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Henna-Riikka Rossi

THE ASSOCIATION OF ENDOMETRIOSIS ON BODY SIZE, PAIN PERCEPTION, COMORBIDITY AND WORK ABILITY IN THE NORTHERN FINLAND BIRTH COHORT 1966

LONG-TERM EFFECTS OF ENDOMETRIOSIS ON WOMEN'S OVERALL HEALTH

UNIVERSITY OF OULU GRADUATE SCHOOL;
UNIVERSITY OF OULU,
FACULTY OF MEDICINE;
OULU UNIVERSITY HOSPITAL

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Long-term effects of endometriosis on women's overall health

Academic dissertation to be presented with the assent of the Doctoral Training Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium 4 of Oulu University Hospital, on 3 September 2021, at 12 noon

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Abstract

Endometriosis is a chronic, benign gynecological disorder affecting 6–10% of women. It is defined by the presence of endometrial tissue outside of the uterine cavity. Endometriosis is an estrogen-dependent condition manifesting as early as adolescence in many cases. On the other hand, the disease symptoms tend to diminish at menopause due to ovarian aging and a lowered effect of estrogen. Clinical manifestations of endometriosis are pain, infertility, and fatigue. Altogether, endometriosis causes considerable burden and decreases quality of life in affected women during their reproductive years. Although earlier studies on endometriosis-related health aspects have been conducted on reproductive-aged women, research on the effect of endometriosis on women's health during late fertility is comparatively lacking.

The aims of this study were to investigate the association between endometriosis and body size from birth up to 46 years of age, to assess pain sensitivity and severity among women with endometriosis at late fertile age as well as the association between endometriosis and non-gynecological comorbidities. Furthermore, work ability and attachment to working life in women with endometriosis at late fertile age were also examined. The study population was derived from the Northern Finland Birth Cohorts 1966 (NFBC1966) with data linkage to several national registers.

The results showed that endometriosis was associated with lower body weight and leaner body figure at reproductive age but not in childhood nor in adolescence. At late fertile age, a significant association between lean body size and endometriosis was shown only in cases of peritoneal endometriosis, but not in other subtypes. The results of pain sensitivity analysis showed that still at late fertile age, women with endometriosis had 5.5% lower pressure pain sensitivity and 5.3% lower pressure pain tolerance, and they also had more widespread and disturbing pain, than women without endometriosis. Women with endometriosis were shown to have over twofold increased odds for non-gynecological comorbidities. The association was strongest between endometriosis and allergic, infectious, and pain-causing diseases and non-specific symptoms. Lastly, endometriosis was associated with poor work ability and higher disability days at late fertile age, but not with unemployment or early disability retirement.

Altogether, this study shows that even though endometriosis is considered a condition of reproductive age, it does seem to have health- and work-related implications up until late fertile age. Detecting endometriosis behind non-specific symptoms without long diagnostic delay is crucial in order to avoid the prolongation of symptoms. Women with endometriosis should be given more attention in terms of related comorbid conditions and targeted care with a multidisciplinary approach.

Keywords: body size, comorbidity, disability, endometriosis, pain perception, unemployment, work ability

Rossi, Henna-Riikka, Endometrioosin yhteys kehon kokoon, kipuaistimukseen, sairastavuuteen ja työkykyyn Pohjois-Suomen syntymäkohortti 1966 naisilla. Endometrioosin pitkäaikaisvaikutukset naisten yleiseen terveyteen

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Tiivistelmä

Endometrioosi on krooninen, hyvänlaatuinen gynekologinen sairaus, jota esiintyy 6–10 %:lla fertiili-ikäisistä naisista. Endometrioosi määritellään kohdun limakalvon kaltaisen kudoksen esiintymisenä kohtuontelon ulkopuolella. Endometrioosi on estrogeeniriippuvainen sairaus, ja se puhkeaa yleensä kuukautiskierron käynnistymisen jälkeen. Taudin on ajateltu sammuvan estrogeenituotannon loppuessa vaihdevuosi-iässä. Endometrioosi aiheuttaa oireena mm. kipua, hedelmättömyyttä ja väsymystä, mikä johtaa elämänlaadun heikkenemiseen erityisesti lisääntymisiässä. Aiemmat tutkimukset endometrioosin vaikutuksista naisten terveyteen ovat pääasiassa tapaus-verrokkitutkimuksia ja keskittyvät lisääntymisiässä oleviin naisiin. Väestötason tutkimukset endometrioosin vaikutuksesta naisten terveyteen hedelmällisen iän loppupuolella puuttuvat lähes kokonaan.

Tutkimuksen tavoitteena oli arvioida endometrioosin ja kehon koon ja kehon muodon välistä yhteyttä syntymästä 46 ikävuoteen asti. Toiseksi tavoitteenamme oli tutkia endometrioosia sairastavien naisten kipuaistimuksia hedelmällisen iän loppupuolella, sekä endometrioosin ja ei-gynekologisten sairauksien välistä yhteyttä. Lopuksi tutkimme endometrioosia sairastavien naisten työkykyä, työttömyyttä ja varhaista eläköitymistä keski-ikään saakka. Tutkimuksen populaatio koostuu Pohjois-Suomen syntymäkohortti 1966:sta ja aineisto on yhdistetty useisiin kansallisiin rekisteriaineistoihin.

Tulokset osoittivat, että lapsuuden ajan ruumiinrakenne on yhtäläinen endometrioosia sairastavilla naisilla verrattuna naisiin, joilla ei ole todettu endometrioosia. Hedelmällisessä iässä endometrioosia sairastavat naiset ovat hoikempia, mutta myöhäisessä hedelmällisessä iässä endometrioosin ja hoikkuuden välinen yhteys ilmeni vain naisilla, jotka sairastivat peritoneaalista endometrioosin alatyyppiä viitaten mahdolliseen endometrioosin alatyyppien välisiin eroihin patogeneesissa. Tarkasteltaessa endometrioosia sairastavien naisten kipumittausten tuloksia havaittiin, että endometrioosia sairastavilla naisilla oli 5,5 % matalampi kipukynnys ja 5,3 % matalampi maksimaalinen kivunsieto. Kipu oli myös laaja-alaisempaa ja häiritsevämpää vielä myöhäisessä hedelmällisessä iässä verrattuna naisiin, joilla ei ole todettua endometrioosia. Endometrioosia sairastavilla naisilla todettiin yli kaksinkertainen riski muihin ei-gynekologisiin sairauksiin, erityisesti allergioihin, infektioihin ja kipusairauksiin sekä autoimmuuni- ja erityyppisiin ei-spesifisiin oireisiin kuin naisilla ilman todettua endometrioosia. Lopuksi, endometrioosilla näytti olevan yhteys heikentyneeseen työkykyyn ja endometrioosia sairastavilla naisilla ilmeni enemmän sairaslomapäiviä vielä myöhäisessä lisääntymisiässä. Toisaalta lisääntynyttä riskiä työkyvyttömyyteen tai varhaiseen eläköitymiseen ei todettu.

Tutkimus osoittaa, että endometrioosilla on haitallisia vaikutuksia naisten terveyteen vielä myöhäisessä hedelmällisessä iässä. Endometrioosin varhainen havaitseminen on tärkeää asianmukaisen hoidon tarjoamiseksi ja oireiden pitkittymisen välttämiseksi. On tärkeää tarjota endometrioosia sairastaville naisille asiantuntevaa informaatiota taudin vaikutuksista heidän elämäänsä sekä moniammatillista endometrioosin kokonaisvaltaista hoitoa.

Asiasanat: endometrioosi, kehon koko, kipuaistimus, sairastavuus, työkyky, työttömyys

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

I Rossi, H.-R., Nedelec, R., Jarvelin, M. R., Sebert, S., Uimari, O., & Piltonen, T. T. (2021). 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. *Acta obstetricia et gynecologica Scandinavica*, 10.1111/aogs.14090. Advance online publication. https://doi.org/10.1111/aogs.14090

II Vuontisjärvi, S., Rossi, H.-R., Herrala, S., Morin-Papunen, L., Tapanainen, J. S., Karjula, S., Karppinen, J., Auvinen, J., & Piltonen, T. T. (2018). The Long-Term Footprint of Endometriosis: Population-Based Cohort Analysis Reveals Increased Pain Symptoms and Decreased Pain Tolerance at Age 46 Years. *The journal of pain, 19*(7), 754–763. https://doi.org/10.1016/j.jpain.2018.02.005

III Rossi, H.-R., Uimari, O., Terho, A., Pesonen, P., Koivurova, S., & Piltonen, T. (2021). Increased overall morbidity in women with endometriosis: a population-based follow-up study until age 50. *Submitted*.

IV Rossi, H.-R., Uimari, O., Arffman, R., Vaaramo, E., Kujanpää, L., Ala-Mursula, L., & Piltonen, T. (2021). 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. *Acta obstetricia et gynecologica Scandinavica,* 10.1111/aogs.14210. Advance online publication. https://doi.org/10.1111/aogs.14210.

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.

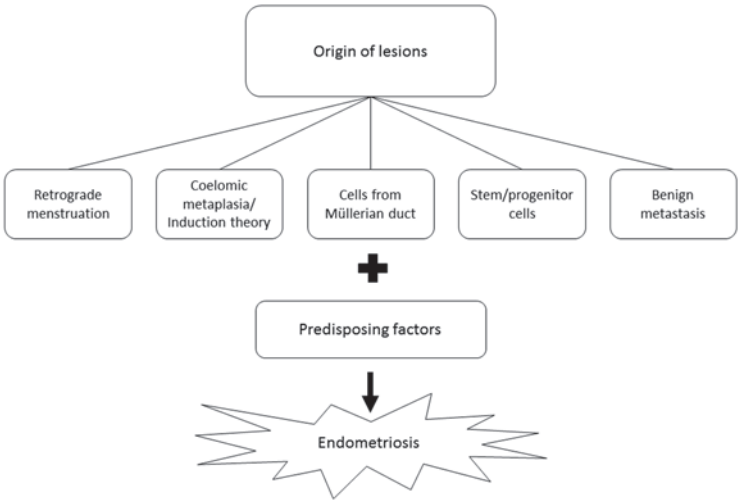

Fig. 1. Theories on the origin of endometriosis.

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.

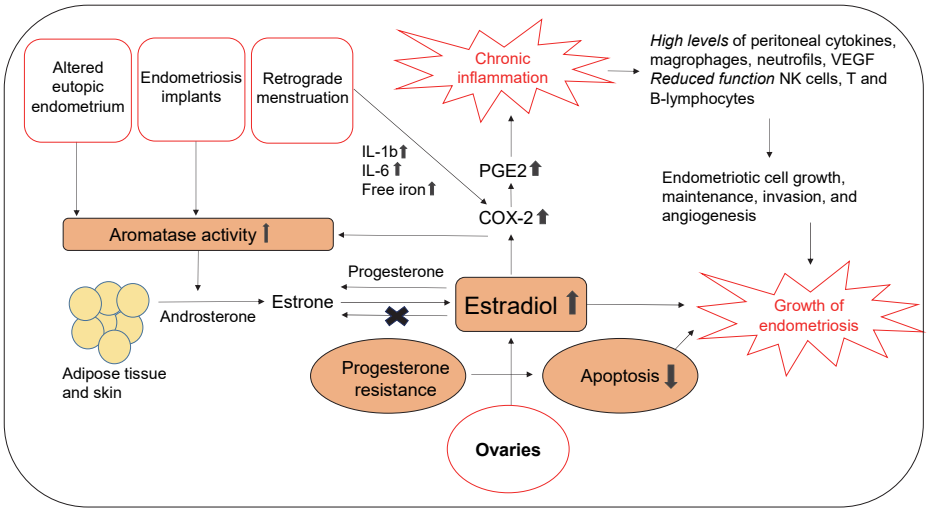

Fig. 2. Simplified pathogenesis cascade of endometriosis.

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.

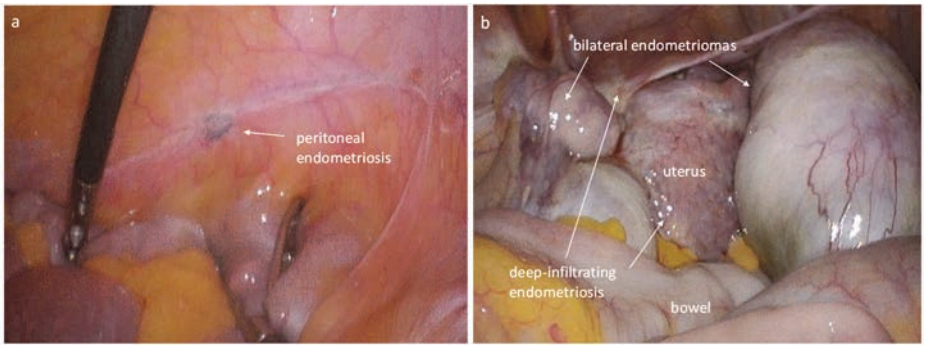

Fig. 3. Laparoscopic appearance of a) superficial/peritoneal endometriosis (SUP) and b) ovarian (OMA) and deep-infiltrating endometriosis (DIE). Permission from the patient to publish.

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.

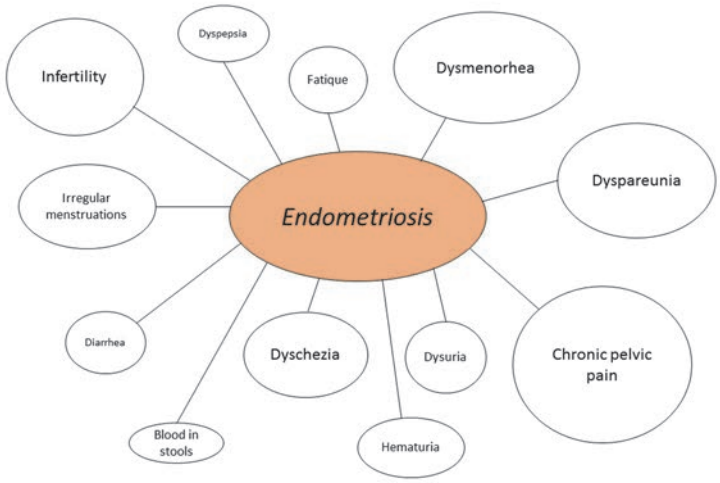

Fig. 4. Symptoms of endometriosis.

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.

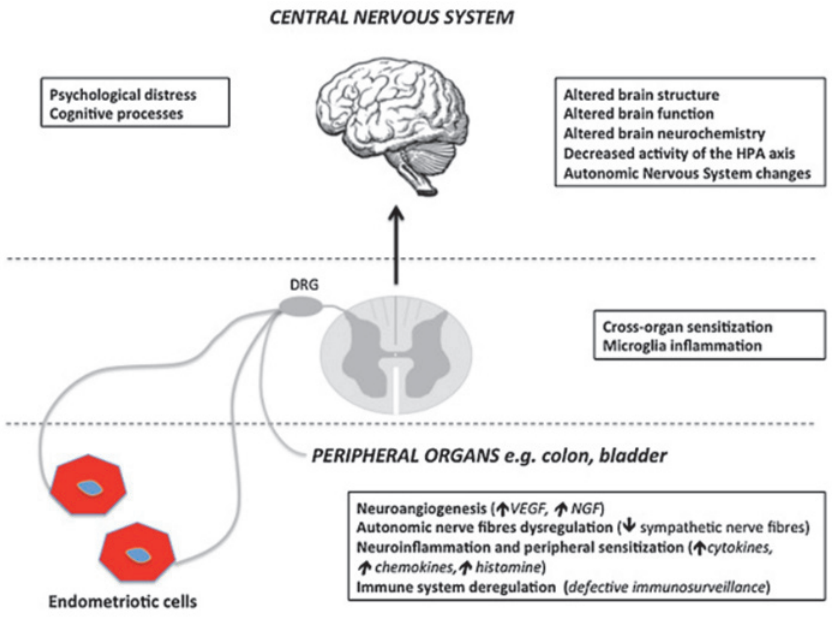

Fig. 5. Endometriosis related pain cascade (figure from Morotti 2016, permission to reuse).

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).

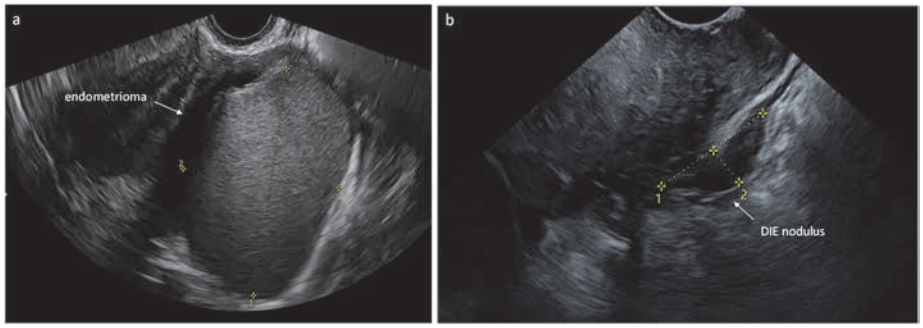

Fig. 6. Transvaginal ultrasound image of a) ovarian endometrioma (OMA) and b) deep-infiltrating endometriosis (DIE) nodulus. Permission from the patient to publish.

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.

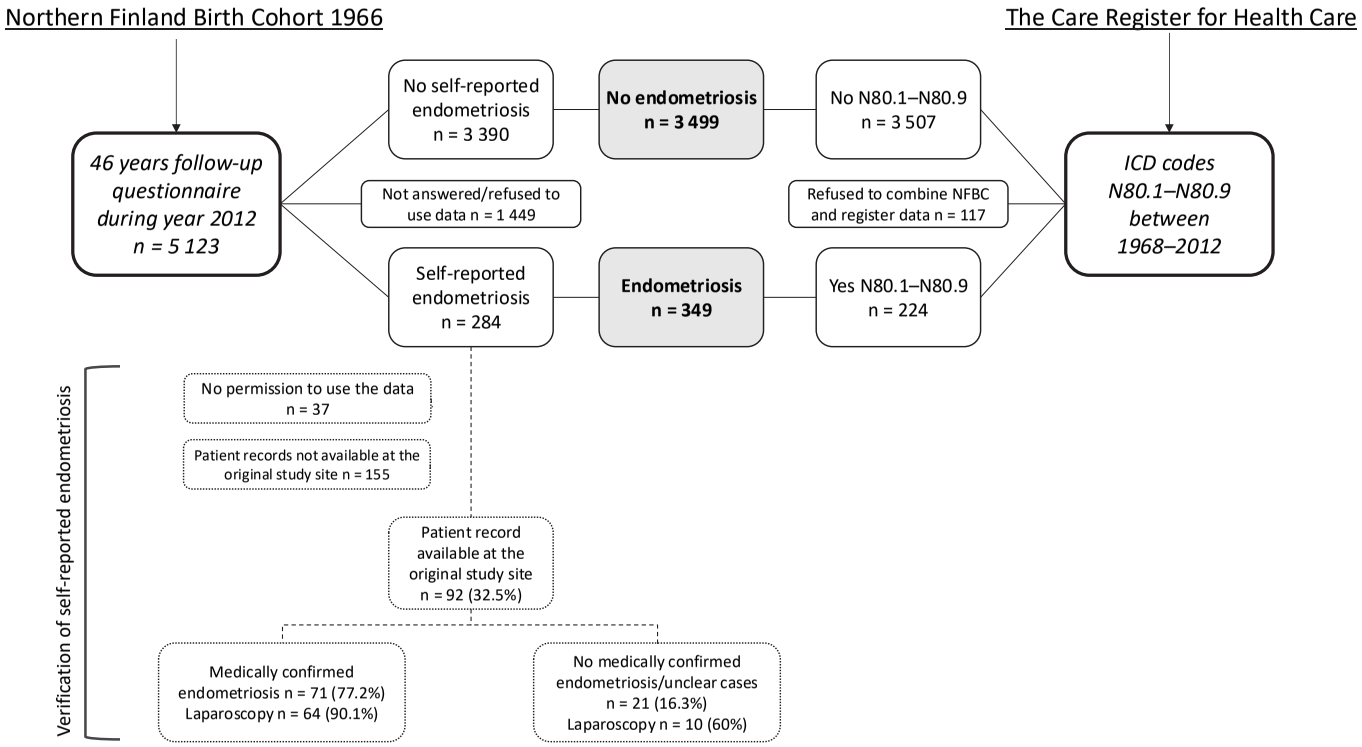

Fig. 7. Flowchart of the study population and verification of self-reported diagnosis of endometriosis according to the patient records available at Oulu University hospital.

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.

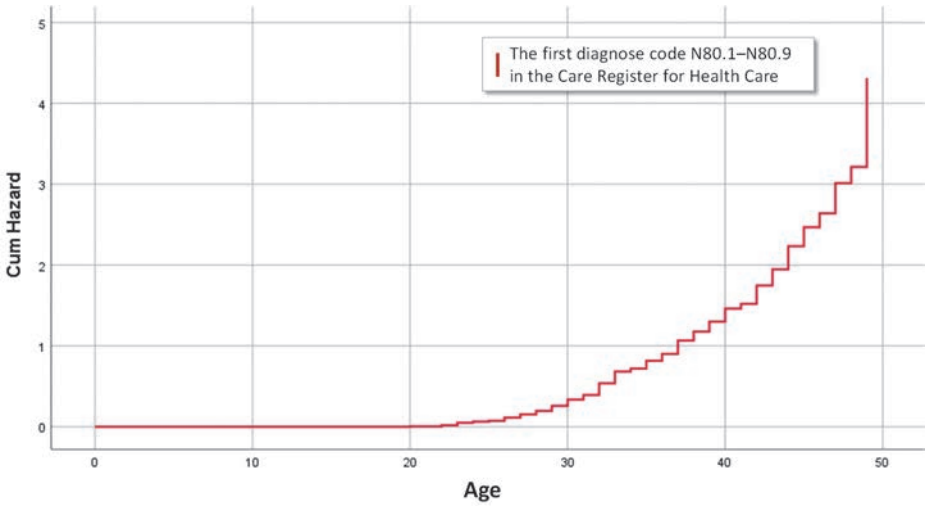

Fig. 8. Accumulating numbers of CRHC diagnosis for endometriosis.

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.

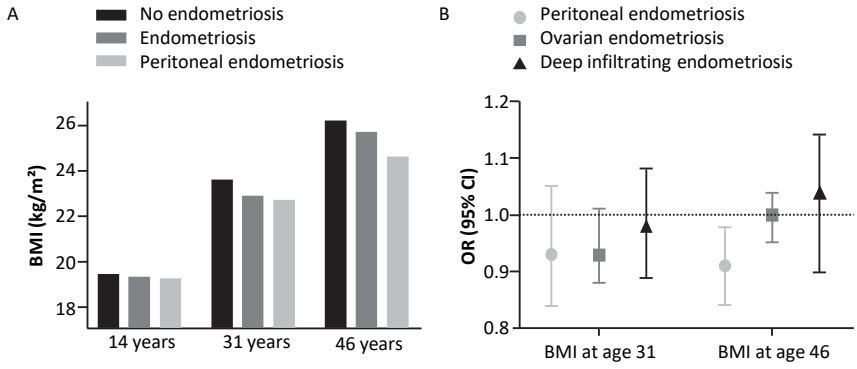

Fig. 9. a) mean BMI at ages 14, 31 and 46 in women without endometriosis (black), women with endometriosis (dark gray) and women with peritoneal endometriosis (light gray), b) association of BMI at ages 31 and 46 in different subtypes of endometriosis.

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.

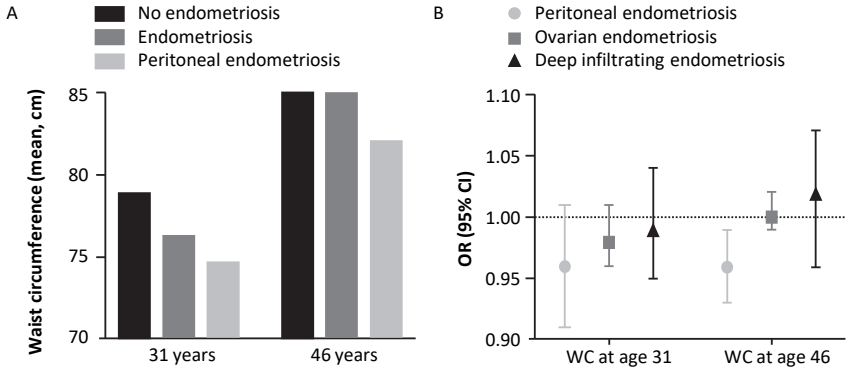

Fig. 10. a) mean WC at ages 31 and 46 in women without endometriosis (black), women with endometriosis (dark gray) and women with peritoneal endometriosis (light gray), and b) association between WC and subtypes of endometriosis at ages 31 and 46.

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.

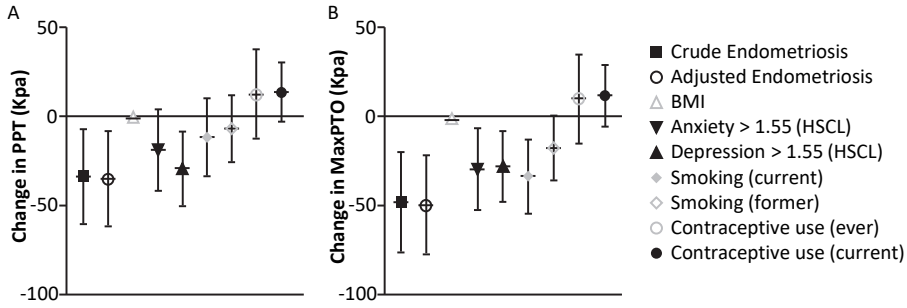

Fig. 11. The effect of different contributors to a) pressure pain threshold (PPT) and b) maximal pain tolerance (MaxPTo). The horizontal reference line reflects the whole study population. Written permission to reuse.

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.

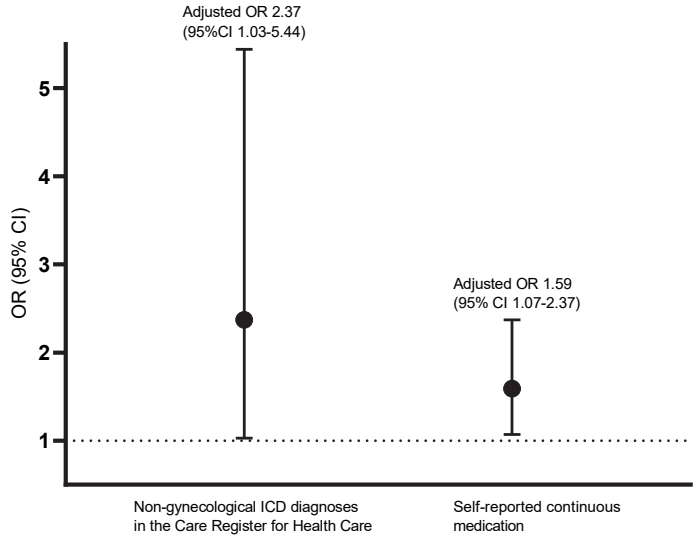

Fig. 12. The association between endometriosis and any non-gynecological diagnosis and continuous use of medication indicating increased overall morbidity in women with endometriosis.

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.

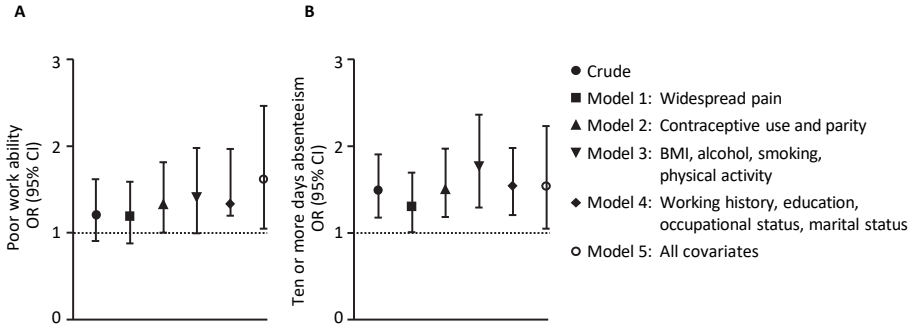

Fig. 13. Association between endometriosis and a) poor work ability b) 10 or more days absenteeism in different multivariate models.

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.

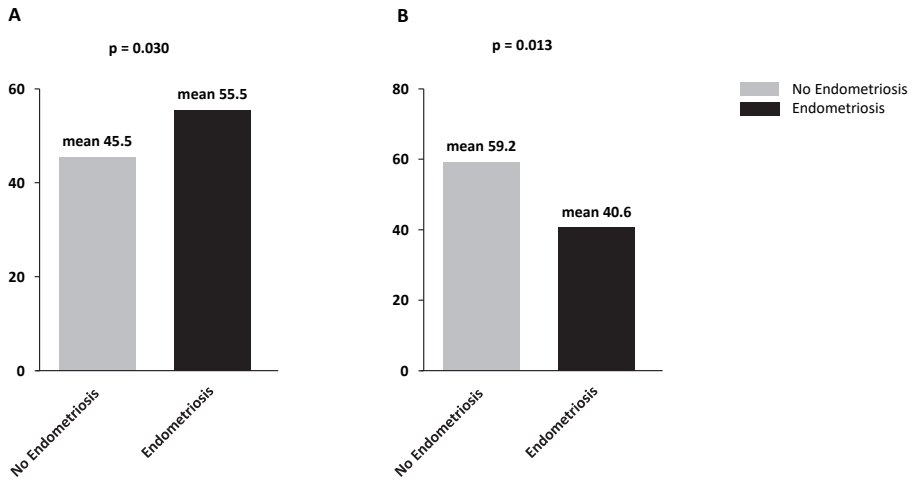

Fig. 14. Register-based a) disability and b) unemployment days in women with or without endometriosis between ages 46–48.

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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I Rossi, H.-R., Nedelec, R., Jarvelin, M. R., Sebert, S., Uimari, O., & Piltonen, T. T. (2021). 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. *Acta obstetricia et gynecologica Scandinavica*, 10.1111/aogs.14090. Advance online publication. https://doi.org/10.1111/aogs.14090

II Vuontisjärvi, S., Rossi, H.-R., Herrala, S., Morin-Papunen, L., Tapanainen, J. S., Karjula, S., Karppinen, J., Auvinen, J., & Piltonen, T. T. (2018). The Long-Term Footprint of Endometriosis: Population-Based Cohort Analysis Reveals Increased Pain Symptoms and Decreased Pain Tolerance at Age 46 Years. *The journal of pain, 19*(7), 754–763. https://doi.org/10.1016/j.jpain.2018.02.005

III Rossi, H.-R., Uimari, O., Terho, A., Pesonen, P., Koivurova, S., & Piltonen, T. (2021). Increased overall morbidity in women with endometriosis: a population-based follow-up study until age 50. *Submitted.*

IV Rossi, H.-R., Uimari, O., Arffman, R., Vaaramo, E., Kujanpää, L., Ala-Mursula, L., & Piltonen, T. (2021). 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. *Acta obstetricia et gynecologica Scandinavica,* 10.1111/aogs.14210. Advance online publication. https://doi.org/10.1111/aogs.14210.

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