individuals with fewer than three BMI measures were excluded from the analysis. The model created four clusters of women with similar BMI trends between ages 2 and 20 years.

2.4 | Body measurements in adulthood

Weight (in kilograms), height (in centimeters), waist circumference (WC; in centimeters), and hip circumference (HC; in centimeters) were measured at the NFBC1966 clinical examinations at ages 31 and 46 years. The BMI was calculated as weight (kg)/height $(m)^2$, and the WHR was calculated as WC/HC. The weight, height, waist, and hip measurement protocols have been described previously.[11]

2.5 | Covariates

Several potentially confounding variables were considered for possible associations with weight development and endometriosis: maternal weight gain during pregnancy, mother's smoking status at pregnancy, gestational age at birth, age at menarche, socioeconomic and relationship status, smoking, physical activity, and hormonal contraceptive use. Maternal and gestational data were collected from hospital and welfare records. The gestational age at birth was classified according to the World Health Organization's criteria for gestational weeks:[13] very preterm, 33^{+6}; preterm, 34^{+0} to 36^{+6}; and at term, 37^{+0}. Data on age at menarche were collected from the 46-year follow-up questionnaire. The socioeconomic status was determined based on the education level (basic, secondary, or tertiary/higher) reported in the questionnaire. The relationship status was determined as "in relationship" based on self-reported marriage or cohabitation at ages 31 and 46 years. Data on smoking habits were collected from self-reports at age 46 years. Individuals reported

never, formerly/occasionally, or currently smoking. Intensity and duration of physical activity data collected from the questionnaires were calculated as metabolic equivalent of task minutes per week.[14] Parity data were collected from the questionnaires at ages 31 and 46 years. At age 46 yearas, respondents were asked if they had ever used hormonal contraceptives. Potential mediation for each confounder was tested using the Sobel test. Analytical models were constructed separately for four time-points: birth and ages 14, 31, and 46 years.

2.6 | Statistical analyses

The statistical analyses were performed using IBM SPSS Statistics software version 22 for Windows (IBM Corp.). Differences in continuous variables were analyzed using the independent samples *t* test or the Mann-Whitney *U* test and the chi-squared test was used to analyze differences in categorical parameters. Pearson correlation was used to test for correlation between BMI and the age at first endometriosis diagnosis. Binary logistic regression analysis was used to explore anthropometrics/body size associations between those with endometriosis and those without. Appropriate confounding factors were included in the multivariate analysis models. Analytical models were constructed separately for four available time-points: birth and ages 14, 31 and 46 years.

The results are reported as odds ratios (ORs) with 95% CIs. To exclude possible outliers in WC and HC measures, a 2 standard deviation (SD) threshold was used as a sensitivity analysis in the logistic regression calculation. A two-sided *P* value less than 0.05 was considered statistically significant. Bonferroni correction was conducted to reduce the risk of Type I Error: the *P* value of <.05/4 (*P* < .0125) denotes statistical significance. Sobel test was used to explore for possible mediation between endometriosis and confounders. Group-based trajectory modeling from the Proc Traj procedure in SAS software version 9.4 (SAS Institute Inc.) was used.

2.7 | Ethical approval

This study was approved by the Ethics Committee of the Northern Ostrobothnia Hospital District on 14 December 2011, registration number ETTMK: 94/2011.

3 | RESULTS

The total endometriosis population consisted of 348 women, of whom 124 only self-reported endometriosis diagnosis and 224 had medically confirmed endometriosis (Figure 1). Other female cohort members were considered women without endometriosis (n = 3487). We categorized the medically confirmed cases into the following endometriosis subtypes: peritoneal endometriosis (n = 59; 26.3%), ovarian endometriosis (n = 107; 47.8%), and deep infiltrating endometriosis (n = 37; 16.5%). The participation rates in the follow-up data collection at ages 31 and 46 years did not differ between the endometriosis and non-endometriosis groups.

3.1 | Baseline characteristics

Mothers of cohort members with and without endometriosis exhibited similar early-pregnancy weight and weight gain during pregnancy, as well as similar smoking rates. Women with and without endometriosis were born at similar gestational ages, and there were no distribution differences among those born as small-for gestational age and those born as large for gestational age (Table 1). The mean age at menarche of women with endometriosis (12.6 ± 1.2 years) did not differ significantly from that of women without endometriosis (12.9 ± 1.2 years; *P* = .898). Likewise, the BMI at menarche did not differ significantly (18.3 ± 2.3 vs 18.5 ± 2.7 kg/m^2). The mean age at endometriosis diagnosis was 31.6 ± 7.3 years (Table 1). As expected, the infertility rate of women with endometriosis was higher than that of women without endometriosis (31% vs 13%; *P* = .014). Women with endometriosis had significantly lower parity at age 46 years (1.9 ± 1.2 vs 2.33 ± 1.8; *P* < .001) and were more likely to have used hormonal contraceptives (93.5% vs 89.3%; *P* = .014; Table 1). No significant differences were observed between the two groups in terms of socioeconomic and relationship status, smoking, or physical activity (Table 1). According to the Sobel test, none of the confounding factors showed mediation for body size measures in adulthood or endometriosis risk.

3.2 | Associations between lifelong body measurements and endometriosis

There were no associations between endometriosis and birthweight, adiposity peak, and adiposity rebound (Table 2). No associations were observed between endometriosis and weight, height, and BMI at age 14 years. The growth trajectory analysis revealed no significantly different trends between women who developed endometriosis and those who did not, and the proportions of women in each trajectory cluster were comparable (Figure S1).

At age 31 years, women with endometriosis exhibited lower mean weight than women without endometriosis (63.4 ± 9.8 vs 65.5 ± 13.0 kg; *P* = .016). They had gained less weight since age 14 years (12 ± 8.2 vs 13.6 ± 9.3 kg; *P* = .004), and their BMI was lower (22.9 ± 4.2 vs 23.6 ± 3.5 kg/m^2; *P* = .016). Women with endometriosis also had a smaller WC (76.3 ± 9.3 vs 78.9 ± 12.0 cm; *P* = .006) and a lower WHR (0.79 ± 0.07 vs 0.81 ± 0.08; *P* = .002; Table 2). The multivariate analysis revealed inverse associations between several body size measures and endometriosis. Lower weight (OR 0.98, 95% CI 0.97-1.00), less weight gain between ages 14 and 31 years (OR 0.98, 95% CI 0.96-0.99), lower BMI (OR 0.94, 95% CI 0.90-0.98), smaller WC (OR 0.98, 95% CI 0.97-1.00), and smaller WHR (OR 0.79, 95% CI 0.63-1.00) were associated with a higher risk of endometriosis.

TABLE 1 Characteristics of the study population in the Northern Finland Birth Cohort 1966

	No endometriosis (n = 3487)	Endometriosis (n = 348)	*P* value
Mother's prepregnancy weight (kg), mean (SD)	56.8 (15.1)	56.9 (14.7)	.856
Mother's pregnancy weight gain (kg) , mean (SD)	11.9 (4.0)	12.1 (4.2)	.654
Mothers smoking at the end of pregnancy, % (n)	4.6 (161)	4.9 (17)	.966
Gestational age at birth			
Very preterm birth (<34 weeks), % (n)	4.0 (14)	2.9 (10)	.360
Preterm birth (34-37 weeks), % (n)	3.8 (132)	4.5 (1579)	
Birth at term (>37 weeks), % (n)	91.7 (3198)	93.1 (324)	
Small for gestational age, % (n)	8.4 (277)	8.2 (27)	.882
Large for gestational age, % (n)	11.3 (371)	7.9 (26)	.064
Age at menarche, mean (SD)	12.9 (1.2)	12.6 (1.2)	.898
BMI at menarche (kg/m^2) , mean (SD)	18.5 (2.7)	18.3 (2.3)	.577
Parity at age 31 years, mean (SD)	1.6 (1.3)	1.3 (1.1)	<.001
Parity at age 46 years, mean (SD)	2.33 (1.8)	1.9 (1.2)	<.001
Mean age at the time of first endometriosis diagnosis (years)	NA	31.6 (7.3)	NA
Infertility by age 46 years, % (n)	13.0 (454)	31.0 (108)	<.001
Hormonal contraceptive use (ever), % (n)	89.3 (2981)	93.5 (315)	.014
Socioeconomical status defined as education level			
Basic, % (n)	6.2 (209)	4.4 (15)	
Secondary, % (n)	63.8 (2143)	61.2 (207)	
Tertiary, % (n)	30.0 (1006)	34.3 (116)	.143
Relationship status:			
Lives in relationship at age 31 years, % (n)	77.9 (2450)	77.5 (252)	.888
Lives in relationship at age 46 years, % (n)	76.8 (2574)	79.3 (268)	.310
Smoking:			
Never, % (n)	56.0 (1861)	59.8 (199)	
Former/Occasional, % (n)	26.6 (885)	21.3 (71)	
Active, % (n)	17.3 (575)	18.9 (63)	.107
Physical activity: MET min/week			
Light at age 31, mean (SD)	508 (487)	521 (490)	.663
Brisk at age 31, mean (SD)	418 (501)	456 (516)	.187
Light at age 46, mean (SD)	519 (487)	538 (485)	.498
Brisk at age 46, mean (SD)	573 (608)	523 (492)	.150

Note: Data reported as mean(SD) or percentages (n). Significance tests for continuous variables were performed by using the independent samples *t* test or the Mann–Whitney *U* test, as appropriate. *P* value <.05 was considered significant.

Differences in numbers vary in different analyses as a result of some missing data.

Abbreviations: BMI, body mass index; MET min/week: metabolic equivalent of task score.

In contrast, HC showed no inverse association (Table 2). The endometriosis subtype analysis showed that women with peritoneal endometriosis had a lower mean BMI (22.7 ± 4.1 vs 23.6 ± 3.5 kg/m^2; *P* = .043) and a smaller mean WC (74.7 ± 9.4 vs 78.9 ± 12.0 cm; *P* = .046) and HC (93.9 ± 6.6 vs 97.1 ± 8.8 cm; *P* = .039) than women without endometriosis, but associations were not significant with the other two subtypes. After adjusting for confounders, the multivariate analysis indicated consistency in terms of OR estimates and effect directionality, although the results were not statistically significant (Table 3). There were no associations between body size measures and ovarian or deep infiltrating endometriosis. The results remained unchanged when the analysis was restricted to ±2SD for WC and HC data.

At age 46 years, women who had developed endometriosis still had a lower mean weight than women without endometriosis (70.4 ± 13.6 vs 72.2 ± 15.0 kg, *P* = .049). However, weight gain since ages 14 and 31 years did not differ significantly between the two groups (Table 2). There were no significant differences in BMI, WC, and HC, but the WHR was slightly lower in women with endometriosis (0.86 ± 0.06 vs 0.87 ± 0.06; *P* = .012). The

TABLE 2 Association between body size measurements and endometriosis at different ages in the Northern Finland Birth Cohort 1966, univariate and multivariate binary logistic regression analysis model

	No endometriosis (n = 3487), mean (SD)	Endometriosis (n = 348), mean (SD)	Univariate OR (95% CI)	Multivariate OR (95% CI)	*P* value
Birth[a]					
Birthweight (g)	3436 (501.0)	3420 (471.9)	0.99 (0.97-1.02)	0.99 (0.92-1.07)	.812
Adiposity peak (age in years)	0.8 (0.1)	0.8 (0.1)	1.30 (0.06-26.7)	0.29 (0.001-29.2)	.602
Adiposity rebound (age in years)	5.6 (1.0)	5.7 (0.9)	1.06 (0.89-1.26)	1.51 (0.86-2.64)	.152
Age 14 years[b]					
Weight (kg)	50.7 (7.9)	50.5 (7.3)	1.00 (0.98-1.01)	0.99 (0.98-1.01)	.506
Height (cm)	161.5 (6.1)	161.5 (5.9)	1.00 (0.98-1.02)	1.00 (0.98-1.02)	.979
BMI (kg/m^2)	19.4 (2.5)	19.3 (2.3)	0.98 (0.94-1.03)	0.98 (0.93-1.03)	.322
Age 31 years[c]					
Weight (kg)	65.5 (13.0)	63.4 (9.8)	0.99 (0.97-1.00)	0.98 (0.97-1.00)	.012*
Weight gain from age 14 to 31 years (kg)	13.6 (9.3)	12.0 (8.2)	0.98 (0.97-0.99)	0.98 (0.96-0.99)	.004*
Height (cm)	164.7 (6.1)	164.7 (6.2)	1.00 (0.98-1.02)	0.99 (1.00-1.02)	.492
BMI (kg/m^2)	23.6 (3.5)	22.9 (4.2)	0.95 (0.92-0.99)	0.94 (0.90-0.98)	.001*
WC (cm)	78.9 (12.0)	76,3 (9.3)	0.98 (0.97-0.99)	0.98 (0.97-1.00)	.024
HC (cm)	97.1 (8.8)	96.1 (7.1)	0.99 (0.97-1.00)	0.99 (0.97-1.00)	.121
WHR	0.81 (0.08)	0.79 (0.07)	0.71 (0.58-0.88)	0.79 (0.63 –1.00)	.051
WHR by categories					
BMI <18.5 kg/m^2			0.45 (0.06-3.19)	NA**	NA**
BMI 18.5-25 kg/m^2			0.71 (0.53-0.97)	0.85 (0.62-1.15)	.292
BMI >25 kg/m^2			0.69 (0.46-1.02)	0.67 (0.43-1.04)	.071
Age 46 years[d]					
Weight (kg)	72.2 (15.0)	70.4 (13.6)	0.99 (0.98-1.00)	0.99 (0.98-1.00)	.262
Weight gain from age 14 to 46 years (kg)	20.7 (12.5)	19.4 (11.6)	0.99 (0.98-1.00)	1.01 (0.99-1.03)	.235
Weight gain from age 31 to 46 years (kg)	7.0 (8.2)	7.4 (7.8)	1.1 (0.99-1.02)	0.99 (0.98-1.00)	.223
Height (cm)	164.8 (6.0)	164.6 (6.2)	1.00 (0.98-1.02)	1.00 (0.98-1.02)	.980
BMI (kg/m^2)	26.2 (5.2)	25.7 (4.7)	0.98 (0.96-1.00)	0.98 (0.95-1.01)	.126
WC (cm)	87.3 (13.1)	85.8 (12.7)	0.99 (0.98-1.00)	0.99 (0.98-1.01)	.231
HC (cm)	100.5 (11.1)	99.9 (10.6)	0.99 (0.98-1.01)	1.00 (0.98-1.01)	.700
WHR	0.87 (0.06)	0.86 (0.06)	0.77 (0.62-0.94)	0.80 (0.62-1.03)	.083
WHR by categories BMI <18.5 kg/m^2			1.36 (0.04-47.17)	NA**	NA**
BMI 18.5-25 kg/m^2			0.58 (0.41-0.84)	0.53 (0.34-0.82)	.005*
BMI >25 kg/m^2			0.89 (0.65-1.22)	0.91 (0.63-1.31)	.600

Note: The odds ratios were calculated per 1 unit change, except WHR per 0.1 unit change. Significant *P* values marked with bold.

Abbreviations: BMI, body mass index; HC, hip circumference; WC, waist circumference; WHR, waist to hip ratio.

In multivariate analysis:

[a]Mother's weight gain during pregnancy, mother's smoking at end of pregnancy, gestational age at birth.

[b]Age at menarche.

[c]Socioeconomical status, relationship status at age 31, smoking status, physical activity at age 31, age at menarche, parity at age 31, lifetime hormonal contraceptive use at age 46 years.

[d]Socioeconomical status, relationship status at age 46, smoking status, physical activity at age 46, age at menarche, parity at age 46, lifetime hormonal contraceptive use at age 46 years.

**P* value significant after the Bonferroni correction.

TABLE 3 Association between adulthood body size measurements and different endometriosis subtypes; multivariate binary logistic regression analysis model

No endometriosis (n = 3487)		Peritoneal endometriosis (n = 59)			Ovarian endometriosis (n = 107)			Deep infiltrating endometriosis (n = 37)		
	Mean (SD)	Mean (SD)	Multivariate OR (95% CI)	*P* value	Mean (SD)	Multivariate OR (95% CI)	*P* value	Mean (SD)	Multivariate OR (95% CI)	*P* value
Age 31 years[a]										
Weight (kg)	65.5 (13.0)	62.3 (9.7)	0.98 (0.94-1.02)	.324	65.0 (9.9)	0.99 (0.96-1.01)	.289	65.5 (11.5)	1.00 (0.96-1.03)	.702
Weight gain from 14 to 31 years (kg)	13.6 (9.3)	13.6 (9.6)	1.00 (0.95-1.04)	.993	13.0 (9.2)	0.97 (0.94-1.00)	.979	15.4 (10.1)	0.99 (0.95-1.04)	.853
Height (cm)	164.7 (6.1)	164.5 (6.5)	0.98 (0.91-1.04)	.490	165.8 (5.5)	1.03 (0.90-1.01)	.243	164.4 (7.8)	1.00 (0.93-1.07)	.640
BMI (kg/m^2)	23.6 (3.5)	22.7 (4.1)	0.93 (0.84-1.05)	.269	23.2 (3.3)	0.93 (0.88-1.01)	.080	23.8 (4.2)	0.98 (0.89-1.08)	.827
WC (cm)	78.9 (12.0)	74.7 (9.4)	0.96 (0.91-1.01)	.132	77.1 (8.2)	0.98 (0.96-1.01)	.150	79.3 (10.8)	0.99 (0.95-1.04)	.743
HC (cm)	97.1 (8.8)	93.9 (6.6)	0.94 (0.88-1.01)	.073	97.1 (6.9)	0.98 (0.95-1.01)	.984	97.4 (7.3)	1.00 (0.94-1.04)	.900
WHR	0.81 (0.08)	0.79 (0.06)	0.74 (0.35-1.53)	.410	0.79 (0.06)	0.71 (0.4 −1.15)	.162	0.81 (0.07)	0.91 (0.46-1.81)	.750
Age 46 years[b]										
Weight (kg)	72.2 (15.0)	66.7 (12.5)	0.95 (0.92-0.98)	.014	71.3 (13.3)	1.00 (0.99-1.02)	.884	74.2 (14.9)	1.01 (0.98-1.03)	.638
Weight gain from 14 to 46 years (kg)	20.7 (12.5)	16.7 (10.8)	0.97 (0.94-1.00)	.049	20.2 (12.0)	1.00 (0.98-1.02)	.966	23.5 (13.1)	1.01 (0.98-1.04)	.838
Weight gain from 31 to 46 years (kg)	7.0 (8.2)	6.8 (6.7)	0.99 (0.95-1.04)	.791	7.3 (6.6)	1.04 (0.98-1.05)	.405	6.2 (10.5)	1.01 (0.95-1.07)	.676
Height (cm)	164.8 (6.0)	165.3 (6.1)	1.01 (0.96-1.06)	.795	165.5 (6.1)	1.03 (0.99-1.07)	.185	164.3 (6.7)	1.00 (0.93-1.06)	.317
BMI (kg/m^2)	26.2 (5.2)	24.6 (4.5)	0.91 (0.84-0.98)	.009*	26.1 (5.0)	1.00 (0.95-1.04)	.817	27.6 (5.9)	1.04 (0.90-1.14)	.943
WC (cm)	87.3 (13.1)	82.1 (12.2)	0.96 (0.93-0.99)	.006*	86.6 (11.1)	1.00 (0.99-1.02)	.954	88.7 (13.3)	1.02 (0.96-1.07)	.578
HC (cm)	100.5 (11.1)	98.1 (9.7)	0.97 (0.94-1.01)	.096	100.0 (9.7)	1.00 (0.98-1.02)	.956	102.5 (12.3)	1.01 (0.98-1.05)	.503
WHR	0.87 (0.06)	0.83 (0.06)	0.37 (0.21-0.64)	<.001*	0.86 (0.06)	1.04 (0.68-1.58)	.861	0.86 (0.05)	1.05 (0.53-2.10)	.884

Note: The odds ratios were calculated per 1 unit change, except WHR per 0.1 unit change. Significant *P* values marked with bold.

Abbreviations: BMI, body mass index; HC, hip circumference; WC, waist circumference; WHR, waist to hip ratio.

In multivariate analysis:

[a]Socioeconomical status, relationship status at age 31, smoking status, physical activity at age 31, age at menarche, parity at age 31, lifetime hormonal contraceptive use at age 46 years.

[b]Socioeconomical status, relationship status at age 46, smoking status, physical activity at age 46, age at menarche, parity at age 46, lifetime hormonal contraceptive use at age 46 years.

**P* value significant after the Bonferroni correction.

multivariate analysis showed an inverse association between endometriosis and WHR among women with a BMI of 18.5-25 kg/m^2 (OR 0.53, 95% CI 0.34-0.82, Table 2). The subtype analysis revealed inverse associations between peritoneal endometriosis and weight (OR 0.95, 95% CI 0.92-0.98), weight gain from age 14 to 46 years (OR 0.97, 95% CI 0.94-1.00), BMI (OR 0.91, 95% CI 0.84-0.98), WC (OR 0.96, 95% CI 0.93-0.99), and WHR (OR 0.37, 95% CI 0.21-0.64; Table 3). In contrast, there was a tendency toward positive associations between all body size measures and ovarian and deep infiltrating endometriosis (OR > 1). The parameters of the model after adjustment were consistent in terms of effect size and directionality but were not statistically significant; therefore, independent effects could not be confirmed. The results remained unchanged when the analysis was restricted to ±2SD for WC and HC data.

4 | DISCUSSION

This prospective population-based birth cohort study found an inverse association between endometriosis, specifically of the peritoneal subtype, and a smaller body size in terms of BMI, WC, and WHR. No associations were found between endometriosis and birthweight or adiposity from childhood to age 20 years.

A few studies have investigated body size in childhood and adolescence in women with endometriosis and have reported conflicting results.[5,15-17] Whereas we found no association between endometriosis and adiposity in childhood or adolescence, the Nurses' Health Study II reported a lower incidence of endometriosis in females with a larger body size at ages 5, 10, and 20 years.[5,18] Farland et al found a lower likelihood of endometriosis in women reporting a large body size at the age of 8 years, at menarche, and at ages 20-25 years.[16] Interestingly, Nagle et al suggested that being overweight at age 10 years but also underweight at age 16 years was associated with a higher risk of endometriosis.[15] Possible explanations for these conflicting results are differences in study designs and between study populations' ethnicities. Moreover, most previous studies used body shape illustrations in a retrospective manner, whereas our study mostly analyzed data obtained from measurements.

Several epidemiological studies have associated a taller or leaner habitus with endometriosis in adulthood.[7,17,19-24] A study assessing the BMIs of 84 patients undergoing laparoscopy for tubal sterilization or as a diagnostic procedure at 5-year intervals between ages 15 and 45 years reported a smaller body size in endometriosis patients.[17] A recent meta-analysis of 11 studies on the association between endometriosis and BMI found a pooled relative risk for endometriosis of 0.67 for every 5 kg/m^2.[22] Moreover, the Nurses' Health Study II cohort data showed an inverse association between BMI and endometriosis, which was stronger in women with infertility.[23] Previous studies' results are in line with our findings regarding adults. We found that lower weight and BMI at age 31 years were associated with a higher risk of endometriosis. The risk was 2% lower for each kilogram of weight and 6% lower for each BMI unit.

Although an association between BMI and endometriosis has been widely reported, data on adiposity distribution are scarce. Our results show a smaller WC and lower WHR among women with endometriosis at age 31 years and lower WHR at age 46 years, specifically in women with peritoneal endometriosis. Similarly, a pear-shaped body figure and concentration of adipose tissue below the waist have been associated with the condition.[17,20,23] Shah et al found that the risk of endometriosis in women with a WHR of less than 0.6 is almost three times higher than that in women with a WHR of 0.7-0.79.[23] McCann et al also reported an association between a low WHR and endometriosis, but only in women under the age of 30.[7]

Overall, in our study, women with endometriosis appeared to gain less weight up to age 31 years and to have a smaller WC and a lower WHR at reproductive age. This could be explained by the natural course of endometriosis, whose symptoms usually appear a few years after menarche, intensify during the years of fertility, and start to recede toward menopause. The persistent association between peritoneal endometriosis and a lean habitus at age 46 years indicates a possible independent role of endometriosis in weight development. Moreover, our subtype analysis supports the usefulness of endometriosis classification, as well as the existence of shared biological processes between endometriosis and adiposity.[8] It should be noted, however, that our study did not consider chronic pain and fatigue affecting eating patterns, long-term calorie intake, or nutrition quality, which may play a role in the association between body size and endometriosis.[25] We were not able to analyze eating patterns, because such data were not available for the NFBC1966. Moreover, as the differences in absolute body size measurements were small, the long-term health outcomes remain elusive.

The association between a leaner habitus and endometriosis raises questions regarding the underlying mechanism. A recent study exploring endometriosis in a mouse model showed reduced body weight and body fat. Interestingly, the difference in body weight and fat was associated with altered expression of genes related to liver metabolism and weight control.[26] Human studies have reported altered expression of metabolism-related hormones such as leptin, which is known to modulate food intake and appetite control, so directly correlating with adiposity.[27] Leptin has been suggested to trigger early development of endometriosis in inflammatory status, and a high concentration may promote angiogenesis.[28] Indeed, some studies have reported leptin overexpression in the serum, peritoneal fluid, and endometrioma of women with endometriosis.[28-30] Another potential mechanism could involve insulin-like growth factor 1 (IGF-1), which exerts anabolic effects and modulates glucose metabolism.[31] Evidence suggests that high IGF-1 levels in plasma and peritoneal fluid are associated with a higher risk of endometriosis.[32] Moreover, a cross-sectional analysis of the Nurses' Health Study II cohort found an inverse association between adult plasma levels of IGF-1 with body size at ages 5 and 10 years and BMI at age 18 years.[33] Further studies are warranted to elucidate the underlying mechanisms.

This study has several strengths. First, it analyzed a large set of population-based data with a homogeneous female population in terms of age, ethnicity, and access to health care. Second, it mostly included data obtained from measurements. Third, it used extensive national register data, including early life and gestational data. Fourth, it performed endometriosis subtype analyses. Overall, our data cover long-term development of weight and weight gain prospectively from birth to 46 years of age and waist and hip measurements in adulthood. Moreover, we included several covariates in our analysis. The self-reported endometriosis diagnosis may be considered a limitation. However, it has previously been validated from hospital records. Moreover, women also exhibited a typical endometriosis profile with regard to pain tolerance, infertility, parity, and oral contraceptive pill use.[9] A Swedish study concluded that self-reported diagnosis is moderately accurate, and its accuracy is even higher when additional information is available.[34] Another limitation is that as body size data at age 14 years were based on parents' reports, they may not be as accurate as the measurements taken by healthcare professionals. Further, a certain degree of selection bias for the study groups cannot be ruled out, although the participation rate of the total NFBC1966 population was high (at age 31 years, the questionnaire response rate was 81%, and the clinical examination participation rate was 77%; at age 46 years, the rates were 72% and 64%, respectively), and the participation rate in the follow-up data collection was equal in the two study groups. The study population homogeneity, although a strength in some respects, constitutes a limitation in other respects, as it limits the generalizability of the findings to other ethnicities or purely hospital-derived populations. Finally, this study found significant correlations but could not establish causation between endometriosis and body size.

5 | CONCLUSION

This study provides further evidence of the association between endometriosis and a smaller body size and lower adiposity, specifically in peritoneal endometriosis, in adulthood but not in childhood or adolescence. Our findings indicate significant differences between endometriosis subtypes, suggesting the importance of classification in endometriosis research. To elucidate the mechanism underlying the association between a lean body shape and peritoneal endometriosis, future studies should explore the direction of causality and investigate the role of factors affecting body size development, such as metabolism and nutrition.

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CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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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 Years

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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 years. Our data are 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 and maximal pain tolerance. The study population consisted of 284 women with endometriosis and 3,390 controls. Our results showed that at age 46 women with a history of endometriosis had a 5.3% lower pressure-pain threshold and 5.1% lower maximal pain tolerance 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; $P < .001$), and their pain was more troublesome and intense. The results were adjusted for body mass index, smoking, depressive/anxiety symptoms, education, and use of hormonal contraceptives. These unique data revealed an altered pain sensation and a greater likelihood of reporting musculoskeletal pain at age 46 years 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.**

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Perspective: ***This population-based cohort study showed decreased pain threshold and maximal pain tolerance in women with endometriosis in the late fertile age of 46 years. The pain was also found to be more bothersome and intense compared with controls.***

Key words: *Endometriosis, pain threshold, pain tolerance, premenopause.*

Endometriosis is an estrogen-dependent, chronic gynecological disorder associated with pelvic pain and infertility, with a prevalence of 6 to 10% in the general population.[6,7,12] Affected women experience dysmenorrhea, deep dyspareunia, dyschezia, and dysuria[12,35] associated with low quality of life.[8] The disorder is underdiagnosed or there is a delay in diagnosis in many cases leading to chronic pelvic pain (CPP).[7,26] Diagnosis is made using laparoscopy or laparotomy, where endometrial lesions are found in extrauterine locations, mainly the peritoneum and ovaries.[6,7,12] Because endometriosis is not curable, its treatments and therapies are targeted at infertility and symptom relief.[7,10] Endometriosis is also associated with other comorbid conditions such as fibromyalgia and chronic fatigue syndrome.[10,26] Moreover, it has a significant adverse effect on work productivity, social activity, family responsibilities, and daily life, resulting in a substantial economic burden on society.[10,28]

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, whereas others do not.[2] Depending on the study population, 30 to 70% of women with CPP have laparoscopic evidence of endometriosis.[19,32] The pain symptoms, however, are poorly correlated to the severity of endometriosis, and the pathophysiology of endometriosis-associated pain remains somewhat elusive.[9,13,21,23,34,35] 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.[3,18,21,30] Previous studies have shown increased pain sensitivity among women with endometriosis, with or without CPP, in response to mechanical stimuli compared with controls.[1] Furthermore, pain threshold studies have suggested hyperalgesia at extrapelvic sites, most likely due to peripheral and/or central sensitization mechanisms in affected women.[5,11,15,21,22]

Endometriosis is anticipated to subside in menopause, because 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 years.

Methods

Study Population

The study population originated from the Northern Finland Birth Cohort 1966 (http://www.oulu.fi/nfbc) which is a unique, large, prospective, longitudinal data set comprising all expected births in 1966 in the Northern Finland area (live-born children n = 12,058, female n = 5,889). 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 used 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 (5,123 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 2,774 (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 Fig 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 3,390 women (92%) reporting no endometriosis who were considered as controls (Fig 1).

Verification of Diagnosis

Self-reported diagnosis of endometriosis has only recently been described in the literature[24]; 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 (Supplementary Fig 1). 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 of 92 women (77.2 %) were diagnosed as having endometriosis, of whom 90.1% were established using laparoscopy/laparotomy. Fifteen women did not have a diagnosis of endometriosis and 6 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

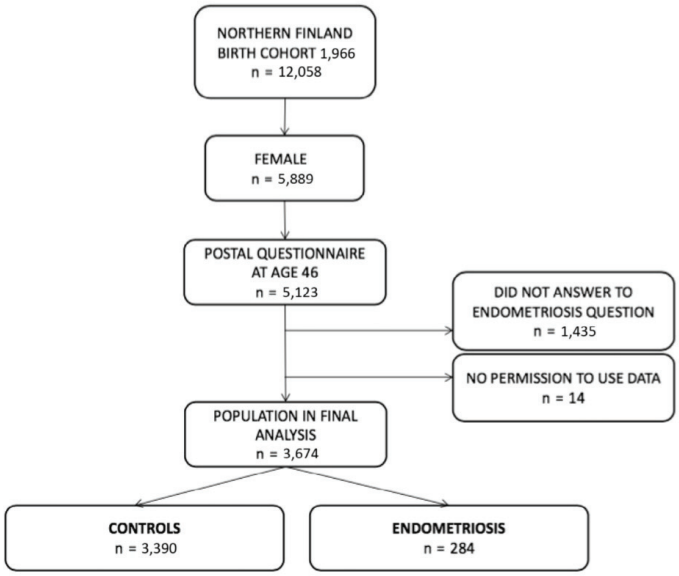

Figure 1. Flow chart showing the study population (endometriosis n = 284, controls n = 3,390) derived from Northern Finland Birth Cohort 1966.

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 and Maximal Pain Tolerance

Pain measurements were carried out in 2,470 controls and 234 women with endometriosis. A few of the 4 measurement-site readings were missing as a result of technical difficulties. Pressure-pain threshold (PPT) and maximal pain tolerance (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 1,200 kPa was reached. The PPT and MaxPTo measurements were taken at 4 anatomical sites in the following order: 1) shoulder; the midpoint of the upper trapezius muscle (subject in a prone position), 2) the midpoint of the tibialis

Table 1. Patient Characteristics in Women With Self-Reported Endometriosis and Controls at Age 46 Years According to Questionnaire Data

	Endometriosis (n = 284),* %	*Controls (n = 3,390)*,* %	P
Endometriosis diagnosis in the national hospital discharge registry	52.0	1.5	
Suffering from infertility	33.8	14.1	**< .001**
No delivery	13.9	9.8	**< .001**
One delivery	24.2	16.2	
More than 1 delivery	61.9	73.9	
Use of hormonal contraceptives			
Ever	93.3	89.2	**.033**
Current	20.2	27.1	**.028**
BMI			
<18.5	.8	.9	.676
18.5 to 24.999	48.5	45.4	
25 to 29.999	32.8	32.8	
≥30	17.8	20.9	
Smoking			
Ever	51.4	52.3	.804
Current	33.6	32.6	
Alcohol use			
Never	6.0	6.2	.603
Light (less than monthly)	11.7	11.7	
Moderate/heavy (at least once in a month)	76.3	77.7	
Education			
Basic	1.8	2.3	.072
Secondary	50.7	57.1	
Tertiary	47.5	40.6	

NOTE. Values in bold P <0.05.
*n varies in some of the variables because of missing questionnaire data.

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 to prevent sensitization of nociceptors at the contact site. The highest value of the 2 measurements was used in the analysis to avoid overestimating pain threshold or tolerance. In addition, mean PPT and MaxPTo values at the 4 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 to 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 to 7 days, 3) 8 to 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 using a numerical rating scale of 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 have you experienced?" We divided the women according to parity into 3 groups: no delivery, 1 delivery, or more than 1 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)?"

Body Mass Index

Height and weight were self-reported and measured at 46 years. In the clinical examinations, participants' weight (in kilograms) was measured with a digital scale, which was calibrated regularly. Height (in centimeters) was measured twice using a standard calibrated stadiometer. Body mass index (BMI) was calculated using measured height (average of 2 measurements) and weight. Self-reported values were used if measured data were 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 2 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 lifelong 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 3 ways: 1) never, 2) light, and 3) moderate or heavy use (women >20 g/d).

Education

Education was classified into 3 groups according to the number of years of education: 9 years, 9 to 12 years, and more than 12 years.

Anxiety and Depressive Symptoms

Anxiety and depressive symptoms were assessed at 46 years of age via the 25-item Hopkins Symptom Checklist.[20,33] The Hopkins Symptom Checklist 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 cutoff point of 1.55 was used to pinpoint anxiety and depression symptoms.[33]

Statistical Analyses

A Tobit regression model[31] 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 1,200 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.

χ^2 Tests were used to analyze the associations between the distribution and numbers of pain sites, and analysis of variance 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 (The R Foundation for Statistical Computing, Vienna, Austria), using the AER package for Tobit regression.

Results

The prevalence of self-reported endometriosis was 8% and verification of the diagnosis was carried out by examining the hospital records (Supplementary Fig 1). 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 years is shown in Fig 2. Self-reported endometriosis was associated with statistically significant decreases in PPT ($P < .05$, Fig 2A) as well as MaxPTo ($P < .001$, 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 to –9.5%]) pain threshold compared with controls ($P < .05$). As for the measurement site, PPT measured at the wrist was significantly lower in women reporting endometriosis (–37.5 kPa, $P < .05$, 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 ($P < .01$). There were no statistically significant effects of BMI, anxiety, smoking, or current or previous contraceptive use on pain threshold measured at the wrist.

MaxPTo was on average –48.2 kPa lower (–5.1% [–2.2 to –8.1%]) among women with endometriosis ($P < .001$, 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, $P < .001$), wrist (–58.2 kPa), shoulder (–53.4 kPa), lower back (–58.0 kPa), and leg (–46.8 kPa).The most significant contributors besides endometriosis that lowered MaxPTo were anxiety, depression, and current smoking status (–29.7 kPa, –28.5 kPa, and –34.2 kPa, respectively; $P < .05$, Fig 2).

The women were also screened for number of musculoskeletal pain sites (0, 1, 2, 3, 4, or 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%, $P < .001$, Fig 3). Overall, the women with endometriosis also reported

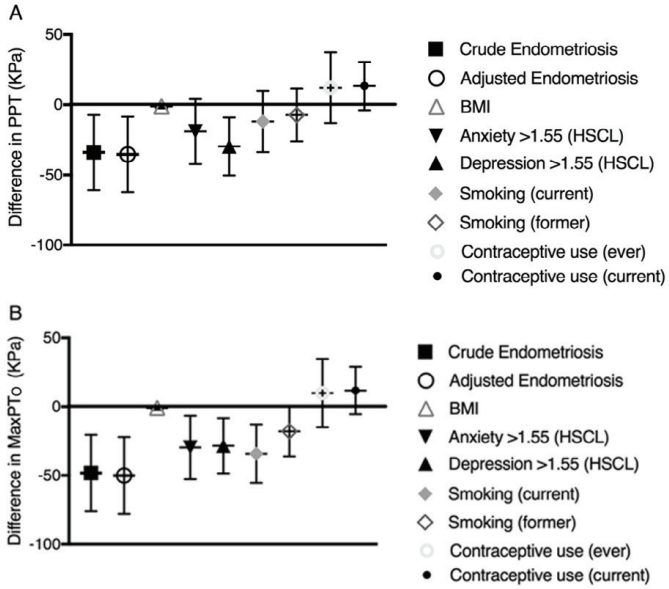

Figure 2. Pain perception in women according to different conditions/confounders at age 46 years. The horizontal reference line reflects the whole study population. Self-reported endometriosis appeared to result in decreases in (**A**) PPT ($P < .05$), as well as (**B**) MaxPTo ($P < .001$) compared with the effect of BMI and contraceptive use at any time. HSCL, Hopkins Symptom Checklist.

Table 2. Tobit Regression Analysis of PPT and MaxPTo in Women With Endometriosis Compared With Controls

		Location of Pressure Pain Measurement			
	Average	Wrist	Shoulder	Lower Back	Leg
Total observations, n	2,609	2,730	2,747	2,635	2,738
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 to –7.3)**	**–37.5 (–67.3 to –7.7)**	–27.8 (–58.9 to 3.2)	–26.9 (–63.0 to 9.1)	–29.9 (–63.5 to 3.7)
Difference, %†	**–5.3% (–1.1,–9.5)**	**–5.8% (–1.2 to –10.4)**	–4.8% (.5 to –10.1)	–3.8% (1.3 to –8.9)	–4.7% (.6 to –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 to –8.6)**	**–36.4 (–66.3 to –6.6)**	–25.7 (–56.5 to 5.0)	–33.8 (–69.5 to 2.0)	–31.3 (–65.0 to 2.3)
Difference, %†	**–5.5% (–1.3 to –9.6)**	**–5.6% (–1.0 to –10.2)**	–4.3% (.8 to –9.4)	–4.9% (.3 to –10.1)	–4.8% (.4 to –10.0)
Constant MaxPTo (crude)	939.9 (932.0–947.9)	932.2 (922.5–941.8)	957.8 (946.2–969.4)	1,031.3 (1,018.9–1,043.8)	941.4 (989.1–1,069.1)
Endometriosis MaxPTo (crude)	**–48.2 (–76.1 to –20.4)**	**–58.1 (–90.6 to –25.6)**	**–55.4 (–93.1 to –17.7)**	**–50.6 (–91.0 to –10.2)**	**–43.7 (–81.0 to –6.3)**
Difference, %†	**–5.1% (–2.2 to –8.1)**	**–6.2% (–2.7 to –9.7)**	**–5.8% (–1.8 to –9.7)**	**–4.9% (–1.0 to –8.8)**	**–4.6% (–.7 to –8.6)**
Constant MaxPTo (adjusted)‡	952.7 (928.2–977.3)	930.8 (901.7–960.0)	997.5 (962.2–1,032.7)	1,029.1 (989.1–1,069.1)	953.2 (917.4–989.0)
Endometriosis MaxPTo (adjusted)‡	**–50.1 (–78.0 to –22.2)**	**–58.2 (–90.8 to –25.6)**	**–53.4 (–90.7 to –16.2)**	**–58.0 (–97.8 to –18.1)**	**–46.8 (–84.2 to –9.5)**
Difference, %†	**–5.3% (–2.3 to –8.2)**	**–6.3% (–2.8 to –9.8)**	**–5.4% (–1.6 to –9.1)**	**–5.6% (–1.8 to –9.5)**	**–4.9% (–1.0 to –8.8)**

Abbreviation: CI, confidence interval.
NOTE. Data are presented as kPa (95% CI), except where otherwise noted. Values in bold P <0.05.
*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.
‡Adjusted for BMI, anxiety and depressive symptoms, smoking, and use of hormonal contraceptives.

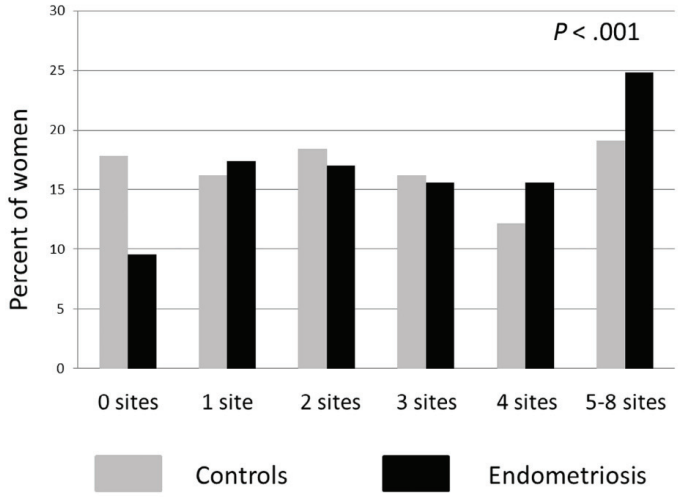

Figure 3. The numbers of reported pain sites in women with endometriosis (black) and in controls (gray) at age 46. Percentages of women experiencing 0, 1, 2, 3, 4 or 5–8 pain sites per year. Fewer women with endometriosis (black bars) reported having no pain sites compared with controls (gray bars) ($P < .001$). The numbers of pain sites were increased in women with endometriosis compared with controls ($P < .001$).

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%, $P < .001$, Fig 3).

As for pain troublesomeness, endometriosis was associated with slightly more troublesome pain at work and during leisure time and sleep ($P = .01$, $P = .02$, $P = .04$ respectively, Fig 4A). After adjusting pain troublesomeness for smoking, BMI, depression, anxiety, and contraceptive use it was still significant during work ($P = .04$) whereas the significance was abolished for pain troublesomeness during leisure time and sleep ($P = .05$, $P = .06$, Fig 4A). Adjusted overall pain intensity was also greater among women with endometriosis versus controls ($P = .03$, Fig 4B).

Discussion

To our knowledge, 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.

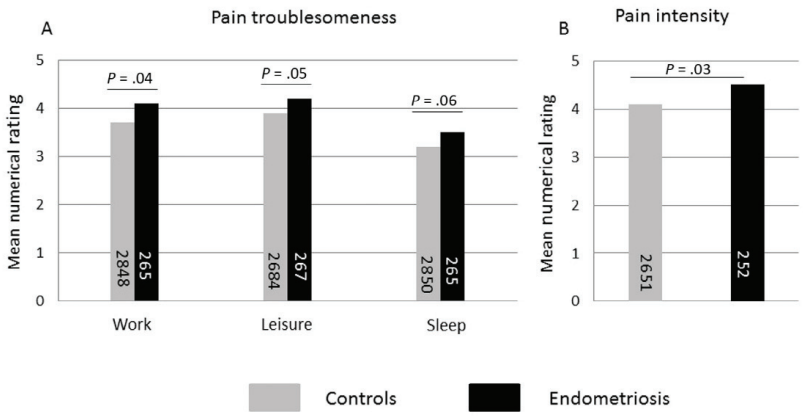

Figure 4. Pain (**A**) troublesomeness and (**B**) intensity in women with endometriosis and in controls at age 46 years. (**A**) The mean pain troublesomeness score was increased in women with endometriosis (black bars) compared with controls (gray bars) at work. A similar trend was seen during leisure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

Our data show a lower PPT and lower MaxPTo among 46-year-old women with a history of endometriosis compared with controls in a population-based study setting. The data add to the body of evidence in the literature showing altered pain sensitivity in endometriosis. Previous studies have been in hospital-related populations.[1,2,4,11] 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 PPT and the MaxPTo were anxiety, depression, and current smoking status. It is worth noting, therefore, that depression has been previously shown to be associated with altered pain perception[14] and interestingly, musculoskeletal pain responses are particularly increased among women with coexpressing endometriosis and anxiety or depression symptoms.[29] Interestingly, past as well as 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.[36] Whether menopause solves the endometriosis-related altered pain responses or makes them worse remains to be evaluated in future studies because 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.[1] Visceral hypersensitivity testing also revealed lower pain thresholds among women with endometriosis in a rectal balloon dilation test[17] 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 PPTs 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.[22] A population-based study carried out by Slater et al, with musculoskeletal pain response testing similar to that used in the present study, showed decreased pain thresholds in women experiencing severe menstrual pain.[27] Because approximately 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.[21] Whether the women with CPP are the ones who also have altered pain perception during late reproductive years remains to be investigated because dysmenorrhea or pelvic pain were not included in the present data.

Women with endometriosis reported more pain sites, and graded pain to be more bothersome and intense compared with controls. This might be because of central and/or peripheral sensitization, which has been shown to result from prolonged noxious pain stimulation sustaining central pain stimulation in these cases.[16,29] Indeed, women with endometriosis have reported increased regional hyperalgesia and allodynia.[29] 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 the pain regulatory system among affected women.[3,29] All in all, delayed diagnosis and prolonged pain sensations may bring about altered pain sensitization among women with endometriosis.

There are several strengths but also some limitations in the present work. To our knowledge, this is the first population-based study carried out to investigate pain perception/sensitivity related to a history of endometriosis in women of late reproductive age. Women with endometriosis were identified from a unique, large population-based data set of homogeneous ethnicity and age and with the possibility to adjust for several confounding factors. The data included objective pain measurements as well as subjective questionnaire data. Moreover, the data collection did not specifically target endometriosis patients or patients only treated in hospitals. Hence, the questionnaires and clinical measurements were carried out in the whole cohort, with minimal self-aware bias. The study also has limitations, which include self-reported endometriosis diagnosis and lack of data on clinical symptoms of endometriosis; thus it is possible that the control group also included women with endometriosis, albeit with milder pain symptoms/sensitivity. However, the control group in the present data set was fairly large and such cases would have been diluted among the controls. Moreover, studies on endometriosis commonly concern only laparoscopically verified cases, and thus women with endometriosis with fewer pain symptoms are most likely under-represented in these studies. The self-reported diagnoses of endometriosis may also be considered as a limitation, although, the diagnosis was validated from the patient records available and from the national hospital discharge register. In a recent study by Saha et al, similar results were presented when self-reported endometriosis diagnoses were verified from patient records.[24] This was further supported by a recent study validating self-reported endometriosis diagnosis in a Swedish national twin registry.[25] 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

procedure is not justified and thus the diagnosis remains clinical. Although our measurements showed statistically significant 5% decreases in PPT and MaxPTo 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 because of lack of available data, thus these aspects remain to be evaluated in future studies.

Conclusions

To our knowledge, this is the first population-based study showing a decreased PPT and a decreased MaxPTo 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 years underlines the fact that endometriosis may have a long-term footprint with regard to 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 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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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpain.2018.02.005.

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III

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

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Abstract

STUDY QUESTION: Is there an association between endometriosis and non-gynecologic diseases in the general female population by age 50?

SUMMARY ANSWER: Women with endometriosis are at a higher risk of several chronic diseases.

WHAT IS KNOWN ALREADY: Chronic inflammation and immune response abnormalities have been identified as possible predisposing factors in the pathogenesis of endometriosis and may act as links to endometriosis-related comorbidities. Previous studies have investigated overall morbidity in women with endometriosis, showing significant associations between endometriosis and several diseases. However, these studies are limited in number and lack population-based approaches to analyzing confounding factors, temporality and subtypes of endometriosis.

STUDY DESIGN, SIZE, DURATION: This is a prospective cohort study of the Northern Finland Birth Cohort 1966, which is a general population–based cohort consisting of 96.3% of all expected births during 1966 in the Northern Finland area. A total of 349 women with endometriosis and 3499 women without endometriosis were identified. The analyzed data spanned the participants' lives up to the age of 50.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Endometriosis case identification was based on 1) national register data and 2) self-reported diagnoses. ICD diagnosis codes from the period 1968–2016 were collected from the Care Register for Health Care, and self-reported lifetime allergic, infectious, and autoimmune symptoms and continuous medication usage data were collected from questionnaires distributed at age 46. The associations between endometriosis and comorbidities were assessed using logistic regression models that included several covariates. Subtype and temporal analyses were also performed.

MAIN RESULTS AND THE ROLE OF CHANCE: Women with endometriosis were on average twice as likely to have non-gynecologic diagnoses as women without endometriosis (aOR 2.37, 95% CI 1.03–5.44). Endometriosis was most strongly associated with allergies, infectious diseases, pain-causing diseases, and respiratory diseases. Moreover, it was associated with nonspecific symptoms and signs (aOR 3.56, 95% CI 2.73–4.64), especially abdominal and pelvic pain (aOR 4.33, 95% CI 3.13–4.76). These diagnoses accumulated in endometriotic women at a significantly younger age than in women without endometriosis and thus may be related to a delay in endometriosis diagnosis.

LIMITATIONS, REASONS FOR CAUTION: The lack of surgical confirmation of endometriosis could be considered a limitation. As our data extended up to the age of 50 years, the possibility of identifying associations between endometriosis and diseases developing at an older age was limited.
WIDER IMPLICATIONS OF THE FINDINGS: Women with endometriosis have a higher risk of several chronic diseases than women without endometriosis and should be given more attention and targeted resources in health care systems. Moreover, endometriosis should be considered in the presence of nonspecific symptoms and abdominal pain, as they may conceal the disease and cause a delay in its diagnosis and treatment.

Keywords: endometriosis, comorbidity, immunological diseases, pain causing disease, diagnostic delay

1 Introduction

Endometriosis is a chronic estrogen-dependent disorder affecting 6–10% of fertile-aged women. It may cause dysmenorrhea, chronic abdominal/pelvic pain, and infertility (Bulun *et al.*, 2019, Zondervan *et al.*, 2020). The etiology of endometriosis is multifactorial, including genetic, environmental, and lifestyle components (Backonja *et al.*, 2017, Saha, Kuja-Halkola *et al.*, 2017). Abnormalities in steroidogenesis, immune response, angiogenesis, inflammation, and apoptosis have been identified as possible predisposing factors in the pathogenesis of endometriosis and may act as links to endometriosis-related comorbidities (Bulun *et al.*, 2019).

The symptoms of endometriosis can be nonspecific and overlap with gastrointestinal and pelvic pain–related diseases, resulting in misdiagnoses and diagnostic delays. Normalization of endometriosis-related symptoms is another main cause of diagnostic delay besides misdiagnosis (Hudelist *et al.*, 2012). Even though the onset of the symptoms may occur soon after menarche, several studies have reported a diagnostic delay of seven to nine years, which results in impaired quality of life (Ghai et al., 2019, Hudelist et al., 2012, Marinho et al., 2018). Moreover, women with endometriosis have several health service contacts before endometriosis diagnosis is established, and patients with longer diagnostic delays accumulate more comorbid diagnoses, which causes heavy social and economic burdens (Epstein et al., 2017, Surrey, E. et al., 2020, Surrey, E. S. et al., 2018).

Endometriosis has been shown to be associated with an increased risk of non-gynecologic comorbidities, such as autoimmune diseases (Nielsen et al., 2011, Shigesi et al., 2019), bowel diseases (Saidi et al., 2020), migraine (Ferrero et al., 2004), mental diseases (Gao et al., 2020), and cardiovascular diseases (Mu et al., 2016). However, only few studies have systematically assessed overall comorbidity in this female population (Choi et al., 2017, Kvaskoff et al., 2015, Parazzini et al., 2017, Teng et al., 2016) and studies have limitations to considering confounding factors, temporality of comorbidities and the effect of endometriosis subtype on morbidity.

The aim of this study was to systemically investigate the prevalence and association of non-gynecologic diagnoses and comorbidities in women with endometriosis using a prospective population-based data set. A subtype analysis and temporal analysis of the accumulation of diagnoses was also performed.

2 Material and methods

Study population

This study was based on the Northern Finland Birth Cohort 1966 (NFBC1966), a population-based birth cohort consisting of 96.3% of all expected births during 1966 in Northern Finland (12 055 mothers, 12 058 live born children, of whom 5889 females, all Finnish Caucasian). This study analyzed the NFBC1966 data collected at the age of 46 years via postal questionnaires and/or clinical examinations (https://www.oulu.fi/nfbc/1966datacollections).

Identification of Women with Endometriosis

Women with endometriosis were identified using two different sources as previously described (Rossi *et al.*, 2021): 1) Endometriosis diagnoses were retrieved from the Care Register for Health Care (CRHC), in which endometriosis cases were identified based on the International Classification of Diseases (ICD) codes 8, 9, and 10 (ICD-8/9: 617.1–617.9; ICD-10: N80.1–N80.9). 2) Given that not all endometriosis diagnoses are hospital-based, further endometriosis case identification was based on self-reported data. At age 46, the women were asked, "Have you ever been diagnosed with endometriosis by a physician?" The self-reported endometriosis diagnosis has been validated previously (Vuontisjärvi *et al.*, 2018). The total endometriosis population consisted of 349 women (ICD-based $n = 224$ and/or self-reported $n = 284$). The dropout rate was similar in the two groups (2.0% vs. 2.2%). For secondary analysis, the ICD-coded endometriosis group was divided into the following subcategories: 59 (26%) peritoneal endometriosis (N80.2 and N80.3), 107 (48%) ovarian endometriosis (N80.1), 35 (16%) deep infiltrating endometriosis (N80.4, N80.5, and N80.8) and other endometriosis 23 (10%). Women who did not have an ICD code for endometriosis and replied "no" to the endometriosis question were considered women without endometriosis ($n = 3499$). A flow chart of the study population is shown in Fig. 1.

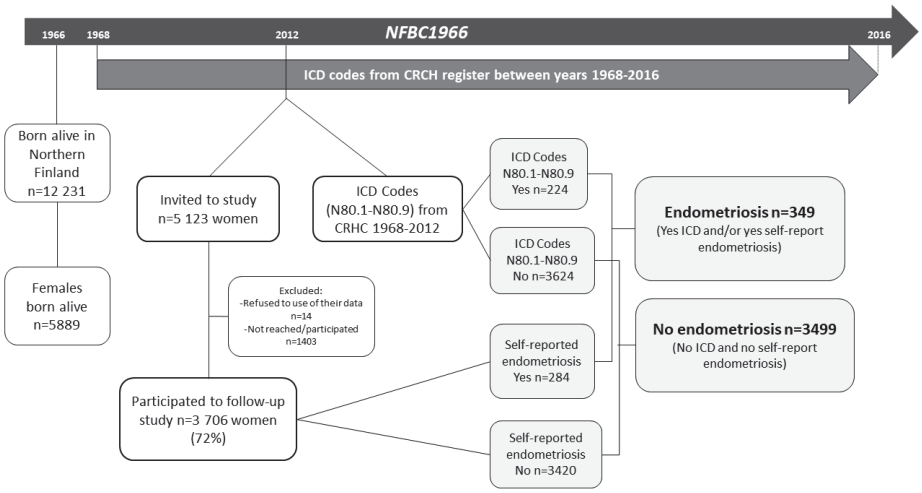

Fig. 1. Flowchart of the data collection and study population. The population of women with endometriosis and women without endometriosis formed in the Northern Finland Birth Cohort 1966 for the present study are marked in light grey.

Comorbidity assessment using national hospital discharge register ICD-code data

The Finnish national CRCH systematically collects data from all patient encounters within the Finnish health care system. The register includes diagnoses according to the World Health Organization's (WHO) ICD codes and dates for each inpatient hospital visit. In the Finnish health care system, ICD codes are used primarily for clinical diagnoses and health surveillance and secondarily for municipal billing. The ICD codes are set by the clinicians discharging the patients. The codes are chosen based on their clinical relevance to the particular hospital visit. Thus, the disease diagnoses are considered accurate and reliable and are part of the national registers that are widely used both in guiding national health care policies and in research (Sund, 2012). The NFBC1966 population was linked to the CRHC using the personal identification code given to each Finnish citizen at birth. Data were available and collected for the period 1968–2016. Diagnosis codes related to genitourinary system diseases (N00–N99) and pregnancy, childbirth, and the puerperium (O00–O94) were excluded from the analysis since they concern

gynecologic morbidity. The ICD codes were divided into main categories and subcategories according to the WHO classification. The main all ICD-10 main and subcategories were analyzed, and certain subcategories of ICD codes were reported in more detail based on the results of the analysis and the existing literature. ICD-8 and ICD-9 codes were converted to ICD-10 codes and included in the analysis as such. The lifetime accumulation of any ICD codes was analyzed to assess the overall morbidity of women with endometriosis.

Self-reported allergic, infectious and autoimmune symptoms and regular medication usage

In the Finnish health care system, allergies and autoimmune symptoms are mainly diagnosed and treated in outpatient clinics and are therefore not obtainable from the CRCH. Thus, self-reported lifetime allergic, infectious, and autoimmune symptoms were collected from the 46-year questionnaires to expand the data. Continuous medication use data were also collected from the questionnaires. The medication data were organized according to the WHO Anatomical Therapeutic Chemical Classification (ATC) system.

Covariates

Several possible confounding variables were considered for associations with endometriosis or morbidities according to the literature: parity and lifetime contraceptive use, body mass index (BMI), smoking, alcohol consumption, physical activity, socioeconomic status, and relationship status. More detailed description of covariates can be found in our earlier studies (Rossi *et al.*, 2021). In short, parity was based on questionnaires and classified as 0, 1–2, and 3 or more. The respondents were asked if they had ever used hormonal contraceptives. Weight and height were measured during 46 year follow-up visit, and BMI was calculated according to these measurements (kg/m^2). The respondents were categorized as nonsmokers, former/occasional smokers, and active smokers. In terms of alcohol consumption, the respondents were classified as abstainers, low-risk drinkers (≤20 g/day), and high-risk drinkers (>20 g/day). Physical activity was calculated as the metabolic equivalent of task (MET) scores in hours per week, considering the frequency and duration of leisure activities (3 METs = light and 5 METs = brisk physical activity). Educational status was categorized into basic (basic or vocational school), secondary (college degree), and tertiary (polytechnic or

university degree). Relationship status was classified as “in a relationship” in the case of self-reported marriage or cohabitation.

Statistical methods

The results of categorical variables were calculated as frequencies and continuous variables were calculated as means with standard deviations (SD). Differences in categorical variables between the study and reference groups were analyzed using Pearson’s χ^2 test. Differences in continuous variable were analyzed using the independent samples t-test. A two-sided *p*-value of less than 0.05 was considered statistically significant. The association between endometriosis and non-gynecologic diagnoses, self-reported symptoms and continuous medication use among women with and without endometriosis were analyzed using a binary logistic regression model. Previously mentioned confounding factors were included in multivariate analysis models. The results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). Benjamini-Hochberg correction was performed to minimize the risk of type I error. Finally, Kaplan-Meier survival analysis (Mantel-Cox estimate) was used to estimate ICD code accumulation in women with and without endometriosis until 2016, when the cohort participants turned 50. These analyses were performed using IBM SPSS Statistics version 24 for Windows and graphs were created using GraphPad Prism version 7.03.

Ethical approval

The NFBC1966 follows the principles of the Declaration of Helsinki and has obtained approval from the Ethics Committee of the Northern Ostrobothnia Hospital District. All participants provided informed consent.

3 RESULTS

The characteristics of the study population are shown in Table I.

Table 1. Characteristics of study population at age 46 years.

Character	No endometriosis n = 3 499	Women with endometriosis n = 349	p-value
	n/mean (%/SD)	n/mean (%/SD)	
Contraception use (ever)	**2 958 (89.2%)**	**299 (93.2%)**	**0.023**
Parity			
0	**303 (9.7%)**	**42 (13.8%)**	
1–2	**1 696 (54.5%)**	**174 (57.0%)**	**0.017**
> 3	**1 111 (35.7%)**	**89 (29.2%)**	
BMI	26.5 (5.3)	26.0 (5.1)	0.113
Smoking			
Non-smoker	1 886 (53.9%)	203 (58.2%)	
Former / occasional	807 (23.1%)	69 (19.8%)	0.419
Smoker	635 (18.1%)	62 (17.8%)	
Alcohol consumption			
Abstainer	383 (11.4%)	46 (13.5%)	
Low-risk drinker	2 707 (80.7%)	274 (80.6%)	0.250
At risk drinker	264 (7.9%)	20 (5.9%)	
Physical activity			
Low	746 (22.2%)	65 (19.2%)	
Moderate	1 376 (41.0%)	150 (44.2%)	0.351
High	1 232 (36.7%)	124 (36.6%)	
Marital status			
Single	784 (22.4%)	70 (20.1%)	0.314
In a relationship	2 715 (77.6%)	279 (79.9%)	
Education			
Basic	210 (6.2%)	15 (4.4%)	
Secondary	2 148 (63.8%)	208 (61.4%)	0.152
Tertiary	1 010 (30.0%)	116 (34.2%)	

Data reported as mean (SD) or percentages (n). Significance tests for continuous variables were performed by using the independent samples t-test or the Mann–Whitney U test, as appropriate. P-value < 0.05 was considered significant. Differences in numbers vary in different analyses as a result of some missing data. P-values are for women with endometriosis compared with control women.

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

ICD diagnoses from CRCH

Women with endometriosis had an average over two-fold overall odds of non-gynecologic diagnoses compared to women without endometriosis and the finding persisted after adjustments (crude OR 3.43, 95% CI 1.51–7.78, adjusted OR 2.37, 95% CI 1.03–5.44) (Figure 2). Women with endometriosis were twice as likely to have non-gynecologic diagnoses as women without endometriosis (adjusted OR 2.37, 95% CI 1.03–5.44) (Fig. 2).

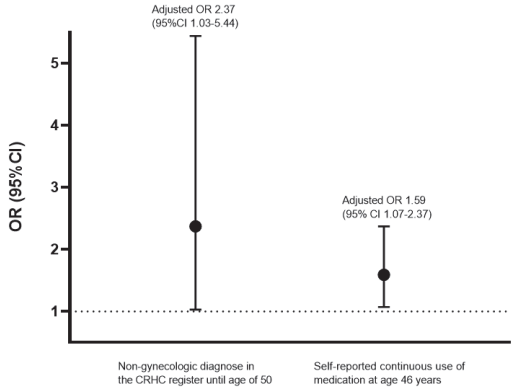

Fig. 2. Association between endometriosis and a) overall morbidity, b) use of medication.

Women with endometriosis had a significantly higher rate of diagnoses according to the ICD-10 codes in several main ICD categories (Table II). In subcategory analysis, the multivariate model showed that endometriosis was significantly associated with the following diagnoses (in order from the strongest to the weakest association): more than twofold odds of "nonspecific symptoms, signs, and clinical findings (R00-R99)" (aOR 2.57, 95% CI 1.81–3.65), especially "abdominal and

pelvic pain (R10)" (aOR 4.33, 95% CI 3.13–6.00); pain-related diagnoses, such as "migraine (G43)" (aOR 2.11, 95% CI 1.34–3.33) and "dorsopathies (M40-M54)" (aOR 1.56, 95% CI 1.16–2.10); nearly twofold odds of "mood disorders (F30-F39)" (aOR 1.86, 95% CI 1.20–2.88), "neoplasms (C00-D48)" (aOR 1.66, 95% CI 1.20–2.30), "infectious diseases (A00-B99)" (aOR 1.65, 95% CI 1.14–2.40), especially "other viral diseases (A25-B34)" (aOR 3.24, 95% CI 1.27–8.27); and "respiratory diseases (J00-J99)" (aOR 1.46, 95% CI 1.06–2.00) and "diseases of the digestive system (K00-K93)" (aOR 1.42, 95% CI 1.04–1.95), especially "diseases of the esophagus, stomach, and duodenum (K20-K31)" (aOR 2.23, 95% CI 1.52–3.27) (Table II).

Table 2. Association between endometriosis and different ICD codes from the Care Register for Health Care.

ICD code	No endometriosis n = 3 499 n (%)	Endometriosis n = 349 n (%)	p-value*	Univariate OR (CI 95%)	Multivariate OR (CI 95%)
Certain infectious and parasitic diseases (A00–B99)	609 (17.4%)	85 (24.4%)	**0.003**	1.53 (1.18–1.98)	1.65 (1.14–2.40)
A00–A09 Intestinal infectious diseases	217 (6.3%)	39 (11.2%)	**0.003**	1.89 (1.32–2.71)	1.61 (1.03–2.52)
B25–B34 Other viral diseases	30 (0.9%)	9 (2.6%)	**0.006**	3.04 (1.43–6.46)	3.24 (1.27–8.27)
Neoplasms C00–D48	948 (27.1%)	156 (44.7%)	**0.006**	2.18 (1.74–2.72)	1.66 (1.20–2.30)
C50–C50 Malignant neoplasm of breast	64 (1.9%)	14 (4%)	**0.012**	2.30 (1.24–4.02)	1.85 (0.85–4.01)
D10–D36 Benign neoplasms	745 (21.6%)	128 (36.9%)	**0.003**	2.13 (1.69–2.69)	1.96 (1.48–2.59)
D25 Leiomyoma of uterus	319 (9.2%)	74 (21.3%)	**0.002**	2.67 (2.01–3.53)	2.17 (1.54–3.08)
D37–D48 Neoplasms of uncertain or unknown behavior	177 (5.1%)	21 (8.4%)	**0.021**	1.69 (1.12–2.54)	1.74 (1.09–2.78)
D39 Neoplasm of uncertain behavior of female genital organs	33 (1.0%)	12 (3.5%)	**0.001**	3.72 (1.90–7.26)	4.15 (1.87–9.18)
Diseases of the blood and blood-forming organs and disorders involving the immune mechanism D50–D89	247 (7.1%)	33 (9.5%)	0.13	1.38 (0.94–2.01))	1.79 (1.07–2.99)
D65–D69Coagulation defects, purpura and other haemorrhagic conditions	32 (0.9%)	8 (2.3%)	**0.026**	2.53 (1.16–5.53)	3.78 (1.55–9.20)
Endocrine, nutritional and metabolic diseases E00–E90	411 (11.7%)	41 (11.7%)	1.00	1.00 (0.71–1.41)	1.09 (0.67–1.78)
Mental and behavioural disorders F00–F99	469 (13.4%)	59 (16.9%)	0.091	1.31 (0.98–1.77	1.55 (1.01–2.38)
F30–F39 Mood [affective] disorders	227 (6.6%)	33 (9.5%)	0.055	1.50 (1.02–2.19)	1.86 (1.20–2.88)

ICD code	No endometriosis n = 3 499 n (%)	Endometriosis n = 349 n (%)	p-value*	Univariate OR (CI 95%)	Multivariate OR (CI 95%)
Diseases of the nervous system, eye, ear G00–H95	1 446 (41.3%)	159 (45.6%)	0.147	1.19 (0.95–1.48)	1.19 (0.87–1.63)
G40–G47 Episodic and paroxysmal disorders	445 (12.9%)	58 (16.7%)	0.06	1.36 (1.01–1.83)	1.47 (1.03–2.09)
G43 Migraine	165 (4.8%)	28 (8.1%)	**0.015**	1.71 (1.15–2.66)	2.11 (1.34–3.33)
G43.0 Migraine with aura	337 (9.0%)	10 (14.5%)	0.141	1.71 (0.87–3.7)	1.99 (0.95–4.16)
G43.1 Migraine without aura	337 (9.1%)	10 (11.9%)	0.384	1.36 (0.69–2.65)	1.55 (0.75–3.18)
Diseases of the circulatory system I00–I99	890 (25.4%)	86 (24.9%)	0.759	0.96 (0.74–1.24)	0.96 (0.66–1.37)
Diseases of the respiratory system J00–J99	1 351 (38.6%)	167 (47.9%)	**0.003**	1.46 (1.17–1.82)	1.46 (1.06–2.00)
J00–J06 Acute upper respiratory infections	375 (10.8%)	50 (14.4%)	0.06	1.38 (1.01–1.90)	1.34 (0.92–1.95)
J60–J70 Lung diseases due to external agents	383 (11.1%)	61 (17.6%)	**0.001**	1.71 (1.27–2.30)	1.63 (1.14–2.32)
Diseases of the digestive system K00–K93	1 352 (38.6%)	147 (42.1%)	0.228	1.16 (0.93–1.45)	1.42 (1.04–1.95)
K20–K31 Diseases of oesophagus, stomach and duodenum	279 (7.3%)	46 (13.3%)	**0.001**	1.78 (1.28–2.49)	2.23 (1.52–3.27)
K55–K64 Other diseases of intestines	279 (8.1%)	38 (11.0%)	0.081	1.40 (0.98–2.01)	1.07 (0.61–1.84)
K58 Irritable bowel syndrome	62 (1.8%)	13 (3.7%)	**0.023**	2.13 (1.16–3.92)	1.89 (0.91–3.93)
Diseases of the skin and subcutaneous tissue L00–L99	628 (17.9%)	72 (20.6%)	0.236	1.19 (0.90–1.56)	1.40 (0.96–2.04)
Diseases of the musculoskeletal system and connective tissue M00–M99	1 552 (44.4%)	185 (53.0%)	**0.005**	1.42 (1.14–1.76)	1.29 (0.94–1.78)
M00–M25 Arthropathies	801 (23.2%)	98 (28.2%)	**0.05**	1.31 (1.02–1.67)	1.27 (0.95–1.71)
M40–M54 Dorsopathies	720 (20.8%)	94 (27.1%)	**0.014**	1.41 (1.10–1.82)	1.56 (1.16–2.10)
M50 Cervical disc disorders	79 (2.3%)	15 (4.3%)	**0.031**	1.93 (1.10–3.39)	1.87 (0.81–4.31)
M60–M79 Soft tissue disorders	636 (18.4%)	81 (23.3%)	**0.038**	1.35 (1.04–1.76)	1.35 (0.98–1.86)
M79 Other and unspecified soft tissue disorders, not elsewhere classified	219 (6.3%)	29 (8.4%)	0.167	1.35 (0.90–2.02)	1.47 (0.92–2.36)

ICD code	No endometriosis n = 3 499 n (%)	Endometriosis n = 349 n (%)	p-value*	Univariate OR (CI 95%)	Multivariate OR (CI 95%)
M80–M94 Osteopathies and chondropathies	94 (2.7%)	16 (4.6%)	0.059	1.73 (1.01–2.97)	1.91 (0.98–3.70)
Congenital malformations, deformations and chromosomal abnormalities Q00–Q99	280 (8.0%)	22 (6.3%)	0.276	0.77 (0.49–1.21)	0.35 (0.15–0.82)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified R00–R99	1 809 (51.7%)	251 (71.9%)	**< 0.001**	2.39 (1.88–3.05)	2.57 (1.81–3.65)
R10–R19 Symptoms and signs involving the digestive system and abdomen	815 (23.6%)	182 (52.4%)	**< 0.001**	3.58 (2.86–4.48)	3.56 (2.73–4.64)
R10 Abdominal and pelvic pain	738 (21.3%)	175 (50.4%)	**< 0.001**	3.75 (2.99–4.70)	4.33 (3.13–6.00)
R50–R69General symptoms and signs	370 (10.7%)	65 (18.7%)	**< 0.001**	1.92 (1.44–2.57)	2.29 (1.64–3.98)
Injury, poisoning and certain other consequencesof external causes S00–T98	1 360 (38.9%)	155 (44.4%)	0.06	1.26 (1.01–1.57)	1.13 (0.82–1.57)

Data reported as numbers (percentages)

Two-sided p-value < 0.05 was considered significant. Significant p-values marked with bold

p* values corrected with Benjamini-Hochberg

In multivariate analysis: lifetime contraceptive use, parity, bmi, alcohol, smoking, educational status, marital status, physical activity

Temporal analysis showed that endometriosis diagnoses started to accumulate after the age of 25 years, and abdominal pain diagnoses started to accumulate around 10 years later, at age 35 (Fig. 3a). There were no differences between the study groups in terms of any ICD code accumulation age (Fig. 3b). However, there was an earlier accumulation of diagnoses related to "symptoms, signs, and abnormal clinical and laboratory findings (R00–R99)", and especially "abdominal and pelvic pain (R10)", in women with than without endometriosis (Fig. 3c and d).

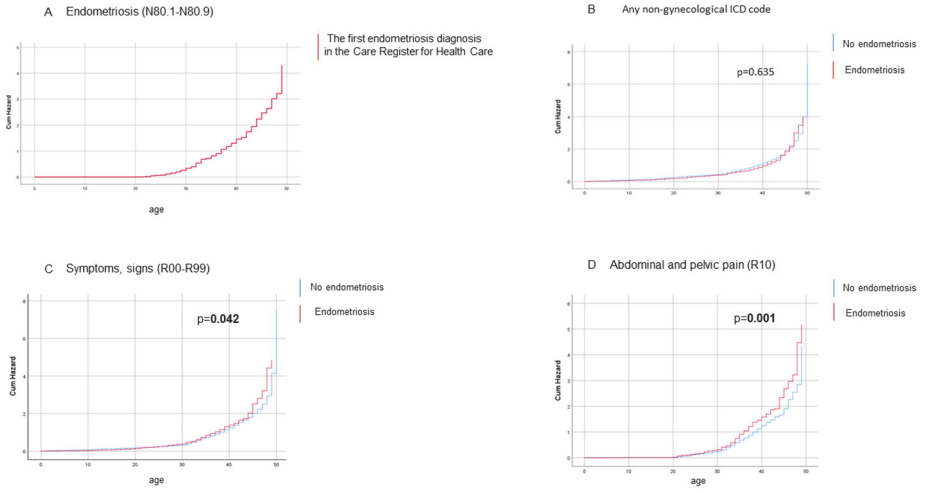

Fig. 3. Mantel-Cox estimate for the lifetime accumulation of a) endometriosis diagnosis, b) any diagnosis, c) R00.R99 diagnosis and d) R10 diagnosis in the CRHC register among women with or without endometriosis until year 2016. Blue: women without endometriosis, red: women with endometriosis.

Stratified analysis of subtypes of endometriosis

The prevalence of diagnosis in the main ICD10 categories did not reach statistical significance between the different endometriosis subtypes, partly due to limited sample size (Supplementary table S I).

Self-reported symptoms and medication usage

In terms of self-reported symptoms, there were significant associations between endometriosis and asthma (aOR 1.51, 95% CI 1.1–2.15), atopic/allergic eczema

(aOR 1.39, 95% CI 1.07–1.81), symptoms of eye allergies (aOR 1.54, 95% CI 1.61–2.04), and emphysema/chronic bronchitis (aOR 1.72, 95% CI 1.01–2.95). Women with endometriosis reported being "more susceptible to infections than other people", and there were significant associations between endometriosis and "recurrent respiratory infections" (aOR 1.36, 95% CI 1.04–1.77), "repeated pneumonia" (aOR 1.55, 95% CI 1.05–2.31), and "hospitalization due to recurrent infections" (aOR 1.75, 95% CI 1.14–2.67). Symptoms related to autoimmune diseases (e.g., dry mouth and dry eyes) were also more prevalent in women with endometriosis (Table III).

Regarding medications, women with endometriosis reported continuous medication use more frequently than women without endometriosis (aOR 2.37, 95% CI 1.03–5.44) (Fig. 2). In the ATC subcategory analysis, only medications labeled "genitourinary systems and sex hormones" in the H-group were associated with endometriosis (aOR 1.83, 95% CI 1.08–3.11) (Supplementary Table SII).

Table 3. Self-reported allergic, infection and autoimmune symptoms at age 46. Univariate and multivariate binary logistic regression analysis model.

Symtom	No Endometriosis n = 3 499 n (%)	Endometriosis n = 349 n (%)	p-value	Univariate OR (95% CI)	Multivariate OR (95% CI)
Questions concerning asthma and allergy					
Asthma	501 (15.4%)	62 (19.2%)	0.138	1.31 (0.97–1.75)	**1.51 (1.10–2.15)**
Emphysema, chronic bronchitis	154 (4.7%)	24 (7.3%)	0.100	**1.58 (1.01–2.47)**	**1.72 (1.01–2.95)**
Atopic, infantile or allergic eczema	**1 344 (41.1%)**	**163 (50.2%)**	**0.019**	**1.44 (1.15–1.81)**	**1.39 (1.07–1.81)**
Allergic eye symptoms	**982 (30.0%)**	**122 (37.3%)**	**0.034**	**1.39 (1.10–1.76)**	**1.54 (1.61–2.04)**
Questions concerning infection symptoms					
Recurrent respiratory infections	**1 396 (42.8%)**	**164 (50.3%)**	**0.042**[a]	**1.36 (1.08–1.70)**	**1.36 (1.04–1.77)**
More susceptible to infections than other people	166 (4.9%)	27 (7.9%)	0.087	**1.66 (1.09–2.53)**	**1.92 (1.06–3.48)**
Pneumonia at least twice	310 (9.2%)	43 (12.6%)	0.095[a]	1.39 (0.99–1.96)	**1.55 (1.05–2.31)**
Hospitalization due to recurrent infections	**368 (11.0%)**	**58 (17.1%)**	**0.028**	**1.68 (1.24–2.27)**	**1.75 (1.14–2.67)**
Questions concerning autoimmune symptoms					
Dry eyes	**1 253 (37.3%)**	**150 (44.2%)**	**0.048**	**1.33 (1.06–1.67)**	1.27 (0.93–1.74)
Dry mouth	**440 (13.1%)**	**66 (19.4%)**	**0.014**[a]	**1.59 (1.20–2.12)**	**2.11 (1.43–3.12)**
Solar dermatitis	967 (28.8%)	117 (34.5%)	0.092	**1.30 (1.03–1.65)**	1.34 (0.96–1.86)
Thrombocytopenia	**81 (2.4%)**	**18 (5.4%)**	**0.028**	**2.28 (1.35–3.86)**	**2.53 (1.33–4.83)**
Joint pain	1 228 (36.5%)	147 (43.4%)	0.056	**1.33 (1.06–1.70)**	1.29 (0.93–1.78)

Data reported as numbers (percentages)

Two-sided p-value < 0.05 was considered significant. Significant p-values marked with bold

Differences in numbers vary in different analyses as a result of some missing data.

p* values corrected with Benjamini-Hochberg

In multivariate analysis: lifetime contraceptive use, parity, bmi, alcohol, smoking, educational status, marital status, physical activity

[a] Significant in the CRHC register

4 Discussion

This population-based study shows that women with endometriosis have an increased risk of several diseases and symptoms by the end of their fertile lives. Nonspecific symptoms and immunological, allergic, infectious, and pain-related diseases showed the strongest associations with endometriosis. Endometriosis was also associated with mood disorders, benign neoplasms, and respiratory diseases. In line with the increased comorbidity rate, medication usage was higher in affected women at age 46. The stratified analysis of subtypes of endometriosis showed no statistically significant differences in morbidity regarding different subtypes of endometriosis.

Few previous studies, and even fewer prospective population-based studies, have investigated the association between endometriosis and overall morbidity. Previous reviews have found that women with endometriosis have a higher risk of ovarian and breast cancers, cutaneous melanoma, asthma, some autoimmune and cardiovascular diseases, diabetes mellitus, chronic liver disease, rheumatoid arthritis, and pelvic inflammatory diseases (Kvaskoff *et al.*, 2015, Teng *et al.*, 2016). A study from Italy reported found that endometriosis is associated with gastrointestinal and immunological diseases and gynecologic and thyroid cancers (Parazzini *et al.*, 2017). Thus, our findings support previous findings on the associations between endometriosis and asthma and allergic and immunological symptoms. Moreover, we found an association between endometriosis and infections requiring hospitalization, which is consistent with the CRHC data, in which women with endometriosis showed a trend toward a higher risk of acute upper respiratory infection diagnosis. Furthermore, we found significant associations between endometriosis and neoplasms, several pain conditions (e.g., migraine and dorsopathies), mood disorders, respiratory and digestive system diseases, and nonspecific symptoms. Conversely, and unlike earlier studies, we found no associations between endometriosis and endocrine and metabolic diseases or circulatory system diseases. However, the fact that the participants were followed up until the age of 50 years may have resulted in an underestimation of such associations.

In line with our findings, several earlier studies have reported that allergic manifestations, asthma, and atopic diseases are more prevalent in women with endometriosis (Bungum *et al.*, 2014, Ferrero *et al.*, 2005, Matalliotakis *et al.*, 2012). The pathogeneses of these conditions bear certain similarities. Almost all types of immune cells seem to be dysregulated in the peritoneal fluid of affected

women, with increased levels of peritoneal neutrophils and macrophages, reduced cytotoxic function of natural killer cells, and aberrant numbers of T and B lymphocytes (Selam *et al.*, 2002). Also, a shared genetic mechanism underlying allergies and endometriosis has been suggested. Rahmioglu *et al*. (2014) showed that carrier of the C allele of the acid phosphatase locus 1 polymorphism play a role in allergic manifestations with a concomitant risk of endometriosis (Rahmioglu *et al.*, 2014). These mechanisms may also lead to susceptibility to infection. We found that endometriosis was associated with diagnoses related to the respiratory system, including asthma, upper respiratory tract infections, and pneumonia.

Regarding autoimmune diseases, two population-based studies, a Danish register study and the Nurses Health Study II, reported a higher risk of several autoimmune diseases, such as systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis, and multiple sclerosis, in women with endometriosis (Harris *et al.*, 2016, Nielsen *et al.*, 2011). We did not find any associations between endometriosis and such diseases in the CRHC data. However, this might be due to the Finnish health care system, in which milder conditions, such as Sjögren's syndrome, are often diagnosed in outpatient clinics and thus may not be found in hospital-based data. However, our self-reported data showed a significant association between endometriosis and autoimmune symptoms (e.g., dry mouth). The association between endometriosis and immune functions may suggest impaired immune surveillance in women with endometriosis. Given that endometriosis is an estrogen-dependent disease, this comorbidity may also be suggestive of steroid hormone response alterations, while estrogens have been shown to act as immune stimulants (Ahmed *et al.*, 1999). Furthermore, an experimental study showed that steroid hormones promote specific immunologic events in some types of autoimmune diseases (Quintero *et al.*, 2012).

Whether immune function dysregulation increases the risk of neoplasms in women with endometriosis remains unclear. A previous study found decreased expression of genes implicated in DNA repair, which may increase the risk of malignancy (Mirza-Aghazadeh-Attari *et al.*, 2019). Among malignant neoplasms, ovarian cancer has been most consistently associated with endometriosis (Kim *et al.*, 2014, Saavalainen, Lassus, But, Tiitinen, Härkki, Gissler, Pukkala *et al.*, 2018). A meta-analysis found that endometriosis is associated with a 1.2–1.8 times higher risk of ovarian cancer (Kim *et al.*, 2014). Likewise, a Finnish register-based study found that ovarian endometriosis is associated with an increased risk of ovarian cancer, especially endometrioid and clear cell carcinomas (Saavalainen, Lassus, But, Tiitinen, Härkki, Gissler, Pukkala *et al.*, 2018). On the other hand, findings

regarding the associations between endometriosis and other cancers have been conflicting. The same Finnish study group found that women with surgically confirmed endometriosis have a similar risk of breast cancer to the general population, but among women below the age of 40, incidence of breast cancer were increased in women with endometriosis (Saavalainen *et al.*, 2019). Melanoma and thyroid cancer have also been associated with endometriosis, but the data are controversial (Saavalainen, Lassus, But, Tiitinen, Härkki, Gissler, Heikinheimo *et al.*, 2018). In present study, we found no significant associations between endometriosis and malignant neoplasms. It should be noted, however, that cancers occur more commonly in older women, whereas our study population consisted of women under 50 years of age, thus limiting the possibility of finding any associations. Off the scope of our study, we found a significant association between endometriosis and benign gynecologic neoplasms: leiomyomas of the uterus and uncertain ovarian tumors, which explains the higher rate of neoplasms among women with endometriosis.

Women with endometriosis suffer from chronic pelvic pain and prolonged noxious pain stimulation, which may lead to central and/or peripheral sensitization (Brawn *et al.*, 2014, Morotti *et al.*, 2016). Like our study, previous studies have reported increased regional hyperalgesia and allodynia, altered musculoskeletal pain response, and increased pain sensitivity in women with endometriosis (Stratton *et al.*, 2015, Vuontisjärvi *et al.*, 2018). Considering the mechanisms underlying chronic pain, an association between endometriosis and other pain-causing diseases can be expected. In a case-control study, Ferrero *et al*. (2004) showed that the prevalence of migraine is significantly higher among women with than without endometriosis (38.3% vs. 15.1%)(Ferrero *et al.*, 2004). Our analysis also showed an association between endometriosis and migraine. To our knowledge, there are no previous reports on the association between endometriosis and musculoskeletal diseases. In our study, hospital-based ICD codes for musculoskeletal diseases were more frequent in women with endometriosis. This is not surprising, considering that endometriosis-related pain symptoms can be multifaceted (Coxon *et al.*, 2018, Morotti *et al.*, 2016). It is, however, surprising that the prevalence of fibromyalgia did not differ between women with and without endometriosis in our data set, which again might be because fibromyalgia is usually diagnosed and treated in outpatient centers. Moreover, mental distress may lower the pain threshold and induce altered pain responses. Indeed, women with endometriosis have been shown to be at a higher risk of depression, anxiety, stress-related disorders, alcohol/drug dependence, and attention-deficit/hyperactivity disorder than the general

population (Gao *et al.*, 2020). Part of the psychological distress may be due to chronic pain and difficulties in achieving pregnancy (Facchin *et al.*, 2015, Facchin *et al.*, 2017). Our data showed a nearly two times higher likelihood of mood disorders. Conversely, we found no association between endometriosis and depression or anxiety.

A recent meta-analysis showed a more than twofold risk of irritable bowel syndrome (IBS) in endometriosis (Saidi *et al.*, 2020), although the association is difficult to ascertain, given the shared gastrointestinal symptomatology between these two conditions (Saidi *et al.*, 2020, Wu *et al.*, 2018). We found no significant association between endometriosis and IBS, which might be due to the diagnosis and treatment of IBS in outpatient centers, as well as due to the limited sample size. However, the association between endometriosis and digestive syndromes as a whole was significant. Furthermore, women with endometriosis had more diagnoses of "symptoms, signs, and abnormal clinical and laboratory findings not classified elsewhere" (R00-R99), especially ICD codes related to "abdominal and pelvic-related symptoms" (R10), which had a more than fourfold likelihood in women with endometriosis. In Kaplan-Meier analysis, the accumulation of R00–R99 codes occurred significantly earlier in women with than without endometriosis. This may be attributed to the known diagnostic delay. Although patients may seek medical attention for their symptoms, endometriosis may remain undetected. Hospital-based endometriosis diagnoses started to accumulate after the age of 25 years, and the mean age of diagnosis was almost 32 years.

There are several strengths in our study. Compared to earlier studies, our study represents a population-based birth cohort with a long-term follow-up of 50 years and no ethnic variation. We used a two-source data strategy to detect endometriosis cases at the population level—medically confirmed and self-reported cases—which offered a high specificity of cases. Data from national registers include medically confirmed diagnoses, reducing the misclassification bias that may occur when using self-reported data only. On the other hand, self-reported data may reflect milder cases and symptoms that are diagnosed and treated in outpatient centers. We were also able to show the temporal accumulation of diagnoses using Kaplan-Meier analyses. Furthermore, we performed stratified analyses of the subtypes of endometriosis (peritoneal, ovarian, and deep infiltrating), although significance of this analysis was limited due to small number of cases. It should be noted that even if data could not reach the statistical differences, partly due the limited sample size, neoplasms (C00-D48), endocrine and metabolic diseases (E00-E90) and musculoskeletal diseases (M00–M99) seemed to be more prevalent in deep

endometriosis, whereas infectious diseases (A00-B99) seemed to be more prevalent in ovarian endometriosis.

This study also has certain limitations. Despite above mentioned advantage of using self-reported data, the self-reported diagnoses of endometriosis may be considered a limitation. However, self-reported endometriosis diagnosis has been validated in our previous studies and enables a wider detection of cases (Vuontisjärvi *et al.*, 2018). Previous studies have also concluded that self-reported diagnoses can be considered moderately accurate, and that accuracy improves when additional information is available (Saha, Marions *et al.*, 2017, Shafrir *et al.*, 2021). It must be noted that even though laparoscopy is the golden standard for endometriosis diagnosis, the operation is not justified in some cases, which may lead to selection bias in surgically based, clinically rooted case-control studies. Our data set included women up to the age of 50 years, which limits the possibility of identifying associations between endometriosis and diseases that develop at older ages. Finally, we did not link our data with a cancer registry; therefore, the associations between endometriosis and cancers may have been underestimated.

Conclusion and implications

Our findings suggest that women with endometriosis are at a higher risk of several chronic diseases. A deeper understanding of these associations is needed to provide new insights into the causes and consequences of endometriosis. Early diagnosis of endometriosis without a long diagnostic delay is crucial for improving women's health and reducing the social, economic, and personal burdens of endometriosis and related disorders. Women with endometriosis should be given more attention and targeted resources in health care systems to achieve more efficient and targeted care in multidisciplinary settings.

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Supplemental table I. Prevalence of ICD codes from the Care Register for Health Care in different subtypes of endometriosis.

ICD group	Peritoneal endometriosis n=59	Ovarian endometriosis n=107	Deep-infiltrating endometriosis n=35	p-value
Certain infectious and parasitic diseases (A00–B99)	12 (20.3)	31 (29.0)	7 (20.0)	0.36
Neoplasms C00–D48	27 (45.8)	48(44.9)	23 (65.7)	0.09
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism D50–D89	4 (6.8)	14 (13.1)	6 (17.1)	0.28
Endocrine, nutritional and metabolic diseases E00–E90	7 (11.9)	7 (6.5)	7 (20.0)	0.07
Mental and behavioral disorders F00–F99	9 (15.3)	16 (15.0)	7 (20.0)	0.77
Diseases of the nervous system, eye, ear G00–H95	27 (45.8)	39 (36.4)	19 (54.3)	0.15
Diseases of the circulatory system I00–I99	17 (28.8)	23 (21.5)	11 (31.4)	0.39
Diseases of the respiratory system J00–J99	31 (52.5)	52 (48.6)	21 (60.0)	0.50
Diseases of the digestive system K00–K93	31 (52.2)	45 (42.1)	17 (48.6)	0.41
Diseases of the skin and subcutaneous tissue L00–L99	11 (18.6)	25 (23.4)	7 (20.0)	0.76
Diseases of the musculoskeletal system and connective tissue M00–M99	30 (50.8)	53 (49.8)	23 (65.7)	0.24
Congenital malformations, deformations and chromosomal abnormalities Q00–Q99	7 (11.9)	7 (6.5)	2 (5.7)	0.41
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified R00–R99	43 (72.9)	81 (68.6)	24 (73.6)	0.70
Injury, poisoning and certain other consequencesof external causes S00–T98	26 (44.1)	48 (44.9)	16 (45.7)	0.99

Data reported as numbers (percentages). Two-sided p-value < 0.05 was considered significant.

Supplemental table II. Self-reported use of continuous medication at age 46.

ATC group	No endometriosis n = 3 499	Endometriosis n = 349	p-value[a]	Univariate OR (CI 95%)	Multivariate OR (CI 95%)
A: Alimentary tract and metabolism	739 (22.2%)	91 (26.9%)	0.048	1.29 (1.00–1.67)	1.21 (0.85–1.73)
B: Blood and blood forming organs	140 (4.2%)	8 (2.4%)	0.111	0.55 (0.27–1.14)	0.53 (0.19–1.49)
C: Cardiovascular system	579 (17.4%)	58 (17.2%)	0.922	0.99 (0.73–1.33)	0.78 (0.49–1.24)
D: Dermatolocical	149 (4.5%)	14 (4.1%)	0.780	0.92 (0.53–1.62)	0.83 (0.37–1.85)
G: Genito urinary system and sex hormones	**236 (7.1%)**	**44 (13.0%)**	**< 0.001**	**1.96 (1.39–2.77)**	**1.83 (1.08–3.11)**
H: Systemic hormonal preparations excluding sex hormones and insulins	242 (7.3%)	29 (8.6%)	0.377	1.20 (0.80–1.79)	1.47 (0.86–2.50)
J: Anti-infectives for systemic use	59 (1.8%)	12 (3.6%)	**0.035**	2.04 (1.09–3.84)	1.98 (0.84–4.67)
L: Antineoplastic and immunomodulating agents	78 (2.3%)	8 (2.4%)	0.975	1.01 (0.48–2.11)	0.90 (0.31–2.57)
M: Musculo-skeletal system	1 771 (53.1%)	193 (57.1%)	0.164	1.17 (0.94–1.47)	1.19 (0.87–1.64)
N: Nervous system	1 070 (32.1%)	123 (36.4%)	0.109	1.21 (0.96–1.53)	1.37 (0.99–1.89)
P: Antiparasotic products, insectisides and repellents	28 (0.8%)	4 (1.2%)	0.518	1.41 (0.49–4.05)	1.96 (0.65–5.93)
R: Respiratory system	633 (19.0%)	76 (22.5%)	0.121	1.24 (0.95–1.62)	1.40 (0.97–2.03)

ATC group	No endometriosis n = 3 499	Endometriosis n = 349	p-value[a]	Univariate OR (CI 95%)	Multivariate OR (CI 95%)
S: Sensory organs	83 (2.5%)	12 (3.6%)	0.242	1.44 (0.78–2.69)	1.16 (0.48–2.78)

Data reported as numbers (percentages)

Two-sided p-value < 0.05 was considered significant. Significant p-values marked with bold

In multivariate analysis: lifetime contraceptive use, parity, bmi, alcohol, smoking, educational status, marital status, physical activity, except group G

Group G; Multivariate analysis: parity, bmi, alcohol, smoking, educational status, marital status, physical activity

IV

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ORIGINAL RESEARCH ARTICLE

The association of endometriosis with work ability and work life participation in late forties and lifelong disability retirement up till age 52: A Northern Finland Birth Cohort 1966 study

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Abstract

Introduction: Endometriosis may cause a deterioration of daily functioning due to related symptoms such as pain, fatigue and psychological distress. Accordingly, endometriosis may jeopardize work ability, as suggested in mainly survey-based case–control studies, including clinically established cases at fertile age. This is the first general population-level study to evaluate how endometriosis is associated with (1) self-rated work ability and sick leave dates at age 46 years, (2) registered disability and unemployment days between age 46 and 48 and (3) lifelong emergence of registered disability retirement up to age 52.

Material and methods: Endometriosis case identification was based on the Care Register for Health Care and self-reported diagnosis from a population-based birth cohort, which covers 96% of children born in Northern Finland in 1966. A total of 348 women with endometriosis and 3487 women without endometriosis were identified. Questionnaire data on Work Ability Index Score was collected at age 46. Unemployment and disability days were determined from the Social Insurance Institution of Finland and the Finnish Center for Pensions registers. Finally, each individual's first-ever granted pension decision and diagnoses were collected until age 52 years. The associations between endometriosis and work ability were assessed using logistic regression models.

Results: Endometriosis was associated with poor work ability at age 46 (odds ratio [OR] 1.62, 95% confidence interval [CI] 1.06–2.47). Furthermore, the association between endometriosis and over 10 days of absenteeism was increased (OR 1.53; 95% CI 1.05–2.23). Between ages 46 and 48, women with endometriosis had 10 days more disability days (55.5 vs 45.5, p = 0.030) in comparison to women without

Abbreviations: CI, confidence interal; FCP, Finnish Center for Pensions; ICD, International Classification of Diseases codes; IRR, incidence rate ratios; NFBC1966, Northern Finland Birth Cohort 1966; OR, odds ratio; SII, Social Insurance Institution.

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endometriosis, but 20 days less unemployment days (40.6 vs 59.2 days, p = 0.013). There were no differences in early retirement between the study groups until age 52. **Conclusions:** Our study showed that endometriosis associates with poor work ability at age 46. Women with endometriosis have more disability days. However, their employment rate and risk of early retirement are comparable to those of women without endometriosis at late fertile age.

KEYWORDS
disability, employment, endometriosis, register-based study, retirement, work ability

1 | INTRODUCTION

Endometriosis is a common chronic disease affecting 6%–10% of fertile-aged women.[1] Associated symptoms, such as chronic pain, fatigue and psychological distress, may impair daily functioning, even at work.[2-5] Given that endometriosis occurs during the same years as education and career building, career development may be affected. Due to the need to promote sustainable careers in aging societies, the identification of health conditions associated with poor career outcomes is of critical importance.[6] However, the role of chronic gynecological diseases such as endometriosis, remains poorly understood.

Previous studies suggest that the role of endometriosis on women's ability to work is undermined.[4,7–11] Using a modified Work Ability Index (WAI), a Danish case–control study showed that women with endometriosis aged 26–35 years reported poorer work ability and more sick days than women without endometriosis.[10] Other studies using the Work Productivity and Activity Impairment (WPAI) questionnaire indicate that women with endometriosis report major losses regarding hours of missed work, impairment of work tasks, productivity losses and impairment of daily life activities.[9,11] Concerning employment status, cross-sectional case–control studies suggest that women with endometriosis are less likely to be employed and practicing their desired profession.[4,8] A longitudinal case–control study in the USA evaluated endometriosis-related exits from the workforce and found increased risks of sick leave and short-term disability.[12] However, although previous studies quite unanimously agree that endometriosis has adverse effects on work life, the evidence remains limited, as all but one study[12] utilize self-reported data and cross-sectional designs and mainly cover the years of fertility. Moreover, all case–control studies stem from specialized clinics or patient organizations, whereas population-level studies are lacking.

To our knowledge, this is the first general population-level study on the association between endometriosis and work ability, including a life course approach to disability retirement. Using the unique data from the Northern Finland Birth Cohort 1966 (NFBC1966) linked to national registers, we evaluated the associations of endometriosis with (1) self-rated work ability and sick leave at the age of 46 years, (2) registered unemployment and disability days during individually determined 2-year follow-up periods starting from the 46th-year study, and (3) emergence of registered disability retirement from age 16 up to the age of 52 years.

Key message

Endometriosis associates with poor work ability but not unemployment or early retirement at late fertile age.

2 | MATERIAL AND METHODS

The NFBC1966 is a general population-based cohort consisting of 96.3% of all expected births during 1966 in Northern Finland (12 055 mothers, 12 058 live-born children, 5889 girls).[13] In this study, we utilized: (1) the follow-up study at age 46 including postal questionnaires, (2) diagnoses from the Care Register for Health Care (CRHC) until age 46 years and (3) participation in the workforce registered by the Social Insurance Institution (SII) and the Finnish Center for Pensions (FCP) (Figure 1).

2.1 | Identification of women with endometriosis

Women with endometriosis were identified from the NFBC1966 using previously validated methodology.[14] First, we used data from the CRHC, which systematically recorded all diagnoses during hospital visits between 1968 and 2012 using International Classification of Diseases (ICD) codes.[15] The ICD-9 and 10 codes for endometriosis (617.1–617.9 and N80.1–N80.9, respectively) were used for case identification. ICD-8 codes were converted to ICD-9 codes and included. The age at first diagnosis was collected. Secondly, we used data from the 46th-year questionnaire mailed to all NFBC1966 participants living in Finland (5123 women; response rate 72%), including the question: "Have you ever been diagnosed with endometriosis by a physician?"; if yes, at what age, followed by a multiple choice question whether the diagnosis was based on gynecological examination, ultrasound or laparoscopy/surgery. Finally, by combining the 281 self-reported doctor-diagnosed, and the 224 register-based cases, we found a total of 348 endometriosis cases. Among the self-reported cases, 54% reported having been diagnosed by surgery, 30% by ultrasound and 8% in gynecological examination.

As a reference group, all women without a hospital-based ICD code for endometriosis and who replied "no" to having been

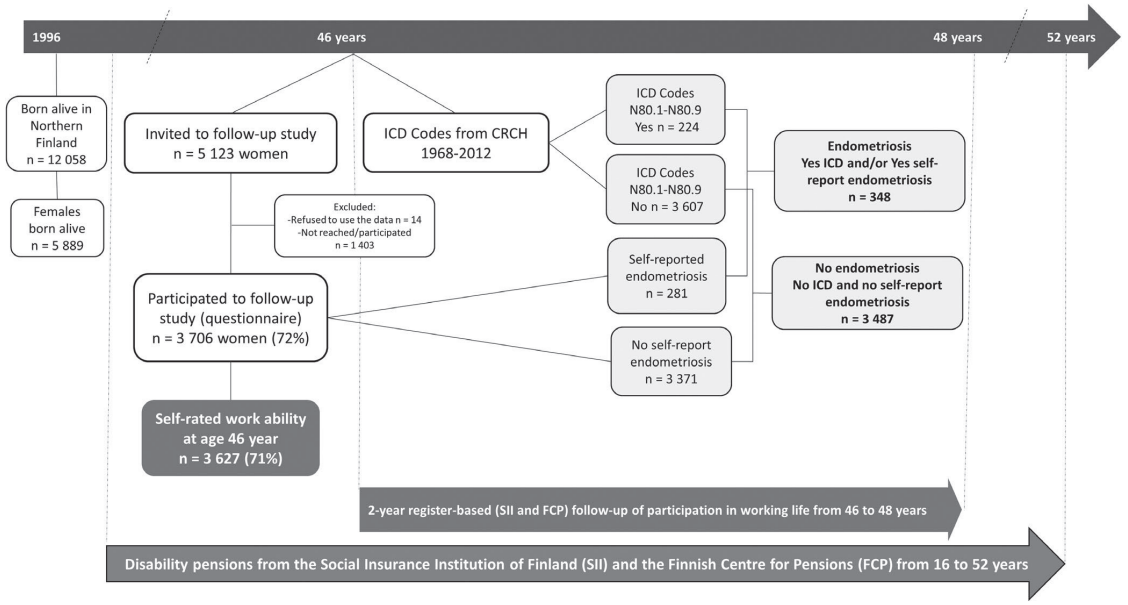

FIGURE 1 Flowchart of the data collection and study population. The population of women with endometriosis and women without endometriosis formed in the Northern Finland Birth Cohort 1966 for the present study are marked in light grey and the registers are marked in dark grey

diagnosed with endometriosis, were considered women without endometriosis (*n* = 3487). A flow chart of the study is shown in Figure 1.

2.2 | Questionnaire data on work ability

Perceived work ability at age 46 was measured with two items of the Work Ability Index, a validated tool for research.[16,17] First, the respondents rated their current work ability (scale from 0 to 10), which we classified as good (scores 8–10) or poor work ability (0–7) based on previous studies.[16,17] Secondly, we inquired about sickness absenteeism with the question: "How many days have you been absent from work due to health issues within the last 12 months?", dichotomized into 0–9 and ≥10 or more days.

Regarding retirement intentions, answers to "Have you considered retiring before normal retirement age due to medical or other reasons?" were divided into "no retirement intention" and "intention to retire".[18]

2.3 | Register data on 2-year follow-up of unemployment and disability days

The individually determined 2-year (730-day) follow-up started from the day the woman returned the 46th-year questionnaire. All days of employment and self-employment are recorded by the FCP. Based on the FCP and SII registers, each day with any type of unemployment compensation or a medically certified disability benefit was coded either as an unemployment day or a disability day; overlaps were coded as a disability day.

Sickness allowances are registered by the SII after a deductible time of 10 weekdays, 4 weekdays for entrepreneurs. In cases of accidents, they are registered by the FCP after 4 weekdays. Sickness allowance can be paid for a year, after which eligibility for a fixed-term (rehabilitation subsidy) or permanent disability pension, either full- or part-time, is evaluated.

2.4 | Registered new disability pensions

Using the participants' data from age 16 to 52 years in the SII and FCP registers, we determined the date and diagnoses of the first-ever disability pension of any type, either permanent or fixed-term, full- or part-time, as an indicator of long-term disability. The follow-up lasted until the end of 2018.

2.5 | Covariates

Several endometriosis-related, health-related and socioeconomic covariates were considered (Table 1). Regarding pain, the number of musculoskeletal pain sites (0–8) during the previous 12 months was illustrated using a drawing in the questionnaire. More than three pain sites was considered widespread pain based on our previous study.[14] Regarding other endometriosis-related covariates, the respondents were asked about ever having used hormonal contraceptives (yes/

no) and their parity status, divided into no delivery, one to two deliveries, and three or more deliveries.

Regarding health-related covariates, 46th-year clinical study data on weight (kg) and height (m) were used to calculate body mass index (kg/m^2). Missing measurements were replaced with self-reported values. For health-related behavioral factors, alcohol consumption was divided into three categories: abstinence, low-risk drinking (≤20 g/day) and high-risk drinking (>20 g/day). Smoking status was divided into no smoking, previous/occasional smoking and regular smoking. Physical activity was divided into low, moderate and high, depending on the amount of exercise during leisure time.[16]

Regarding socioeconomic factors, relationship status at age 46 was determined as marriage or cohabitation or lack thereof. Education was categorized into basic (basic or vocational school), secondary (college degree) and higher (polytechnic or university degree). The occupational status reflecting the type of work was divided into four categories: white collar, blue collar, entrepreneur and other (not working). Self-reported employment history was divided into continuous (working always or mostly on long-term or permanent contracts) or discontinuous (short- or long-term contracts with unemployment periods, mainly short-term contracts, mostly unemployed, mostly supported working, or never in paid employment). The employment status at age 46 (employment, unemployment or disability day) was obtained from the registers on the first day of the 2-year follow-up.

2.6 | Statistical analyses

Statistical analyses were performed using IBM SPSS STATISTICS 25 and R 3.6.1. Means with standard deviations (SD) for continuous variables and frequencies for categorical variables were calculated. Differences were analyzed using the independent samples *t* test or the Mann–Whitney U test. Categorical parameters were evaluated using the chi-square test. A two-sided *p* value <0.05 was considered statistically significant.

The associations between self-reported poor work ability and sick leave among women with and without endometriosis at age 46 were analyzed with binary logistic regression models reporting odds ratios (OR) with 95% confidence intervals (CI), first unadjusted. We then separately adjusted the models for widespread pain, contraception and parity, health-related factors and socioeconomic factors. Lastly, we adjusted for all covariates. As sensitivity analysis, we replicated all models by comparing women with ICD-coded (hospital-treated) endometriosis only with those without endometriosis.

Poisson regression analyses for the prospective 2-year participation in working life were used to report incidence rate ratios (IRR) with 95% CI for unemployment and disability days for women with and without endometriosis, first unadjusted. We then separately adjusted the analyses for their employment status at the beginning of the follow-up to account for baseline disability and unemployment, followed by adjustments and sensitivity analyses analogous to those of the logistic regression models.

Finally, we used Kaplan–Meier survival analysis with Mantel–Cox estimates to estimate the lifetime emergence of disability pensions for women with and without endometriosis until 2018, when the participants turned 52. Since the number of diagnoses in individual decisions varied, only the ICD code frequencies were calculated.

2.7 | Ethical approval

This study was conducted according to STROBE guidelines for cohort studies and the principles of the Declaration of Helsinki. All participants provided written informed consent to combine the NFBC study data with the register data. The study was approved by the Ethics Committee of the Northern Ostrobothnia Hospital District (latest registration number: 94/2011) on 14 December 2011.

3 | RESULTS

Women with endometriosis experienced more widespread pain than women without endometriosis (71.4% vs 62.6%; $p = 0.002$), had used contraception more often (93.2% vs 89.2%; $p = 0.023$) and had lower parity. The mean age at first endometriosis diagnosis was 31.6 years (SD 7.3). Health behavior, socioeconomic characteristics and employment status at age 46 did not differ significantly between the two groups (Table 1).

At age 46, endometriosis was not associated with poor work ability in the unadjusted model or when considering widespread pain (Table 2). However, in the final multivariate analysis, endometriosis was associated with poor work ability (OR 1.62, 95% CI 1.06–2.47). In sensitivity analysis considering only register-based endometriosis cases ($n = 224$), the results patterned analogously, although not quite reaching statistical significance in the final model (OR 1.35, 95% CI 0.89–2.05). Moreover, women with endometriosis more often reported over 10 days' sickness absenteeism during the previous year (33.5% vs 25.4%; $p = 0.001$), as revealed by the unadjusted logistic regression (OR 1.49, 95% CI 1.17–1.90), with a slightly lower risk after adjusting for pain (OR 1.30) but a higher risk after adjusting for health-related factors (OR 1.75) and when considering all covariates (OR 1.53, 95% CI 1.05–2.23) (Table 2). In sensitivity analysis among women with registered diagnoses, the results again followed the main pattern, with slightly stronger figures (OR 1.78, 95% CI 1.26–2.51) in the final model.

During the register-based 2-year follow-up, the women with endometriosis had on average 10 more disability days compared with unaffected women (55.5 vs 45.5 days; $p = 0.030$). In the Poisson regression, considering all potential confounders, women with endometriosis had a higher risk of disability days (IRR 1.35, 95% CI 1.31–1.38) (Table 3). However, the affected women had around 20 fewer unemployment days compared with unaffected women (40.6 vs 59.2 days; $p = 0.013$), as reflected in a lower risk of unemployment days (IRR 0.88, 95% CI 0.86–0.91) in the final model (Table 3). The risks for disability (IRR 1.54, 95% CI 1.50–1.57) and unemployment

TABLE 1 Characteristics of the study population in the Northern Finland Birth Cohort 1966.

	No endometriosis, *n* = 3487 (%/SD)	Endometriosis, *n* = 348 (%/SD)	*p* value
Widespread pain	**1933 (62.6%)**	**222 (71.4%)**	**0.002**
Contraception use (ever)	**2958 (89.2%)**	**299 (93.2%)**	**0.023**
Parity			
0	**303 (9.7%)**	**42 (13.8%)**	
1–2	**1696 (54.5%)**	**174 (57.0%)**	**0.017**
≥3	**1111 (35.7%)**	**89 (29.2%)**	
Self-rated health			
Good	2256 (67.4%)	223 (66.0%)	0.589
Poor	1090 (32.6%)	115 (34.0%)	
BMI	26.5 (5.3)	26.0 (5.1)	0.113
Alcohol consumption			
Abstainer	383 (11.4%)	46 (13.5%)	
Low-risk drinker	2707 (80.7%)	274 (80.6%)	0.250
At-risk drinker	264 (7.9%)	20 (5.9%)	
Smoking			
Non-smoker	1886 (53.9%)	203 (58.2%)	
Former/occasional	807 (23.1%)	69 (19.8%)	0.419
Smoker	635 (18.1%)	62 (17.8%)	
Physical activity			
Low	746 (22.2%)	65 (19.2%)	
Moderate	1376 (41.0%)	150 (44.2%)	0.351
High	1232 (36.7%)	124 (36.6%)	
Education			
Basic	210 (6.2%)	15 (4.4%)	
Secondary	2148 (63.8%)	208 (61.4%)	0.152
Tertiary	1010 (30.0%)	116 (34.2%)	
Occupational status			
White collar	1233 (37.5%)	132 (40.2%)	0.252
Blue collar	1543 (46.9%)	145 (44.2%)	
Entrepreneur	286 (8.7%)	35 (10.7%)	
Other	266 (6.9%)	16 (4.9%)	
Marital status			
Single	784 (22.4%)	70 (20.1%)	0.314
In a relationship	2715 (77.6%)	279 (79.9%)	
Employment history			
Continuous	2314 (70.6%)	242 (73.3%)	0.300
Discontinuous	963 (29.4%)	88 (26.7%)	
Employment status at age 46*			
Employment day	2860 (86.6%)	291 (86.6%)	
Unemployment day	229 (6.9%)	21 (6.3%)	0.797
Disability day	212 (6.4%)	24 (7.1%)	

Data reported as mean values (SD) or count numbers (%). Significance tests for continuous variables were performed by using the independent samples *t* test or the Mann–Whitney *U* test, as appropriate.

Two-sided *p* values <0.05 were considered statistically significant.

Differences in numbers vary in analyses as the result of missing data.

*Registered data in the beginning of the 2-year follow-up.

TABLE 2 Self-reported work ability and work absenteeism in women with endometriosis and women without endometriosis at age 46 in a population-based dataset

	Poor work ability, OR (95% CI)	Ten or more days absenteeism, OR (95% CI)
Crude OR (95% CI)	1.22 (0.92–1.62)	**1.49 (1.17–1.90)**
Model 1, OR (95% CI)	1.20 (0.89–1.60)	**1.30 (1.01–1.69)**
Model 2, OR (95% CI)	**1.35 (1.01–1.82)**	**1.52 (1.18–1.97)**
Model 3, OR (95% CI)	**1.41 (1.00–1.99)**	**1.75 (1.29–2.36)**
Model 4,OR (95% CI)	**1.37 (1.02–1.83)**	**1.54 (1.20–1.97)**
Model 5, OR (95% CI)	**1.47 (1.06–2.04)**	**1.53 (1.05–2.23)**

OR:The odds ratios were calculated per 1 unit change.

Model 1: widespread pain.

Model 2: contraceptive use, parity.

Model 3: smoking, alcohol, BMI, physical activity.

Model 4: working history, educational level, occupational status, marital status.

Model 5: All.

TABLE 3 The risk for disability and unemployment between age 46 and 48 years in women with endometriosis during a 2-year follow-up. Data from the register of Social Insurance Institution of Finland

	Disability days, IRR (95% CI)	Unemployment days, IRR (95% CI)
Crude OR (95% CI)	**1.21 (1.19–1.23)**	**0.69 (0.67–0.70)**
Adjusted with baseline employment status	**1.15 (1.13–1.17)**	**0.65 (0.64–0.66)**
Model 1, IRR (95% CI)	**1.27 (1.26–1.28)**	**0.70 (0.69–0.70)**
Model 2, IRR (95% CI)	**1.42 (1.40–1.44)**	**0.66 (0.65–0.67)**
Model 3, IRR (95% CI)	**1.31 (1.28–1.34)**	**0.76 (0.74–0.78)**
Model 4, IRR (95% CI)	**1.38 (1.35–1.40)**	**0.79 (0.78–0.81)**
Model 5, IRR (95% CI)	**1.35 (1.31–1.38)**	**0.88 (0.86–0.91)**

IRR: Incidence rate ratios were calculated per one unit change.

Model 1: widespread pain.

Model 2: contraceptive use, parity.

Model 3: smoking, alcohol, BMI, physical activity.

Model 4: working history, educational level, occupational status, marital status.

Model 5: all.

days (IRR 0.96, 95% CI 0.93–0.98) remained similar in the sensitivity analysis among women with registered endometriosis diagnoses.

At age 46, women with and without endometriosis reported retirement intentions similarly (48% vs 44.6%; $p = 0.232$). Likewise, the lifelong emergence of registered disability retirement up to the age of 52 years ($n = 18$, 5.2% vs $n = 153$, 4.4%, respectively; $p = 0.515$) did not differ in the two groups (Figure 2). In terms of diagnoses, no

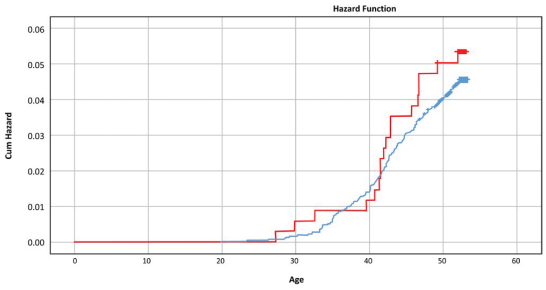

FIGURE 2 Mantel–Cox estimate for the lifetime emergence of disability pensions among women with or without endometriosis until 2018. Blue: women without endometriosis ($n = 153$, 4.4%), Red: women with endometriosis ($n = 18$, 5.2%)

decision warranting a disability pension mentioned endometriosis. The most common ICD classes in both groups were F (mental and behavioral disorders) and M (diseases of the musculoskeletal system and connective tissue) (Table S1).

4 | DISCUSSION

This unique general population-based register-linkage study supports and expands earlier evidence on endometriosis being associated with poorer work ability and sickness absenteeism, even at a late fertile age. On the other hand, we found no association between endometriosis and unemployment between the ages of 46 and 48 years or with lifelong emergence of disability retirement up to age 52.

A recent review suggests that endometriosis negatively impacts women's professional lives.[3] Studies based on Work Productivity and Activity Impairment surveys have estimated lower productivity at work resulting from absenteeism, presenteeism, productivity losses and activity impairments. In this study, we focused on the risk and associated factors for actual exit from the workforce. Previously, a Danish study found that associations between endometriosis and sickness absenteeism and poorer work ability were aggravated by fatigue, pain, depression and long intervals between symptom onset and diagnosis.[10] In this study, endometriosis was associated with poor work ability, self-reported sickness absence and registered disability days. The fact that the associations were stronger when socioeconomic and health-related risks of work disability were considered, may reflect previous evidence of shortcomings in being diagnosed experiences by women with poorer work ability,[10] linked with a lower socioeconomic status. Since our registered disability days underestimate shorter absenteeism, we conclude that endometriosis is associated with increased sickness absenteeism, even at a late fertile age.

Previous findings on the employment prospects of women with endometriosis are mixed. Some studies have found that women with endometriosis have longer professional lives compared with unaffected women.[3,4] In contrast, a previous study showed that women with surgically confirmed endometriosis reported having considered

health in their career decisions and worked less often in their desired profession than other women.[4] Other previous evidence suggests that women with endometriosis are highly motivated in their work.[10] The fact that women with endometriosis suffer more often from infertility and have lower parity than non-affected women, may lead to greater commitment to a working career. In our study, based on full coverage of registered unemployment days, endometriosis did not predict unemployment during the 2-year follow-up.

Given that mental distress and pain disorders are major causes of early retirement,[19–21] women with endometriosis could be at risk. We found only one previous US study that used registered company-based insurance claim data to evaluate the risk of leaving the workforce, including early retirement.[12] This retrospective study showed that women with endometriosis had a greater risk of sick leave and short-term disability in the beginning of the 5-year follow-up but not of early retirement.[12] Likewise, we found no differences in reported disability retirement up to the age of 52 years between women with and women without endometriosis. Notably, no disability retirement decisions included endometriosis among the diagnoses, although endometriosis may present with or induce multisite pain syndromes impairing functioning.[3,10] Considering the natural course of the disease, an increase in disability retirement should have occurred during the fertile years, but we found no such evidence. Since endometriosis eases off with menopause, later endometriosis-related retirement is unlikely. At present, our results suggest that endometriosis is not associated with early disability retirement.

Methodologically, our dual-source strategy to detect endometriosis cases at population level is an important starting point. Regarding validity of diagnosis, the lack of histologic/surgical confirmation may be considered a limitation; however, such an approach is not feasible in a general population setting. Instead, we were able to use reliable and comprehensive registered data on hospital-based diagnoses. To detect the remaining diagnoses, obtained in the private sector and public healthcare centers, we used questionnaires. Our instrument has been validated as a reliable method with high specificity.[22] Finally, when restricting the analysis only to the hospital-based cases, the results remained largely similar. Nevertheless, if there were many undiagnosed cases among controls, our results would be underestimates. Unfortunately, the potential role of diagnostic or treatment delay on work ability cannot be assessed in our dataset, as we have no information on the time from symptom onset to diagnosis. Neither can we grasp the type of symptoms, the use and/or effectiveness of other medical therapies besides contraceptives, assisted fertility therapies or surgical treatments. Should these have mitigated losses on functioning among women with endometriosis, our results on the associations would again be underestimates. Whilst we adjusted for parity, all related factors such as infertility- or family-related absences and burdens affecting attachment to working life could not be considered.

Our data stem from a population-based unselected birth cohort covering all employment sectors, with no significant differences regarding education and occupational status between the study groups. Nevertheless, the healthy worker effect in occupational epidemiology[23] merits consideration due to its tendency toward null in estimations. Generally, the healthiest individuals in any group are more likely to be hired and remain employed. Thus, women still employed at a late fertile age, after hardships related to endometriosis, might have the mildest phenotypes of the disease or be otherwise healthy, which might underestimate the actual effects of endometriosis. Altogether, the strengths of our study include its large representative general population sample, the wide range of covariates measured with established survey instruments, and linkage to national register data. However, our results may not be generally applicable to other countries or cultures given the unique nature of the Finnish healthcare and retirement system, representing a Nordic social welfare society setting.

For healthcare practitioners, we encourage recognition of the relevance of organizing timely care for endometriosis to promote work ability. Notwithstanding impaired work ability and the need for sick leave, it is encouraging that we found no major risks of unemployment or early disability retirement at a late fertile age. Providing this information in patient counseling might be helpful to affected women, who might face a career-related crisis due to their diagnosis and worry about their employability over the years. If possible, job modifications such as part-time or remote work during the most distressing phases should be considered.[24] Lastly, careful recording of endometriosis in medical certificates could serve to allocate appropriate resources for this patient group to improve diagnostics and adequate care.

5 | CONCLUSION

Women with endometriosis at a late fertile age have poorer work ability and take sick leave more frequently than unaffected women. However, the disease does not increase their risk of unemployment or disability retirement.

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AUTHOR CONTRIBUTIONS

H-RR, LA-M, EV, TTP, OU and RA planned the study; EV, LK and H-RR statistics and figures; H-RR, OU, RA, TTP and LA-M wrote the manuscript.

CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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