Epidemiology of Endometriosis in Women of Arab Ancestry

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Abstract

Introduction

Investigating the epidemiology of endometriosis in women of Arab ancestry, in the context of regionally important environmental and genetic effects, will provide us with a better understanding on the endometriosis phenome across different populations. Under the following initiative, the Middle Eastern Women Research Association: the MAR'A project, the study aimed to investigate for the first time in women of Arab ancestry:

(1) Associations of symptomatology, risk factors, phenotypic profile, and comorbidities with endometriosis
(2) Assess the impact of endometriosis on health-related quality of life (HRQoL), work productivity, activity impairment, physical activity, and diagnostic delay
(3) Conduct a candidate gene association study (CGAS) on variants in wingless-type MMTV integration site family member 4 (*WNT4*) and the Vezatin (*VEZT*) in women with endometriosis.

Method

The MAR'A Project is a case-control study with multiple hospital and population-based sites across the United Arab Emirates, between August 2018 and August 2019. In total, 2,610 (518 endometriosis cases; 2092 controls) premenopausal women, aged 18-50 years, without a previous surgical diagnosis of endometriosis and self-reported ethnically Arab, were recruited. The study design of a case-control study compared incident endometriosis cases (n=518) with the following two comparison groups to evaluate potential risk factors: (1) ascertainment criteria (hospital controls (n=1251) vs. population controls (n=841)); and (2) symptomatic criteria (symptomatic controls (n=1331) vs. asymptomatic controls (n=761)). A subset of the samples (100 endometriosis cases and 100 hospital controls) was selected for the CGAS. Standardized, validated questionnaires, basic anthropometric measurements and saliva samples were collected from consenting participants.

Results

(1) Women with endometriosis had a lower BMI and WHRadjBMI, reported a higher frequency of pain phenotypes (dysmenorrhea, chronic pelvic pain, dysuria, and dyschezia) with greater severity, earlier age of symptom onset, and higher pain catastrophizing score, in comparison to controls. Similar to the Western population studies, women with endometriosis had earlier age at menarche, shorter menstrual cycle, heavier menstrual flow, and longer duration of menstrual phase. Women with endometriosis had a higher frequency of miscarriages, ectopic pregnancy, preterm birth, and emergency caesarean section.
(2) The average diagnostic delay was 11.61 years, with single women experiencing 15.81 years of diagnosis delay. HRQoL scores were significantly impaired in women with endometriosis, for both the Physical and Mental Composite Scores, affecting work productivity and activity impairment.
(3) A significant association was observed for SNP rs12320196 (OR=1.60 (95% CI: 1.05, 2.45), p=0.027) intronic to the *VEZT* gene, and SNPs rs12037376 (OR=1.89 (95% CI: 1.06, 3.37), p=0.029) and rs3820282 (OR=1.90 (95% CI: 1.05, 3.46), p=0.033) intronic to the *WNT4* gene.

Conclusion

This study provided novel findings of the clinical presentation and risk factors of endometriosis among Arab women from a combined hospital and population-based sites. Along with the presence, duration and severity of the pain phenotypes, adverse reproductive outcomes, and comorbidities, Arab women experience among the highest diagnostic delay of endometriosis. Social exacerbation and cultural factors may influence management of endometriosis-associated pain, leading to psychological distress and significant impacts on HRQoL. Further research must be conducted among Arab women to improve early diagnosis and provide culturally sensitive clinical care.

This thesis is dedicated to my family,

for their endless love, support, and encouragement.

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Preface

The findings presented in this thesis are based on the analyses of data from a case-control study of Arab ancestry women living in the United Arab Emirates, 'the Middle Eastern Women Research Association: the MAR'A project', of which I am the principal investigator, in collaboration with the Nuffield Department of Women's Reproductive Health at the University of Oxford, the World Endometriosis Research Foundation consortium, Centre of Biotechnology at Khalifa University and College of Medicine at the United Arab Emirates University. This study was supported by a steering group comprising the following persons:

Professor Krina Zondervan	Head of Department; Professor of Reproductive and Genomic Epidemiology; Co-Director Endometriosis Care Centre
Professor Christian Becker	Associate Professor; Co-Director Endometriosis Care Centre; Consultant Gynaecologist and Subspecialist in Reproductive Medicine
Dr. Nilufer Rahmioglu	Senior Research Scientist at the Wellcome Trust Centre for Human Genetics and Nuffield Department of Women's and Reproductive Health
Professor Habiba Alsafar	Associate Professor of Genetics and Molecular Biology; Director of the Khalifa University, Centre for Biotechnology
Professor Moamar Al-Jefout	Associate Professor at the Obstetrics and Gynaecologist department in UAEU and Mutah Faculty of Medicine in Jordan; Consultant Obstetrics and Gynaecologist

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List of abbreviations

AFS	American Fertility Society
ART	Assisted Reproductive Technology
ASRM	American Society for Reproductive Medicine
BMI	Body Mass Index
BP	Bodily Pain
CGAS	Candidate Gene Association Study
CPP	Chronic Pelvic Pain
DEEP	Deep Infiltrating Endometriosis
EFI	Endometriosis Fertility Index
EPHect	Endometriosis Phenome and Biobanking Harmonization Project
EPQ-M	Endometriosis Participant Questionnaire Minimum
EPQ-S	Endometriosis Participant Questionnaire Standard
ESHRE	European Society of Human Reproduction and Embryology
GCC	Gulf Cooperative Council
GH	General Health
GnRH	Gonadotropin Releasing Hormone
GSWH	Global Study of Women's Health
GWAS	Genome-Wide Association Studies
HPG	Hypothalamic-Pituitary Gonadal
HRQoL	Health-Related Quality of Life
ICSI	Intracytoplasmic Sperm Injection
IDEA	International Deep Endometriosis Analysis
IUI	Intra-Uterine Insemination
IVF	In Vitro Fertilization

LD	Linkage Disequilibrium
MAF	Minor Allele Frequency
MCS	Mental Component Summary
MET	Metabolic Equivalent
MH	Mental Health
MRI	Magnetic Resonance Imaging
mtDNA	Mitochondrial DNA
NRS	Numerical Rating Scale
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PCOS	Polycystic Ovary Syndrome
PCS	Physical Component Summary
PF	Physical Function
rASRM	Revised American Society for Reproductive Medicine
RE	Role Emotional
REDCap	Research Electronic Data Capture
RP	Role Physical
SF	Social Functioning
SF-36v2	36-Item Short Form Health Survey
sf-MPQ	Short Form McGill Pain Questionnaire
SNP	Single Nucleotide Polymorphisms
SOP	Standard Operating Procedures
TVS	Transvaginal Ultrasound Scan
UAE	United Arab Emirates
UK	United Kingdom
USA	United States of America

VAS	Visual Analogue Scale
VEGF	Vascular Endothelial Growth Factor
VEZT	Vezatin
VT	Vitality
WBC	White Blood Cells
WERF	World Endometriosis Research Foundation
WHO	World Health Organization
WHRadjBMI	Waist-To-Hip Ratio Adjusted For BMI
WNT4	Wingless-Type MMTV Integration Site Family Member 4
WPAI	Work Productivity and Activity Impairment

Chapter 1. Introduction

1.1 Endometriosis

Endometriosis is an oestrogen-dependent, inflammatory condition that is defined by the presence of endometrial glands and stroma in an ectopic location, including the pelvic peritoneum, reproductive organs (ovaries, Fallopian tubes), or other visceral organs in the abdominopelvic cavity[1]. Recently, pelvic endometriosis has surgically been classed into three phenotypes: (1) superficial peritoneal endometriosis, in which endometriotic tissue is found superficially involving peritoneum lining and pelvic structures; (2) endometrioma, in which a cyst lined with endometrial tissue develops within the ovary; and (3) deep infiltrating endometriosis (DEEP), defined as endometriotic nodular lesions 5mm or greater in size, below the surface of peritoneum and pelvic structures, in the cul-de-sac, on uterosacral ligaments, the rectovaginal septum, the recto-sigmoid colon, or the bladder[2]. The biological basis for classification into three sub-phenotypes is, however, unclear.

Women with endometriosis may be asymptomatic or may experience infertility and/or a variety of pelvic pain phenotypes[3], including dysmenorrhea (pain during menstrual bleeding), dyspareunia (pelvic pain associated with intercourse), dyschezia (pelvic pain related to bowel movement), dysuria (painful urination), and non-cyclical pelvic pain that can be continuous or intermittent[4,5].

Endometriosis is a common condition affecting an estimated 10% of women mostly within the reproductive age range[6,7]. However, the true prevalence is difficult to establish as the presence of lesions may go undetected unless symptoms, such as infertility or pain, prompt visual confirmation by surgical intervention[8]. In addition, we do not know what pathological changes qualify as 'onset' of disease, nor do we have the means to measure these changes as they occur. When considering evidence derived from population-based studies of the prevalence of symptoms and findings at laparoscopy, clinical studies show that 40-80% of women with endometriosis experience chronic pelvic pain[6,9,10], and 20-50% infertility[6,7,10]. Estimates of the prevalence of endometriosis from asymptomatic fertile women undergoing tubal ligation varied from 1-43%, with a mean of 4%[9,11].

The wide variations in reported prevalence rates by symptomatology group (infertility and pelvic pain) may be linked to the underlying characteristics of those groups and the requirement of surgical investigation to accurately diagnose the cases. The problems associated with the use of surgically confirmed patients to define the prevalence of endometriosis are well recognized[9], and include personal, social, cultural and financial issues. Health systems across the world may vary in the pathway or ease of access to secondary care services. The perceived seriousness of symptoms, pain threshold and the availability or access to pharmaceutical treatment determine whether a woman seeks care and, thus, her chances of being scheduled for laparoscopy or laparotomy[6]. Furthermore, the likelihood of a woman being diagnosed with endometriosis at surgery may depend on the experience of the surgeon in identifying the lesions, and the region in which the women resides[9].

Although there is a growing body of evidence to suggest that endometriosis is a complex disease caused by the interplay between environmental and genetic factors[6,7], the mechanisms of disease onset and progression remain largely unclear. In addition, the lack of adequate understanding of the symptomatology, phenotypic profile, and risk factors of endometriosis has led to an average of 6-10 years of diagnostic delay from symptom onset among endometriosis patients[12–14]. Diagnostic delay occur at a medical level and an individual patient level mainly due to delays in referral from primary care to a specialist, patients' lack of awareness of endometriosis and their inability to distinguish abnormal menstrual and symptom factors, and discrimination from family and work colleagues due to the discrediting attributes[14,15].

Given the potential effects of this chronic disease on personal lives, health care systems, and the global community, it is important to advance our understanding of the complex pathways leading to diagnosis, management, and treatment in different populations, to improve the outlook for affected women. Collecting comprehensive data from all patient populations is critical to understand if there are intrinsic differences in the pathophysiology of endometriosis, in terms of race, genetics, environmental and socioeconomic factors.

1.1.1 Stages of endometriosis

The American Society for Reproductive Medicine (ASRM), formerly called the American Fertility Society (AFS), released the AFS endometriosis surgical staging system in 1975. It was subsequently revised and republished as the revised-ASRM (rASRM) in 1996[16]. The rASRM has a standardized form that categorizes endometriosis into four stages based on extent of the disease in the pelvic cavity. The standardized form for rASRM includes questions on the endometriotic lesion size, depth of lesion invasion in the peritoneum and ovaries (endometriosis score), density and amount of adhesion involving the ovaries and Fallopian tubes, and degree of posterior cul-de-sac involvement. The staging can be assessed by the surgeon that is performing the therapeutic or diagnostic laparoscopy, with additional analyses of the histology of the lesions. While the rASRM classification has been accepted globally and is easy to use for physicians to explain the degree of endometriosis in simple terms to patients, the severity of pain phenotypes and infertility are not correlated with rASRM stage[17].

The four stages are:

- Stage I (minimal): characterized by superficial lesions and filmy adhesions, with a score of 1–5.
- Stage II (mild): characterized mostly by superficial lesions with some deep lesions in cul-de-sac, with scores between 6 and 15.
- Stage III (moderate): often presence of endometriomas on the ovary and more adhesions, with a score of 16–40.
- Stage IV (severe): frequently characterized by large endometriomas on the ovary and more adhesions, often obliteration of the posterior cul-de-sac, with a score above 40.

1.1.2 Diagnosis

Direct visualization of endometriotic lesions at laparoscopy (visual inspection of the abdominopelvic cavity) has been considered the gold standard for the diagnosis of endometriosis[18]. The European Society of Human Reproduction and Embryology (ESHRE) guidelines recommend that a histological examination

should be performed to confirm the diagnosis[19]. Due to the importance of surgical investigation, on average, patients take 6–10 years from the onset of symptoms to obtain the precise diagnosis[14,20].

Data from centres with sufficient experience suggest that transvaginal ultrasound scan (TVS) and pelvic magnetic resonance imaging (MRI) have shown high rates of sensitivity and specificity suggesting that the dogma of laparoscopy as the blanket gold standard for all endometriosis may need to be revisited and refined[19]. TVS can identify endometriomas, but the absence of ovarian cysts cannot eliminate the diagnosis of superficial endometriosis. TVS with bowel preparation can detect deep lesions affecting the bladder, bowel, and rectovaginal pouch. Pelvic MRI is used to detect large peritoneal nodules affecting bladder, bowel or ureter[21]. The International Deep Endometriosis Analysis (IDEA) group proposed a 4-step approach that focuses on the visualization of significant markers of endometriosis (i.e., endometrioma, DEEP, adenomyosis, or pelvic adhesions)[22]. The first step consists of examining the uterus and adnexa for endometriomas. The second step includes ovarian mobility, site-specific tenderness, and localization of free peritoneal fluid. The third step evaluates the Pouch of Douglas obliteration status. The final step consists of diagnosing and localization of DEEP in the anterior and posterior compartments.

1.1.3 Pathogenesis

Despite the comprehensive definition of endometriosis, there is limited understanding of the pathogenesis of the disease. Retrograde menstruation is regarded as an important origin of the endometrial deposits, but other factors are involved, including endocrine and metabolic environment, epithelial–mesenchymal transition, neurogenesis, and altered immunity and inflammatory responses in genetic susceptible women[23]. Genetic susceptibilities are beginning to be delineated, although they are insufficiently established to confirm cause and effect, and subsequent development of endometriosis. The proposed theories of aetiology of endometriosis and the roles of the immune system, hormones, and genetics are explained below.

1.1.3.1 Theories of aetiology

The classical theories of pathogenesis are:

- Retrograde menstruation (Sampson's theory, 1927): This is a widely accepted hypothesis based on evidence of back flow of menstrual effluent in the peritoneal cavity through the Fallopian tubes[24]. However, retrograde menstruation was later described as a common physiological phenomenon found in over 90% of menstruating women, yet only 10% have endometriosis[25,26]. In addition, viable endometrial cells are found in the peritoneal fluid of over 70% of women with and without endometriosis[27]. Thus, the presence of endometrial tissue in the pelvis does not necessarily cause the disease; rather, endometrial cells' unique survival mechanism and a favourable peritoneal environment can encourage implantation, proliferation, angiogenesis, and growth in affected women.

- Metaplastic transformation (Meyer's theory, 1903): The coelomic metaplasia theory proposed that endometriotic cells in the peritoneal pluripotent cells can change into endometrial cells by originating from the metaplasia of coelomic epithelium sharing a common embryonic precursor. This theory includes biochemical or immunological factors that may induce endometrial differentiation of undifferentiated cells[28,29].

- Lymphatic or hematogenous spread (Halban's theory): The lymphatic or vascular system has been proposed to assist endometriotic tissue to disseminate from the uterus and to extra pelvic sites. This theory is supported by cases where endometriosis is found in remote sites like the brain or pleura but does not explain the mechanism in which the cells proliferate in these extra pelvic sites[30]. Extra-pelvic endometriosis is supported by the theory of lymphatic and blood metastasis[31].

- Tissue injury and repair theory: The direct transplantation theory during tissue trauma or surgical procedures demonstrate that endometrial cells may become incorporated at surgical sites (the site

of an episiotomy or a caesarean section), leading to endometriosis and pelvic trauma[32]. The localized oncogenic cascade and lack of immunological response may result in implant survival.

- Mullerian theory: The Mullerian theory proposes the misplacement of endometrial tissue during fetal development, which explains the diagnosis of endometriosis in non-menstruating women or, very rarely, in men receiving oestrogen therapy[33,34]. The differentiation of bone marrow stem cell lineages, such as mesenchymal or endothelial stem cells, into endometriosis has been proposed[35].
- Denervation and reinnervation theory: This theory considers nerve injury results in pelvic trauma or chronic straining as a causative factor for endometriosis and pelvic pain[36].

Not one of these classical theories can explain all cases of endometriosis. It is likely, therefore, that different mechanisms for the pathogenesis of endometriosis act in conjugation with various innate and acquired factors, such as genetics, environmental or immunological factors[37].

1.1.3.2 Dysfunctional immune system

Various immunological and inflammatory processes have been implicated in the development of endometriosis. Cell-mediated immunity is deficient in women with endometriosis because endometrial cells evade immune clearance, hence promoting implantation and inflammation through the suppression of natural killer cells and T-lymphocyte activity[38–40]. While white blood cells (WBC) are unable to recognize that endometrial deposits are evading and proliferating outside the uterine cavity, macrophages increases the vascular supply of endometrial implants and enhances the spread and progression of endometriotic deposits by increasing the production of growth factors and cytokines (tumour necrosis factors and interleukin) of the endometrial cells[7,40–45].

Angiogenesis after implantation is an important step in the pathogenesis of endometriosis, where vascular endothelial growth factor (VEGF) has high concentrations in the peritoneal fluid and eutopic endometrium of endometriosis patients close to menstruation and identified fibrosis of the implants[46]. Cyclooxygenase-2 and Prostaglandins-E2 are products of the inflammatory cascade that are found to be upregulated in eutopic

and ectopic endometrial tissue of endometriosis patients[47–49]. These products are known to enhance oestrogen synthesis through activation of steroidogenic genes[50].

1.1.3.3 Role of hormones

Endometriosis is an oestrogen-dependent disorder. Oestrogen and progesterone, predominantly produced by the ovaries, play major roles in endometriotic tissue growth through the alterations of oestrogen signalling and expression of aromatase in the endometriotic implants[51]. The aromatase enzyme activates steroidogenesis and catalyses the biosynthesis of oestrogen[50]. Given that prolonged exposure to oestrogen increases endometriosis risk, women with earlier age at menarche, shorter menstrual cycle, and fewer pregnancies are associated to endometriosis[52].

Progesterone triggers a uterine endometrial response and limits endometrial growth by inhibiting: (1) oestrogen-dependent proliferation of epithelial cells; (2) secretory maturation of the glands; and (3) transformation of stromal cells into specialized decidual cells[53]. Inflammation could induce progesterone resistance by altering the progesterone signalling pathway through interference with proinflammatory transcriptional factors. Hence, inflammatory response contributes to the steroid hormone expression that is critical in endometriotic lesion formation, due to the triggering of an angiogenic response, tissue-adhesive properties and activity of matrix metalloproteinases[54].

1.1.3.4 Genetic and epigenetic factors

There is clear evidence of a familial inheritance of endometriosis in a polygenic manner[52]. Twin and family-based studies have shown that there is consistent evidence to support heritability to be around 50%[55–57]. Women with a first degree relative with endometriosis has a seven to 10 times greater risk of developing endometriosis and is more likely to have a more advanced stage at the time of diagnosis[58,59]. Although the risk may be attributed in some families to one or more high-penetrance susceptibility loci with near-Mendelian inheritance[60], the evidence increasingly points to endometriosis being inherited as a complex

genetic trait in which multiple genes that confer susceptibility to the disease interact with each other and the environment to produce the disease phenotype[61].

Genetic association and linkage studies have led to the identification of loci that alter women's risk of developing endometriosis and provide new insights into potential underlying pathways. The contribution of genetic factors has been supported by many studies[59,60,62–65]. Genome-wide association studies (GWAS) have been published for endometriosis, in women of European[66–68] and in Japanese ancestry populations[69], demonstrating genome-wide significant variants implicated in the regulation of cell cycle and transcription, in inflammation, cell adhesion and signalling, oxidative stress and metabolism.

The most recent GWAS on endometriosis included 58K cases and 733K controls and revealed 27 genome-wide significant loci associated with the condition (Table 1.1) [68,70–75]. Interestingly, most of the conducted GWAS have highlighted that the signals for most loci have greater effect sizes for rASRM stage III/IV disease, thus suggesting that these loci affect mainly the advanced stage of endometriosis. In addition, endometriosis share a genetically-associated comorbidity with other chronic pain conditions, migraine, infertility, and main obesity-related genetic risk-variants[59,76]. However, further research is warranted to determine whether gene expression is associated with any lesion characteristics (e.g., anatomic subtype), or affect the development of endometriosis-associated symptoms, such as pain or infertility

Table 1.1. Genome-wide significant loci (n=27) from the latest and largest GWAS meta-analysis of endometriosis, stage III/IV, stage I/II and infertile endometriosis. This table was extracted from Rahmioglu et al, 2018 (Table 2).

Chr	Lead SNP	Position (hg19)	RA (RAF)	Overall Endometriosis		Stage III/IV Endometriosis		Stage I/II Endometriosis		Infertile Endometriosis		Nearest Gene/ Cytoband
				OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	
Previously reported loci												
1	rs12037376	22462111	A (0.19)	1.16 (1.13-1.19)	2.85×10^{-22}	1.23 (1.15-1.32)	1.33×10^{-9}	1.17 (1.08-1.26)	7.43×10^{-5}	1.21 (1.11-1.31)	4.24×10^{-6}	*WNT4/1p36.12*
2	rs11674184	11721535	T (0.61)	1.11 (1.09-1.14)	1.47×10^{-18}	1.17 (1.11-1.23)	1.13×10^{-8}	1.09 (1.02-1.16)	6.82×10^{-3}	1.05 (0.99-1.12)	0.11	*GREB1/2p25.1*
2	rs4141819	67864675	C (0.30)	1.05 (1.03-1.06)	$3.08\times10^{-10*}$	1.09 (1.03-1.15)	1.53×10^{-3}	1.07 (1.00-1.14)	0.03	1.06 (1.00-1.14)	0.05	*ETAA1/2p14*
2	rs10167914	113529183	C (0.32)	1.08 (1.05-1.11)	5.37×10^{-10}	1.13 (1.07-1.20)	1.05×10^{-5}	1.06 (1.00-1.13)	0.06	1.13 (1.05-1.19)	5.61×10^{-4}	*IL1A/2q13*
2	rs1250247	216299629	C (0.28)	1.07 (1.05-1.10)	3.88×10^{-8}	1.12 (1.06-1.18)	6.82×10^{-5}	1.09 (1.02-1.16)	9.67×10^{-3}	1.09 (1.02-1.16)	0.01	*FN1/2q35*
4	rs10012589	56002689	A (0.72)	1.10 (1.07-1.13)	5.69×10^{-13}	1.21 (1.14-1.28)	1.86×10^{-10}	1.08 (1.01-1.15)	0.02	1.11 (1.04-1.19)	2.07×10^{-3}	*KDR/4q12*
6	rs6938760	19802104	A (0.39)	1.09 (1.06-1.11)	2.89×10^{-12}	1.13 (1.08-1.19)	1.88×10^{-6}	1.06 (1.00-1.13)	0.05	1.10 (1.04-1.17)	1.16×10^{-3}	*ID4/6p22.3*
6	rs7759516	151838245	C (0.18)	1.14 (1.11-1.17)	1.35×10^{-18}	1.27 (1.19-1.35)	6.58×10^{-13}	1.03 (0.96-1.12)	0.41	1.08 (1.00-1.17)	0.04	*CCDC170/6q25.1*
6	rs71575922	152554014	G (0.16)	1.15 (1.12-1.19)	1.71×10^{-18}	1.30 (1.22-1.39)	3.63×10^{-14}	1.10 (1.02-1.19)	0.02	1.14 (1.05-1.23)	2.36×10^{-3}	*SYNE1/6q25.1*
7	rs12700667	25901639	A (0.72)	1.08 (1.05-1.11)	8.63×10^{-10}	1.20 (1.13-1.27)	3.15×10^{-9}	1.06 (0.99-1.13)	0.08	1.12 (1.05-1.20)	5.75×10^{-4}	*7p15.2/7p15.2*
7	rs55909142	46673774	C (0.6)	1.08 (1.05-1.10)	8.76×10^{-11}	1.14 (1.08-1.20)	1.61×10^{-6}	1.06 (1.00-1.13)	0.05	1.11 (1.05-1.17)	6.23×10^{-4}	*7p12.3/7p12.3*
9	rs9987548	22173075	A (0.4)	1.09 (1.06-1.12)	2.29×10^{-13}	1.19 (1.13-1.25)	6.90×10^{-11}	1.05 (0.99-1.12)	0.11	1.16 (1.09-1.24)	7.14×10^{-7}	*CDKN2-BAS1/9p2*
11	rs74485684	30242287	T (0.84)	1.15 (1.12-1.19)	1.32×10^{-18}	1.22 (1.14-1.31)	3.54×10^{-8}	1.10 (1.02-1.20)	0.01	1.17 (1.08-1.27)	2.34×10^{-4}	*FSHB/11p14.1*
12	rs12320196	95712695	C (0.3)	1.08 (1.05-1.10)	3.38×10^{-9}	1.14 (1.08-1.20)	2.66×10^{-6}	1.09 (1.02-1.16)	0.01	1.10 (1.03-1.17)	4.15×10^{-3}	*VEZT/12q22*
Novel loci												
1	rs1894692	169467654	A (0.98)	1.18 (1.13-1.24)	$2.88\times10^{-13*}$	1.63 (1.28-2.07)	5.99×10^{-5}	1.12 (0.88-1.43)	0.34	1.34 (1.06-1.71)	0.02	*SLC19A2/1q24.2*
1	rs495590	172152202	G (0.52)	1.07 (1.05-1.10)	6.73×10^{-10}	1.11 (1.06-1.17)	3.22×10^{-5}	1.06 (1.00-1.12)	0.05	1.07 (1.01-1.14)	0.02	*DNM3/1q24.3*
4	rs2510770	95479372	A (0.33)	1.05 (1.03-1.06)	$8.25\times10^{-10*}$	1.06 (1.01-1.12)	0.03	1.06 (0.99-1.13)	0.08	1.08 (1.01-1.15)	0.02	*PDLIM5/4q22.3*
5	rs13177597	82052282	G (0.13)	1.06 (1.04-1.08)	$1.30\times10^{-8*}$	1.15 (1.06-1.24)	6.81×10^{-4}	1.07 (0.97-1.17)	0.16	1.11 (1.01-1.22)	0.04	*ATP6AP1L/5q14.2*
7	rs62468795	23530051	G (0.85)	1.10 (1.07-1.14)	8.05×10^{-09}	1.14 (1.06-1.22)	5.2×10^{-4}	1.15 (1.06-1.26)	1.24×10^{-3}	1.08 (0.99-1.18)	0.08	*IGF2BP3/7p15.3*
8	rs10090060	75257608	A (0.58)	1.08 (1.06-1.11)	5.72×10^{-11}	1.08 (1.02-1.14)	3.85×10^{-3}	1.09 (1.02-1.15)	6.80×10^{-3}	1.11 (1.05-1.18)	4.83×10^{-4}	*GDAP1/8q21.11*
10	rs1802669	21827796	A (0.34)	1.07 (1.05-1.10)	5.52×10^{-9}	1.09 (1.03-1.15)	2.14×10^{-3}	1.09 (1.03-1.16)	6.08×10^{-3}	1.09 (1.02-1.16)	6.41×10^{-3}	*MLLT10/10p12.31*
10	rs796945	90150837	C (0.37)	1.07 (1.05-1.10)	1.78×10^{-9}	1.08 (1.03-1.14)	2.83×10^{-3}	1.05 (0.99-1.12)	0.10	1.11 (1.05-1.18)	5.80×10^{-4}	*RNLS/10q23.31*
12	rs17727841	102809630	G (0.81)	1.06 (1.04-1.08)	$5.33\times10^{-11*}$	1.17 (1.09-1.25)	4.95×10^{-6}	1.06 (0.98-1.14)	0.16	1.03 (0.95-1.11)	0.46	*IGF1/12q23.2*
14	rs7151531	93113547	C (0.29)	1.07 (1.04-1.10)	3.80×10^{-8}	1.10 (1.04-1.16)	8.37×10^{-4}	1.01 (0.95-1.08)	0.76	1.11 (1.04-1.18)	1.82×10^{-3}	*RIN3/14q32.12*
15	rs4923850	40352278	A (0.47)	1.05 (1.04-1.06)	$3.07\times10^{-13*}$	1.10 (1.04-1.15)	4.42×10^{-4}	1.03 (0.97-1.09)	0.40	1.07 (1.01-1.13)	0.03	*BMF/15q15.1*
17	rs66683298	46277748	C (0.61)	1.08 (1.06-1.11)	1.73×10^{-10}	1.10 (1.04-1.16)	3.71×10^{-4}	1.10 (1.04-1.17)	1.93×10^{-3}	1.06 (1.00-1.13)	0.04	*SKAP1/17q21.32*
17	rs76731691	63960269	G (0.94)	1.08 (1.05-1.11)	$9.27\times10^{-9*}$	1.20 (1.08-1.34)	9.77×10^{-4}	1.25 (1.10-1.42)	7.29×10^{-4}	1.14 (1.01-1.29)	0.04	*CEP112/17q24.1*

* The overall endometriosis association results are from the combined meta-analysis including replication evidence that unrevealed genome-wide significant results. Discovery overall endometriosis GWAS meta-analysis results for these variants were: rs4141819 $p=9.5\times10^{-8}$, OR=1.06, 95% CI=1.04-1.09; rs1894692 $p=4.18\times10^{-6}$, OR=1.22, 95% CI=1.12-1.33; rs2510770 $p=1.03\times10^{-6}$, OR=1.06, 95% CI=1.04-1.09; rs13177597 $p=9.9\times10^{-6}$, OR=1.08, 95% CI=1.05-1.12; rs17727841 $p=6.09\times10^{-8}$, OR=1.08, 95% CI=1.05-1.12; rs4923850 $p=1.06\times10^{-7}$, OR=1.06, 95% CI=1.04-1.09; rs76731691 $p=1.06\times10^{-6}$, OR=1.13, 95% CI=1.07-1.18.

1.1.4 Symptoms of endometriosis

1.1.4.1 Pain typology

Pain associated with endometriosis is chronic, subjective, and multi-dimensional. The mechanisms to explain why the presence of endometriosis lesions results in increased sensitivity or perception of painful symptoms remain poorly understood but potential mechanisms include inflammation, hormonal stimulation of endometriotic lesions, stimulation of neural pathways, or a mixture of the above factors[77]. It is also notable that central nervous system sensitization to painful stimuli can cause chronic pelvic pain even without continuing stimulation and this may explain the persistence of pain in women even after removal of lesions[78–80].

Pathophysiology

Pelvic pain with endometriosis has a complex pathophysiology, synthesizing peripheral and central pain mechanisms, through a wide network of interacting mechanisms likely involving inflammatory, nociceptive, and neuropathic pain[81–87]. The inflammatory pain is a consequence of pro-inflammatory cytokine expression that may modulate pain signalling. Tumour necrosis factor, chemokines, and interleukin bind to nociceptive receptors activating the peripheral nerve stimulation and sensitization, hence triggering nociceptive pain[85]. Increased uterine contraction, active inflammation and neurogenesis around endometriotic lesions may lower the threshold of peripheral sensitization and facilitate signal transmission to central sensitization and myofascial pain[84,88,89]. Prostaglandins-E2 and nerve growth factors enhances the expression of neuropeptides to increase central sensory and sympathetic fibre signal transmission, leading to hyperalgesia[90]. Microenvironment variation in local inflammation may arise from the expression of the endometriosis epithelium, from surrounding immune cells, and from the peripheral nerve cells.

Prolonged peripheral sensitization and ongoing central nerve stimulation may lead to central sensitization[83]. Central sensitization is an amplification of pain through neuroplasticity in the central nervous system that can lead to long periods of dysfunctional pain[87]. The effect of central sensitization can explain chronic pain

conditions, such as painful bladder syndrome, irritable bowel syndrome, and myofascial pain, and it is associated with pain catastrophizing[86]. Another mechanism is cross sensitization, which is the convergence of pain signals originating in an organ that are sensed in a nearby structure through crossing neurons along the pain signal pathway[91]. In some cases, central sensitization can become autonomous and occur independently of the peripheral stimulus, which occurs when women continue to experience pelvic pain after complete excision of endometriosis and removal of the nociceptive stimuli[81,92]. This is also demonstrated with changes in the regional grey matter volume within the central pain systems and altered brain chemistry[93–95]. Cross-organ sensitization may also explain the co-existence of pelvic comorbidities in patients with chronic pelvic pain. Cross-organ sensitization consist of viscero-visceral or viscero-somatic convergence of the spinal cord, where nociceptive input from one part of the body can affect neuronal activity from an adjacent body structure[96].

Treatment of pelvic pain

Treatment of pelvic pain associated with endometriosis depends on the presence and severity of scar tissue, location, extent and depth of the endometriosis implants, and the pain generator(s) and severity[97]. Treatment approaches differ if a patient appears to have peripheral pain, central pain or both pain mechanisms[98]. Given the progressive and recurring nature of the disease, all the available medical treatments will only treat the lesions and symptoms, rather than cure the disease[97].

Empirical treatments with a combination of combined or progesterone-only oral contraceptive pills and non-steroidal anti-inflammatory drugs (NSAIDs) are common treatment options for patients with endometriosis-associated pain[99]. If successful, the need for surgical diagnosis may be avoided. Creating a hypoestrogenic environment, which causes amenorrhea, decreases systemic oestrogen production, blocks prostaglandin, and minimizes inflammation[100,101]. To target the production or action of steroid hormones, progestogens, anti-progestogens, combined oral contraceptive pills, hormonal intrauterine devices, gonadotropin releasing hormone (GnRH) antagonists, aromatase inhibitors, and androgenic steroids are

provided. However, many of these treatments have unwanted side effects, and discontinuation of the treatment will lead to recurrence of the symptoms.

The currently available medical treatments may interfere with normal ovarian function and production of ovarian steroids by suppressing ovarian activity and/or reducing adequate menstrual flow, which can cause menopausal symptoms and bleeding. Surgical treatment by total excision and ablation is usually offered after medical treatment failure[18]. However, hormonal suppressive medical therapy is usually required post-operatively to prevent recurrence[102]. An updated recent systematic review and meta-analysis shows that at 12 months post-surgery, endometriosis-associated symptoms (dysmenorrhea, CPP and dyschezia) showed a significantly greater improvement with laparoscopic excision compared with ablation[103]. However, the reported recurrence rates of endometriosis lesions after surgery and its associated symptoms are high and vary from approximately 21% after 2 years, to around 40–50% at 5 years, and increases more over time[104]. One study showed that up to 30-40% of women reported recurring of their dysmenorrhea within one year of laparoscopy, in patients who did not receive any other treatments[105]. A recent Cochrane review demonstrated that there is unclear evidence whether laparoscopic surgery improves overall pain compared to diagnostic laparoscopy only[106]. Further research is warranted to improve treatment method that targeted to pain generator(s), with considerations of including a multidisciplinary care.

The treatment for endometriosis with the highest reoperation-free rate (92%) in seven years follow-up is surgical menopause through hysterectomy and bilateral oophorectomy[107]. However, endometriosis reoccurrence may occur, and could only be considered for women with endometriosis who have failed to respond to available conservative treatments and have completed their family. However, this may be an issue in some countries due to local policies, traditional norms, and religious beliefs.

Countries in the Middle East, and other Muslim-majority regions, adhere to the Islamic Sharia principles, the legal practice derived from the teaching of the Quran. These religious legal interpretations encompass nearly every social structure, area of human activity and aspect of government, including the laws and regulations associated to permanent forms of sterilization. Given that the procreation of children is strongly

encouraged under the Islamic law for married couples, there are strong reservations and regulations implemented regarding legality of permanent methods of female sterilization, with the exception for health reasons. In the United Arab Emirates (UAE; the UAE Federal law No. (10) of 2008 effective to date), women would require approval from their husband, three medical physicians, and the governmental authorization entity to proceed with a bilateral oophorectomy, which is often restricted to women that have more than 10 children or a medical illness that could endanger her life in the future due to pregnancy. On November 7, 2020, a government decree was published to slightly alter this law by not restricting to the number of children or the association to a medical illness, however a non-objection certificate from the husband and the approval of a medical and government committee is still required. This law is applicable in Saudi Arabia, Kuwait, Bahrain, Oman, and Qatar, and similar to other Middle Eastern countries where Islamic law influences the laws of countries in the region and is central in determining legal issues.

Pelvic pain could be present as a part of a chronic pain syndrome, such as central sensitization, fibromyalgia and myofascial pain, without any evidence of endometriosis[86,108]. Such chronic pain conditions require a multidisciplinary approach for focused pain management through medical therapy, psychological support, cognitive behavioural therapy, counselling, pain education, and physical therapy[109].

1.1.4.2 Infertility

It is estimated that 25–50% of women with infertility have endometriosis and approximately 30–50% of patients with endometriosis are infertile[110]. There are multiple reasons why some women suffer from endometriosis-associated infertility, which may include endocrine disturbances, anatomical distortions due to adhesions in more severe disease, or alterations in immune cell function.

Pathophysiology

Endometriosis affects each aspect of a woman's reproductive function and may adversely affect fecundity by different mechanisms. Ectopic endometrial cells lead to an inflammatory process, which produce reactive oxygen species, and can interrupt folliculogenesis, fertilization and ovarian function[111]. Barriers on

oocyte transfer or an unfavourable environment for oocytes may occur due to large endometriomas. Changes in the eutopic endometrial receptivity, such as alteration of oestradiol, progesterone, and cytokines concentrations, may reduce the chance of blastocyst implantation[114]. Anatomical distortion of the pelvic cavity from endometriosis is possibly related to infertility, more so in advanced stages, with a mechanical obstruction of the reproductive tract[114,115].

Treatment of infertility for endometriosis

Treatment choices for women with endometriosis-associated infertility should consider a woman's age, ovarian reserve, the location of endometriomas, pelvic anatomy, and duration of infertility[6,116]. Medical treatment is not recommended because all current medications used for endometriosis are hormonal and block ovulation, therefore, women with endometriosis proceed with ovarian stimulation, assisted reproductive treatment (ART), or surgical treatments. The management of endometriosis-related subfertility should involve multidisciplinary team and input from fertility experts[117]. The Endometriosis Fertility Index (EFI) is a fertility tool that includes parameters such as patients age, duration of infertility, pregnancy history and endometriosis severity according to the ASRM score. It predicts spontaneous pregnancy rates in women with surgically confirmed endometriosis, and is useful to provide reassurance to patients with good prognoses, and assist those with poor prognoses to avoid wasting time and money to treatment[115].

Surgical excision is usually required in cases of large endometrioma, DEEP, and pelvic adhesion when considering fertility preservation in young patients[102]. The recommendation to offer excision or ablation may be associated with better pain relief, improves the pregnancy rate, and decreases recurrence. This will improve the anatomy and eliminate lesions that contribute to an unfavourable inflammatory milieu in the pelvis, potentially increasing fertility. However, surgery may not completely correct anatomical distortion and biochemical factors, which may impair ovarian function and reserve, and cause a detrimental effect on oocyte quality or resulting on endometriosis receptivity with further adhesions[118,119]. Due to the lack of high-quality randomized controlled trials, it is uncertain if operative laparoscopy yields in live birth rates

or adverse pregnancy outcomes[120]. Further studies must investigate the effectiveness of operative laparoscopy on women with endometriosis, depending on the progression of endometriosis to a symptomatic state, progression of the extent of disease in terms of volume of lesions, location of lesions in infertile women, and timing of surgery.

Ovulation stimulation and intra-uterine insemination (IUI) is often recommended in young women with good signs in terms of normal ovarian reserve, patent tubes and partner's semen analysis[121]. In vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) can bypass endometriosis-related inflammation and, in some cases, immediate referral to IVF, rather than surgery, is recommended for women with advanced maternal age, male-factor infertility, and low ovarian reserve[114]. Additionally, other cases with low likelihood of natural conception can be considered for a post-operative IVF referral based on the surgical assessment of the pelvic endometriosis[122,123]. However, comparison of the results of ART for patients with endometriosis-associated infertility has not revealed any differences in live birth rates[124–127]. Due to high levels of clinical heterogeneity with endometriosis, challenge lies in identifying sufficient protocols for ART modalities in patients with endometriosis-associated infertility.

1.1.5 Impact on quality of life

Endometriosis is a painful disease with high impact on women's (and their families) social and financial lives, and their mental state. The symptomatology associated to endometriosis causes chronic, multifactorial pain phenotypes, reduced fecundity, and psychological morbidity. Symptomatic women with endometriosis report a negative effect on health-related quality of life (HRQoL) due to its impact on major life activities, such as work, school, daily activities, economic impact and self-care[14,128–131].

The impact of endometriosis on HRQoL is also known to be greater than the impact of many other gynaecological and non-gynaecological conditions on HRQoL[132,133]. The effect is increased by the lack of adequate understanding on the symptomatology, risk factors and phenotypic profile of the condition, as well as the sense of loss of control experienced by women, who sometimes turn to empirical treatments as a means of gaining control of their lives[134,135]. Women with endometriosis report significant impairment in

physical and mental HRQoL, when compared to healthy participants, and have an increased risk of developing anxiety and depression[136–138].

The Global Study of Women's Health (GSWH), a cross-sectional study conducted in 10 countries among women undergoing their first laparoscopy for symptoms suggestive of endometriosis, demonstrated a negative impact of endometriosis on HRQoL and work productivity. Country-specific differences were observed in the GSWH study, specifically for the duration of diagnostic delay (3 to 10 years), diagnostic incidence rates (34.8% to 100%), prevalence of moderate/severe disease rASRM stage, staging; 30-40% in most centres, but nearly 90% in other countries), and monetary loss from endometriosis-associated work absenteeism and presenteeism (varying from US$208 to US$23,712). Collecting comprehensive data from all patient populations is critical to understand if there are intrinsic differences in the pathophysiology of endometriosis, in terms of race, genetics, environmental and socioeconomic factors.

Women who experienced longer diagnostic delays reported greater impairment in HRQoL[14]. The lack of awareness and inadequate non-invasive diagnostic tools causes a substantial delay in diagnosis[139]. Given that surgical investigation is required for accurate diagnosis of endometriosis, it can also cause adverse effects related to post-operative complications. Medical treatment may relieve symptoms, however patients often have to take these pharmacological therapies for a long time, leading to impairment of HRQoL due to side-effects[140,141]. Given the potential effects of this chronic disease on personal lives, health care systems, and the global community, it is important to advance our understanding of the complex pathways leading to diagnosis, management, and treatment in different populations, to improve the outlook for affected women.

1.1.5.1 Work productivity and activity impairment

Women with endometriosis have reported altering their career trajectories due to endometriosis, including taking time off work, opting for part-time employment, losing chances for promotion due to absenteeism, or choosing a less stressful job[142]. Tiredness, frequent pain, more severe pain, greater use of sick days, and depression at work were associated with decreased work ability.

The GSWH study reported that absenteeism (p=0.019), presenteeism (p=0.033), and overall work productivity losses (p=0.014) were more frequently associated to women with endometriosis when compared with symptomatic controls[14]. This study showed that each affected patient lost on average 10.8 hours of work per week, primarily due to decreased effectiveness and the total average annual cost of woman with endometriosis estimated at €9579 in healthcare costs, treatment, and loss of work. Costs were higher with the presence of infertility, the existence of CPP, with increasing severity of endometriosis and a diagnostic delay[143]. Indirect costs of productivity loss were twice as large as the direct healthcare costs of endometriosis-associated symptoms.

1.1.6 Risk factors for endometriosis

Several epidemiological studies have also shown that there are groups of women at a higher risk of developing endometriosis. Menstrual, reproductive, sociodemographic, lifestyle and physical characteristics are putatively associated with the risk of endometriosis, but several practical difficulties often threaten the validity of the methodological approaches used in the definition and quantification of this risk. Published literature are compromised by potential sources of bias, including methodological heterogeneity, disparity in racial/ethnic groups, low sample size and ascertainment bias, suggesting the possibility of reduced statistical power.

Challenges in endometriosis research exists when attempting to define the cases and a comparison group. The heterogeneous endometriosis symptoms, requirement of surgically visualized diagnosis, and pathological findings makes the selection of an appropriate case definition challenging. Given that laparoscopy is the gold standard for diagnosing endometriosis, it brings bias to epidemiological studies because hospital patients may not be representative of the general population, and a subset of the women may be excluded from the analyses: (1) women whose symptoms are managed less invasively using medical treatments (anti-inflammatory treatments or oral contraceptives), (2) women who have not proceeded with surgical investigation, or (3) women who cannot afford a surgical procedure. Selecting a comparison group remains critical as it is important to avoid the inclusion of undiagnosed cases among the controls, whilst

being representative of the population from which cases are drawn. However, these highly selected women who do proceed with pelvic surgery are a biased sample of those from the underlying population and can reduce risk estimates since such controls may share similar lifestyle and other characteristics as cases. These challenges mean that any study that generates risk estimates must pay careful attention to the definition of its study population and to include multiple control groups to test sensitivity of results to control definition, and to avoid overestimates or underestimates of common risk factors.

In addition, to understand the relationship with modifiable risk factors, incident cases should be selected. Given the diagnostic delay of 6-10 years, the temporal relationship between exposure and disease must be interpreted when considering modifiable risk factors, as symptom onset may have preceded an endometriosis diagnosis by many years, leading to changes to exposures. Assessment in such a population may yield risk factors associated with the time of detection of endometriosis, rather than care-seeking and disease detection.

A related issue in identifying and quantifying endometriosis risk is the need for careful consideration of which factors may act as confounders or modifiers of the association of factors to endometriosis[144]. Confounding may occur when the true effect of the exposure on endometriosis is distorted by some other factor, leading to inaccurate estimates of effect. In the literature, most studies use either established confounders or the change-in-estimate approach to determine confounders to control for. The latter approach may be more accurate as confounders are added to a model if their addition or deletion from the original model changes the estimate of risk by 10% or more[145].

Case-control and cross-sectional studies have been unable to establish a clear temporal relation between exposure risk factors and endometriosis. Prospective cohort studies are the gold standard for the assessment of exposure risk factors as they are less prone to differential measurement error from poor recall of past exposures, less susceptibility to selection bias, and could study multiple comorbid conditions to endometriosis. The temporal sequence between exposure and endometriosis can be elucidated clearly to establish causal associations by use of repeated biologic measures or repeated updates of self-reported

exposures, with an adjustment needed for the advancement of diagnosis by screening to ensure a common baseline for the time-to-event analysis. It is well established that women's health cohorts such as the Nurses' Health Study from the USA[146] and the Million Women Study from the UK[147] have been crucial in investigating how various reproductive and lifestyle factors affect endometriosis and other gynaecological diseases.

1.1.6.1 Sociodemographic factors

Socioeconomic status and educational level

Women with a higher socio-economic status have a higher likelihood of being diagnosed with endometriosis. However, this might arguably be due to unequal possibilities to afford a visit to a healthcare provider[139]. Similarly, women with endometriosis had a higher level of education, which perhaps gave them better knowledge and opportunities to seek correct diagnosis[10,148,149]. On the other hand, studies have demonstrated that symptoms strongly interfere with their life opportunities, leading to time off from school, lack of concentration, or having to leave the education completely. These findings on educational and work impact attributed to endometriosis-associated pain are consistent with other chronic pain conditions in young women, which are also associated with increased risk of reduced educational attainment[150,151]. Similar problems were experienced in a workplace[142,152] where career growth was negatively affected by endometriosis, including experiences of absenteeism, presenteeism and loss of work productivity[153].

Race and ethnicity

Ethnicity can also play a large role in endometriosis, where some studies have suggested that the risk of endometriosis is greater in white women compared to Black and Asian women[154]. Historical changes in the perceived infrequency of endometriosis in Black women were reported, and diagnostic bias in which symptoms were attributed to pelvic inflammatory disease[155]. Studies have suggested that Middle Eastern and Asian women are at higher risk of endometriosis compared with white women, with a lower risk among African American women[154,156–158]. However, in another study, after adjusting for social class and reason

of the diagnostic procedure, there were no significant differences across the ethnicities of the participants[156,159]. When investigated the association of severity of endometriosis (rASRM) and ethnicity, a prospective registry at a tertiary referral centre demonstrates that women of East and South East Asian ethnicity had increased rates of stages III-IV of endometriosis, in comparison with whites and other ethnicities, which may be due to: (1) women of East/South East Asian descent may be at increased risk of more advanced stages of endometriosis, and/or (2) women of East/South Asian descent may only seek surgical investigation for severe symptomatic episodes, where stage I-II could be less symptomatic[160]. Although there does appear to be variation in prevalence of endometriosis among various ethnic groups, the literature on this topic is insufficient to draw strong conclusions due to methodological limitations. Further research must be conducted to investigate the impact of ethnicity on the clinical presentation and symptomology of women with endometriosis to be able to provide accurate prevalence estimates.

Body mass index and waist-to-hip ratio

There is an inverse association between endometriosis and a woman's current body mass index (BMI) and waist-to-hip ratio adjusted for BMI (WHRadjBMI)[10,161–166], even though obesity is thought to increase bioavailable oestrogen levels via increased adiposity and aromatase activity[167], and might be expected to increase the risk of endometriosis. However, this may be explained by a genetic link where the intergenic locus on 7p15.2 was associated with endometriosis and body fat distribution[168]. A stronger and more consistent relationship exists after adjusting for confounding factors, including age, age at menarche, parity, and contraceptive use. However, there are several biases that should be taken into consideration prior to inferring any temporal relationships between BMI and endometriosis, such as: inverse relationship between BMI and social class, diagnostic difficulties and reluctance to perform surgery in women with higher BMI, and reduced menstrual exposure in women with high BMI with irregular anovulatory cycle[10,169,170]. Furthermore, the endocrine imbalances associated with obesity are linked to abdominal visceral adiposity, suggesting that there may be other measures of adiposity that better correlate to endometriosis risk than obesity. An inverse association between endometriosis and waist-to-hip and waist-to-thigh ratios in women

<30 years has been reported, suggesting that body fat distribution and childhood BMI may be a potentially better marker for endometriosis risk[171]. In a prospective cohort study, an inverse association was present when investigating birthweight, childhood and early adulthood BMI and incidence of laparoscopically confirmed endometriosis, independent of adult BMI and menstrual cycle characteristics[172,173].

Smoking

While a lot of studies have been investigating smoking and its relation to endometriosis, the results seem inconclusive. Early reports have demonstrated that smoking could be a protective factor[174], because smoking reduces the levels of circulating oestrogens[175], and impairing the conversion of androgens into oestrogens[176,177]. Therefore, the risk of endometriosis would be expected to be lower in smokers. However, a meta-analysis of 38 studies did not support any link between smoking and risk of endometriosis[174]. The conflicting nature of the findings in the literature on the relationship of endometriosis and cigarette smoking is difficult to understand. Some authors have suggested that although the contents of cigarette smoke reduce circulating oestrogens, smokers are also exposed to exogenous oestrogens in the form of dioxins, increasing endometriosis risk[161]. The differences may also be due to the fertile status, where a prospective cohort study demonstrated a positive association among fertile women and an inverse association among infertile women[10].

Physical activity

The association between physical activity and endometriosis risk is also inconclusive; however, physical activity may confer a protective effect on endometriosis by decreasing oestrogen production, decreasing ovarian stimulation, and reducing the exposure to menstrual flow[178]. This will reduce the levels of bioavailable oestrogen by increasing the levels of serum hormone binding globulin and increasing systemic levels of anti-inflammatory cytokines. While some studies have demonstrated a positive effect of exercise on the reduced risk of endometriosis[9,179,180], a prospective cohort study demonstrated no association[170]. Further research must be conducted to elucidate the temporal relation between physical activity and endometriosis.

1.1.6.2 Menstrual characteristics and hormonal use

The higher frequency and volume of menstrual reflux associated with endometriosis support Sampson's theory of retrograde menstruation and may modify the risk. Early menarche (<12 years of age), a short interval between menstrual cycles, and heavy menstrual flow have been shown to be associated with an increased risk of endometriosis[52,156,162,181], which is consistent with the conceptual role of increased exposure to menstruation and the role of oestrogen exposure in endometriosis. A prospective cohort study demonstrated that shorter menstrual cycles (<26 days) during late adolescence (18-22 years) were associated with a greater rate of endometriosis compared to 26-31 day menstrual cycles[182].

Epidemiologic data have consistently observed a protective effect of current oral contraceptive use, whereas former use seems to increase risk[9,183–185]. A positive association between oral contraceptive use and endometriosis risk may relate to the fact that oral contraceptives reduce oestrogen production and is associated with endometrial atrophy, therefore reduce the risk of endometriosis[186]. Furthermore, they produce a reduction in menstrual flow, and this reduces the likelihood of retrograde menstruation. However, there are some difficulties with understanding the exact nature of the relationship between endometriosis risk and oral contraceptive use because oral contraceptives are often prescribed as a first line of treatment, and it is impossible to tell if those who are taking oral contraceptives and are subsequently diagnosed with endometriosis developed the disease before or after the exposure. The negative association between oral contraceptive use and endometriosis risk could be due to low doses of oestradiol and progesterone, which increases the risk of implantation and lesion growth[9]. A prospective cohort study demonstrated that the rate of laparoscopically confirmed diagnosis of endometriosis was decreased among current oral contraceptive users but increased among past users[182]. Further studies must be conducted to explicitly describe the reason for initiation of oral contraceptive use and preceding gynaecologic symptoms.

1.1.6.3 Fertility and reproductive characteristics

The relationship between endometriosis and infertility has been debated for many years and poses a challenge to investigate infertility as a symptom of endometriosis due to sociodemographic factors and

access to healthcare factors. Prospective cohort analyses have shown that women with a history of endometriosis have a higher risk for infertility compared with women without a history of endometriosis, with about 15–40% of women with endometriosis experiencing difficulty conceiving[14,187]. The experience of infertility adds to the burden of endometriosis, negatively affecting psychological health, family and marital relationships, social interactions, and financial status (due to fertility treatment) as well as causing feelings of stigmatization and hopelessness[142,188]. The conceptual link between parity and the risk of endometriosis may relate both to the retrograde menstruation theory and the role of oestrogens[189,190].

The relationship between endometriosis and risk of subsequent adverse pregnancy outcomes is complex. Increased progression of the disease results in anatomical distortion of the pelvic cavity, which may lower the pregnancy rate, leading to miscarriages and ectopic pregnancy[191]. In addition, pregnancy is associated with a period of amenorrhea, reducing exposure to menstrual endometrium, and consequently reduces the risk for endometriosis. The high progesterone levels present in pregnancy inhibit the establishment and growth of endometriotic lesions. Endometriosis may also be associated with altered ovulation and oocyte production, increased concentration of inflammatory cells in the peritoneal fluid, endometrial progesterone resistance, and inadequate uterine contractility. These factors may compromise embryonic development, pregnancy implantation and lead to adverse pregnancy outcomes[110,113,125,192]. Research on the pathogenesis of poor pregnancy outcomes suggests that such disturbances in the peri-implantation period may perpetuate throughout the later stages in pregnancy, such as influence on gestational diabetes, pre-eclampsia, pre-term birth and caesarean section[192,193].

1.1.6.4 Comorbid conditions

Comorbidities allow us to understand the shared genetic and biological influences of endometriosis. Endometriosis has been associated with several types of cancer, autoimmune disease, migraine, cardiovascular diseases, gastrointestinal and gynaecological conditions, suggesting that endometriosis patients may represent a high-risk group for these chronic diseases. An understanding of each of the

associations between endometriosis and comorbid conditions will extend our knowledge and understanding on the causes and consequences of endometriosis.

Cancer

Multiple gynaecological cancers and endometriosis have been linked due to possible shared genetic influences and local or systemic enhancement of aberrant inflammatory and sex steroid hormonal mediators. Endometriosis has been suggested to share some characteristics with malignant tumours, such as local and distant invasion, abnormal tissue growth, resistance to apoptosis and invasion of other tissues, dysfunction of target organs and genetic damage[170,179,194]. A recent systematic review and meta-analyses demonstrated that the following types of cancers were most consistently associated with endometriosis: (1) Ovarian cancer (24 studies; standardized risk ratio (SRR): 1.93 (95% CI: 1.68–2.22)) with a significant association to Clear cell subtype (4 studies; SRR: 3.44(95% CI: 2.82-4.20) and Endometroid subtype (5 studies; SRR: 2.33 (95% CI: 1.82-2.98); (2) Breast cancer (20 studies; SRR: 1.04 (95% CI: 1.00–1.09)); (3) Basal-cell carcinoma (2 studies; SRR: 1.18 (95% CI: 1.11–1.25)); (4) Thyroid cancer (5 studies; SRR: 1.39 (95% CI: 1.24–1.57)); and (5) Cervical cancer (4 studies; SRR: 0.68 (95% CI: 0.56–0.82)). Endometrial cancer (17 studies; SRR: 1.23 (95% CI: 0.97–1.57)) and cutaneous melanoma (7 studies; SRR: 1.17 (95% CI: 0.97–1.41)) were not associated with endometriosis[194].

Immune system conditions

Comorbid immune system conditions have been associated with endometriosis, and have been postulated to be due to shared genetic components, shared immunological abnormalities (high T, B, and natural killer cell counts but decreased activity, high IgG/IgA/IgM autoantibodies and anti-endometrial antibodies) and hormonal factors (oestrogens and prolactin)[195–197]. In a meta-analysis of 26 population-based studies, endometriosis was suggested to be associated with systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis, autoimmune thyroid disorder, coeliac disease, multiple sclerosis, inflammatory bowel disease, and Addison's disease[198]. There are contrasting data regarding the association of asthma and

endometriosis. However, asthma has an extrinsic/allergic type that employs immunoglobulin E-dependent mechanisms and is associated with atopy[199–202].

Migraine

Although the link between endometriosis and migraine is not yet clear, the two conditions share genetic and biochemical mediators. Using a twin-based study approach, shared genetic influences appeared to explain part of their co-occurrence within individuals[203]. Systemic spreading of prostaglandins produced by endometriotic lesions, as well as nitric oxide synthesis, have been postulated to contribute to the increased prevalence of migraine among women with endometriosis[204]. Based on a meta-analysis of 9 studies, there was a significant association between endometriosis and the risk of migraine headache in cohort and case-control studies (OR: 1.36; 95% CI: 1.27, 1.46) and (OR: 2.73; 95% CI: 1.51, 3.94), respectively[205].

Metabolic and cardiovascular disorders

Women with endometriosis have hyperinflammatory milieu, both locally and systemically, that have been correlated with decreased levels of adiponectin and increased levels of leptin[40,206]. Metabolic and cardiovascular disorders are associated with endometriosis because atherosclerotic plaque and the peritoneal fluid have an abundance of inflammatory cytokines, chemokines and growth factors that are involved in the generation of localized inflammation[207]. A prospective cohort study has suggested an association between endometriosis and cardiovascular condition (myocardial infarction, angiographically confirmed angina and coronary artery bypass graft; RR: 1.62, 95% CI: 1.39–1.89)[207]. Hypertension, hypercholesterolemia, and atherosclerosis have shown a greater risk among women with endometriosis, however further research is required[207–211]. Given that women with endometriosis may undergo a variety of hormonal or surgical treatments to alleviate symptoms (surgical menopause), this may contribute to type 2 diabetes risk, as earlier age at menopause is associated with higher risk of diabetes and metabolic syndrome[212].

Gastrointestinal diseases

Gastrointestinal tract is the most common location of extra pelvic endometriosis, and women often suffer from the following gastrointestinal symptoms: bloating, abdominal pain, constipation, diarrhoea, nausea, and vomiting. Irritable bowel syndrome (SIR: 3.10 (95% CI: 2.06–4.67)), ulcerative colitis (SIR: 1.5 (95 % CI: 1.3−1.7)), Crohn's disease (SIR: 1.6 (95 % CI: 1.3−2.0)) are more common in women with endometriosis than in the general population[213,214].

Gynaecological conditions

Gynaecological conditions may share similar genetic pathways, biological pathways (hormonal factors), and inflammatory factors, and specifically relevant to endometriosis are uterine fibroids, polycystic ovary syndrome (PCOS) and uterine structural abnormalities[215,216]. The coexistence of uterine fibroids and endometriosis have been demonstrated in both epidemiological and genetic studies (share genetic risk variants in *WNT4/CDC42*, *GREB1*, *ESR1*, and *FSHB*), possibly due to similarities in molecular mechanisms and progenitor cells[217]. Phenotypic similarity exist between PCOS and endometriosis, such as inflammation, progesterone resistance and altered functioning of the female hypothalamic-pituitary gonadal (HPG) axis[218–220]. However, the diseases manifest in pairs through the diametric disorder hypothesis where they involve dysfunction of the same general biological system but in diametric direction, such as inverse relationship between menarche, reproductive physiology (folliculogenesis, decidualization), morphology (BMI, WHR, fat distribution), and hormone profile (testosterone mediated HPG axis development and female reproductive hormones)[219,221,222]. Mullerian tube abnormalities or inadequate corpus luteal functions are more prone to result in the development of endometriosis in later life, due to three basic mechanisms: (1) an increase in retrograde menstruation due to Mullerian anomalies; (2) coelomic metaplasia; and (3) developmental defect of differentiation or migration of the Mullerian duct system during embryogenesis[223].

1.2 The Middle East as a geographical area of research

The Middle East is home to 6.8% of the world's population, yet it contributes 0.03% towards all scientific research[224–227]. It is a transcontinental region that consists of the Arabian Peninsula Region (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates, Yemen), the Levant region (Cyprus, Iraq, Israel, Jordan, Lebanon, Palestine, Syria, Turkey), the North African region (Algeria, Djibouti, Egypt, Libya, Morocco, Somalia, Sudan, Tunisia), and the Persian region (Iran). Due to different degrees of genetic admixture, higher prevalence of globally rare genetic variations with a highly conserved gene pool, and high burden of genomic regions of homozygosity, the Arab populations are known to have a higher incidence of genetic disorders[228–230]. Due to the lack of whole genome and sequencing data available on public databases of the Arab population, it is difficult to catalogue genetic variation across coding and noncoding regions of the human genome. Comprehensive reference panels of genetic variation for entire populations are paramount for the interpretation of the medical and functional relevance of DNA sequence changes.

The region is an ethnically diverse area that has arisen from a series of social and cultural influences and sits at the crossroads of significant human migration between the African, European, and Asian continents. Collectively, the inhabitants are referred to as "Arabs"; a major pan-ethnic group. There are divergent propositions regarding the origin and genetic architecture of Arabs. Hence, understanding the genetic and historical backgrounds of Arabs should be taken into consideration to understand the true origin of the Arabs.

1.2.1 Genetic background of Arabs

Mitochondrial DNA (mtDNA) analyses and archaeological evidence, as well as human genetic diversity and phylogenetic analyses, suggest that individuals originated in Africa were the first wave of modern human migration occurring approximately 85,000 years ago[231–233]. Two proposed routes of human migration out of Africa and into the Middle East have been postulated. The first route took place across Egypt into the Levantine region[234]. The second "southern" route was from a location within Djibouti across

a relatively shallow stretch of water into Yemen in the Southwestern corner of the Arabian Peninsula[235]. However, it is not clear whether continuous populations occupied the peninsula since its earliest settlement, and whether later immigration waves interbred with previous ones.

Analysis of mtDNA and Y chromosome haplogroups have shown a large number of lineage groups in the area which originated from Iraq and Yemen, suggesting that this area was a staging point where populations congregated and dispersed[236–238]. Similarly, Iran has a diverse array of mtDNA lineages suggesting that the area between Arabia and Asia was a human migration pathway into Asia and Europe[239,240].

1.2.2 Historical background of Arabs

The Arab world hold a unique ethnographic identity, historical background, ancestry, cultural traits, social norms, moral values, religious beliefs, and genealogy. Linguistically, the term 'Arab' was utilized by the Assyrian language, which was defined as composite admixtures of exotic distance, deserts, nomadic warriors, tent dwellers and camel herds. Arab identity was pinned onto an archaic tableau by the classical Greek literature, however, not as a term of self-reference for one ancient Arabian race, but instead as a generic label to describe any group whom they thought was a 'Bedouin'.

Pre-Islamic Era

The original inhabitants of the region led a nomadic existence and moved throughout the peninsula, resulting in settlements that were the crossroads for trade and cultural exchange. At these ports, admixture took place between intermingling populations. Arabians were a scattered array of very diverse people, speaking distinct languages that were organized into different kingdoms and state structures, compromised of many races and ethnicities. These kingdoms localized around the Southern Arabian Peninsula, ruled by successive civilizations of Yemeni origin. Additional kingdoms extended across the region from Central, Eastern to Western Arabia (present day Saudi Arabia, Iraq, Jordan, and Syria). The influence of Persians from Asia has taken place during that time. The immigration of the Azd, a branch of the Qahtanite tribe, from Yemen toward Oman and Iraq is argued to be linked to the arrival of the first Arabs in the region.

Post-Islamic Era

During the Islamic period and the century of Prophet Mohammed (PBUH), Arabic language inscriptions proliferated across the Middle East, allowing the earliest attempts to write the origins of pan-Arabian populations grouped into one ethnic community. Arabs began inhabiting towns across the Middle East and aim to be a collective identity of unique culture, language, and norms. While many today believe that 'Arab' is synonymous with 'Muslim,' Arab and Muslim identities struck separate paths. Regardless of their intertwined origins, Arabs today are comprised different monotheistic religions, yet they are unified by common cultural practices, social linguistic influences and traditional norms[237,241–243].

The Contemporary Middle East

The development of trade routes in more recent history has increased bidirectional gene flow into and out of the region, creating the contemporary diversity of modern Arabia. The Middle East is geographically positioned between the African, European, and Asian continents. Hence, it is not surprising that the Arabian Peninsula is at a significant crossroad in human migration as it represents the epicentre of multidirectional flow between populations of the three continents. Coupled with local migration, the invasion of the Ottoman empire, British empire and Portuguese dominance that occurred between settlements within the peninsula shaped an admixed population[238,244,245].

Today, the Middle East is known as a transcontinental region that represents 6.8% of the world's population, compromising of 24 countries and holds geopolitical importance, wealth of history, cultural heritage, and constitute more than 25 ethnic groups due to intercontinental migration[246,247]. Arabs constitute the majority ethnic group in the region, with 19 out of the 24 Middle Eastern countries known as part of the Arab world.

1.2.3 Factors contributing to health in the Arab population

Consanguinity among the Arab population

Due to cultural and religious customs, consanguineous marriages (inter-familial marriages or marriages in blood-relations and cousin-marriages) are very common and widely accepted in the region. First cousin

marriages account for approximately 50% of marriages in the Arab population[230,248]. Consanguineous offspring have high rates of recessive Mendelian diseases and large numbers of deleterious missense variants. This will denote autozygosity, where the inheritance of identical gene copies from each parent will lead to elevated levels of homozygosity[249]. Autozygous stretches within their genome are likely to harbour loss of function mutations which will lead to complete inactivation or dysfunction of genes, resulting in a high frequency of detrimental mutation carriers in the region, such as sickle cell anaemia and thalassemia[230,248]. Although a consistent positive association between consanguinity and rare mutations leading to monogenic disorders and clustering cases of linkage family studies has been reported, the involvement of common variants has also been demonstrated in common complex diseases in different populations, suggestive of community-specific founder mutations that have increased in frequency[250].

High occurrence of obesity

According to the World Health Organization (WHO), nine Middle Eastern countries have ranked highest in the global obesity statistics, with 70-75% of the population being obese or overweight[251]. The rates of obesity among women are around 50-100% higher than among men[252]. There are various personal and environmental factors that act as barriers for Arab women to participate in physical activity: cultural normal and practices of public modesty, lack of accessible environments and fitness facilities for women to feel comfortable to exercise, lack of supportive social milieu for women, conservative dress that is not suitable for physical activity, and lack of information on the importance of physical activity in schools[253,254]. Obesity is an important risk factor for women's health conditions, specifically PCOS, uterine fibroids and menstrual irregularities[255,256].

Low reproductive health awareness

The lack of sufficient studies on women's quality of life and reproductive health issues in the Middle East demonstrates the need to prioritize this under-investigated field and understand the relative role of environmental and genetic factors. Such data and evidence would provide policymakers in the Middle East

crucial information that could impact public awareness and education, direct critical funding needs, facilitate earlier detection, and allow advice on potential lifestyle interventions.

Nearly all countries within the Middle East have not adopted policies, nor approaches taken on educational measures for reproductive and sexual health of adolescents, effective contraceptive services and strategies, and governmental support for family planning initiatives and services. Minimal emphasis is placed on prevention or early detection strategies that would help mitigate the extensive long-term physical, psychological, social, and professional impacts of reproductive health disorders on women and their families.

Middle Eastern populations are lagging behind on major indices of health and research development, and lack reliable, population based data on the major causes of women's health diseases due to poor reporting and the lack of national registries[257]. The mechanism that connects the generation of knowledge and its implementation in health care and education is poorly developed, and has led to the widespread distribution of risk factors for diseases, such as smoking and obesity[258].

Cultural and traditional factors

Polygamous marriages, strong patriarchal cultures, reticence in disclosing personal matters to the public, and reluctance in seeking care to limit community censorship and victimization is common in the Arab population. These cultural issues limit Arab women's autonomy and may contribute to reproductive and mental health disparities[259,260,269,261–268]. In addition, inadequate knowledge on reproductive health literacy and restricted access to mental health services are neglected public health issues in this region, likely to impact women's wellbeing and clinical management[263,270,271]. Restricted access to services and inadequate knowledge on reproductive health literacy leads to a diminution in women's wellbeing, quality of life and diagnosis[263]. Rigid cultural norms and expectations oblige Arab women to accept and conceal mental distress and physical pain, which may contribute to an elevated risk of developing psychiatric disorders and intensify endometriosis-associated pain due to prolonged diagnosis[272].

Mental health is one of the most neglected public health issues in this region[270,271]. Poor mental health outcomes among Arab women have been associated with strong patriarchal cultures, which limits the autonomy for women and contributes to overall disease burden[259–261]. Women are often ashamed to talk about endometriosis and its symptoms in their workplace or even with their close ones[273]. To interpret mental health and illness among Arab women, it is important to understand how Arab women perceive their role in their social, cultural, and religious context. The collectivist society emphasizes interdependence, where their role as custodians of community culture is to protect their family from any emotional harm. Emphasis is placed upon family privacy, reputation and solidarity, where women may feel reluctant to seek help due to shame and risk of harming the reputation and honour of the family[262,274,275]. Therefore, the cultural expectation for Arab women to conceal mental distress may contribute to poor quality of life and increased risk of developing psychological disorders[262,276].

Even with the right diagnosis, women feel like they must justify themselves (as well as being afraid to seem hypochondriac) because the disease is not visible on the outside[152]. In addition, Arab women find it difficult to cope with society, friends, and family's negative reactions to their illness, where they may be blamed for the pain as a sign of punishment or uncontrolled anger, leading to social humiliation and ridicule[260,275,277–279]. Infertility has psychological effects in terms of anxiety, stress, depression and self-esteem, mostly affecting mental health[280]. While this is common across different populations, it may be intensified in this ethnic group because childlessness strongly influences marital life, and unfortunately may lead to divorce, or becoming a second wife in a polygamous marriage[281,282]. Divorced women in Arab societies suffer emotionally and socially, especially when they are infertile. Existing stigma and discrimination are caused by the lack of knowledge about the disease from public as well as from professionals.

Environmental toxin exposure from war and pollution

Evidence from the deployed veterans in the 1990/1991 Gulf War demonstrated an impact on menstrual cycle dysfunction, dysfunctional uterine bleeding, sudden onset of amenorrhea, and infertility[283–288]. The chronic stressful conditions of a prolonged war may lead to menstrual irregularities due to the inhibition of

the normal pulsatile GnRH secretion and excessive hypothalamic activity of corticotrophin-releasing hormone in response to stress. High exposure toxicants and teratogens that were present during the war have been associated with adverse pregnancy and maternal outcomes, including infertility, miscarriage, birth defects and preterm birth[289–292]. This could be due to neuro-immune mechanisms, an increase in pro-inflammatory markers and toxic exposures that are associated with adverse reproductive outcomes[283,284].

Given that multiple countries across the Middle East have been exposed to heavy periods of war, importation and improper disposal of toxic waste, and haphazard dumping of solid waste in inadequate sanitary landfills, this contributed heavily to the environmental degradation of the country, as well as the long-term exposure of psychological and emotional distress. These challenges are of significant concern for fertility problems and reproductive disorders among Arab women.

1.3 Endometriosis among Arab women

Women's health research is widely under-represented and poorly understood in the Middle East[293]. Reproductive health is a challenging issue among Arab women. There is a paucity of population-based epidemiological studies in Arab women with endometriosis. An improved understanding of the prevalence and risk factors for endometriosis in the region will aid a better understanding of the underlying causal pathways in the Arab ancestry populations. A gynaecology clinic remains the realm of mostly married women that then seek regular check-ups. A young woman may suffer from chronic pain daily and menstrual irregularities, but the hegemony of traditions will prevent her from discussing it. Better understanding women's health problems in this population will therefore address a considerable unmet need.

Prevalence, Symptomatology, Risk Factors and Co-morbidities of Endometriosis: A Systematic Review

As the first part of my thesis work, I conducted and published a systematic review and meta-analysis[293] to investigate the prevalence of common gynaecological conditions in the Middle East. MEDLINE, EMBASE, PsycINFO, Global Health, and Google Scholar databases were searched from database inception until 14 February 2021 to identify relevant studies. Peer-reviewed research articles that reported the

prevalence of PCOS, endometriosis, uterine fibroids, and adenomyosis in the Middle Eastern population, written in English or Arabic, were included in the review. The primary outcome was to estimate the pooled prevalence of PCOS, endometriosis, uterine fibroids, and adenomyosis in the Middle Eastern populations. The secondary outcome was to assess the evidence in the data for the presence of heterogeneity, by conducting subtype-pooled analysis of prevalence estimates of the conditions. Total weighted prevalence was calculated via Freeman–Tukey arcsine transformation and heterogeneity through the I^2 statistic. The quality control, assurance and bias of the studies were assessed by two independent reviewers (M.M. and N.R.) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria[294,295].

For endometriosis specifically, a total of 12 studies were included that estimated the prevalence of endometriosis to be 12.9% (95% CI: 4.2–25.4; range: 4.2–21.0%) of women undergoing laparoscopy, for any indication. Heterogeneity was present between studies due to statistical and methodological inconsistencies between studies, and quality of evidence was low due to sample size and unrepresentative participant selection. This was the first review that reported the pooled prevalence of endometriosis in the Middle Eastern population, suggesting that gynaecological morbidity is a public health concern. Due to the health disparities in women, further research is required to understand the relative roles of environmental and genetic factors in the region to serve as a benchmark for evaluation and comparative purposes with other populations.

A second systematic review and meta-analysis was then conducted to investigate the symptomatology and risk factors of endometriosis in women of Middle Eastern origin. An identical search strategy, selection criteria, data collection and analyses, and assessment of risk of bias was conducted as the previous review[293]. Peer-reviewed articles that reported epidemiological aspects of endometriosis in the Middle Eastern population. The following outcome measures, in association to endometriosis, were pooled via meta-analysis or narrative synthesis: pain history, menstrual history, reproductive history, comorbidities, risk factors, and family history. Meta-analysis was conducted when at least 3 studies met the inclusion criteria

with a total sample size of at least 100 participants per study, to reduce the risk of selection bias, selective reporting of outcomes, reduce methodological bias and decrease heterogeneity within studies. Quality control was performed using GRADE criteria. Total weighted prevalence was calculated via Freeman-Tukey arcsine transformation; pooled effect analyses was calculated via Mantel-Haenszel and DerSimonian-Laird methods; and heterogeneity through I^2 statistic. A total of 11 articles on endometriosis were included (Table 1.2), nine cross-sectional studies and two case-control studies, with five studies receiving a GRADE score of 'low' and six of 'very low'.

Table 1.2. Summary of 11 studies assessing the analytical epidemiological factors of endometriosis.

Country	Study Design	Case: Controls	Covariates	Study Reference	GRADE Criteria
A. Hospital-Based Studies					
Egypt	Case-Control	110:220	Age	[296]	⊕⊕◯◯ LOW
Egypt	Cross-Sectional	469:2024	Age	[297]	⊕⊕◯◯ LOW
Iran	Case-Control	250:153	-	[298]	⊕◯◯◯ VERY LOW
Iran	Cross-Sectional	28:82	-	[299]	⊕◯◯◯ VERY LOW
Iran	Cross-Sectional	341:332	-	[300]	⊕◯◯◯ VERY LOW
Jordan	Cross-Sectional	20:8	-	[301]	⊕◯◯◯ VERY LOW
Saudi Arabia	Cross- Sectional	21:169	-	[302]	⊕◯◯◯ VERY LOW
Turkey	Cross-Sectional	45:1041	Age	[303]	⊕⊕◯◯ LOW
Turkey	Cross-Sectional	14:169	-	[304]	⊕◯◯◯ VERY LOW
B. Population-Based Studies					
Jordan	Cross-Sectional	45: 1727	-	[305]	⊕⊕◯◯ LOW
UAE	Cross-Sectional	55: 3517	-	[306]	⊕⊕◯◯ LOW

As demonstrated in Table 1.3, shorter menstrual cycle length (<21), longer menstrual flow duration (>6 days; Figure 1.1a), menstrual cramps (Figure 1.1b), and irregular menstrual cycle were associated with endometriosis (Figure 1.1c). Dysmenorrhea (Figure 1.1d), chronic pelvic pain (Figure 1.1e), dyspareunia, cold intolerance, infertility, dysuria, and abnormal uterine bleeding showed increased frequency among

women with endometriosis, however, heterogeneity of prevalence rates was moderate and high, likely due to the very low quality of evidence in the studies. Other symptoms, such as diarrhoea and cold intolerance was also associated with endometriosis.

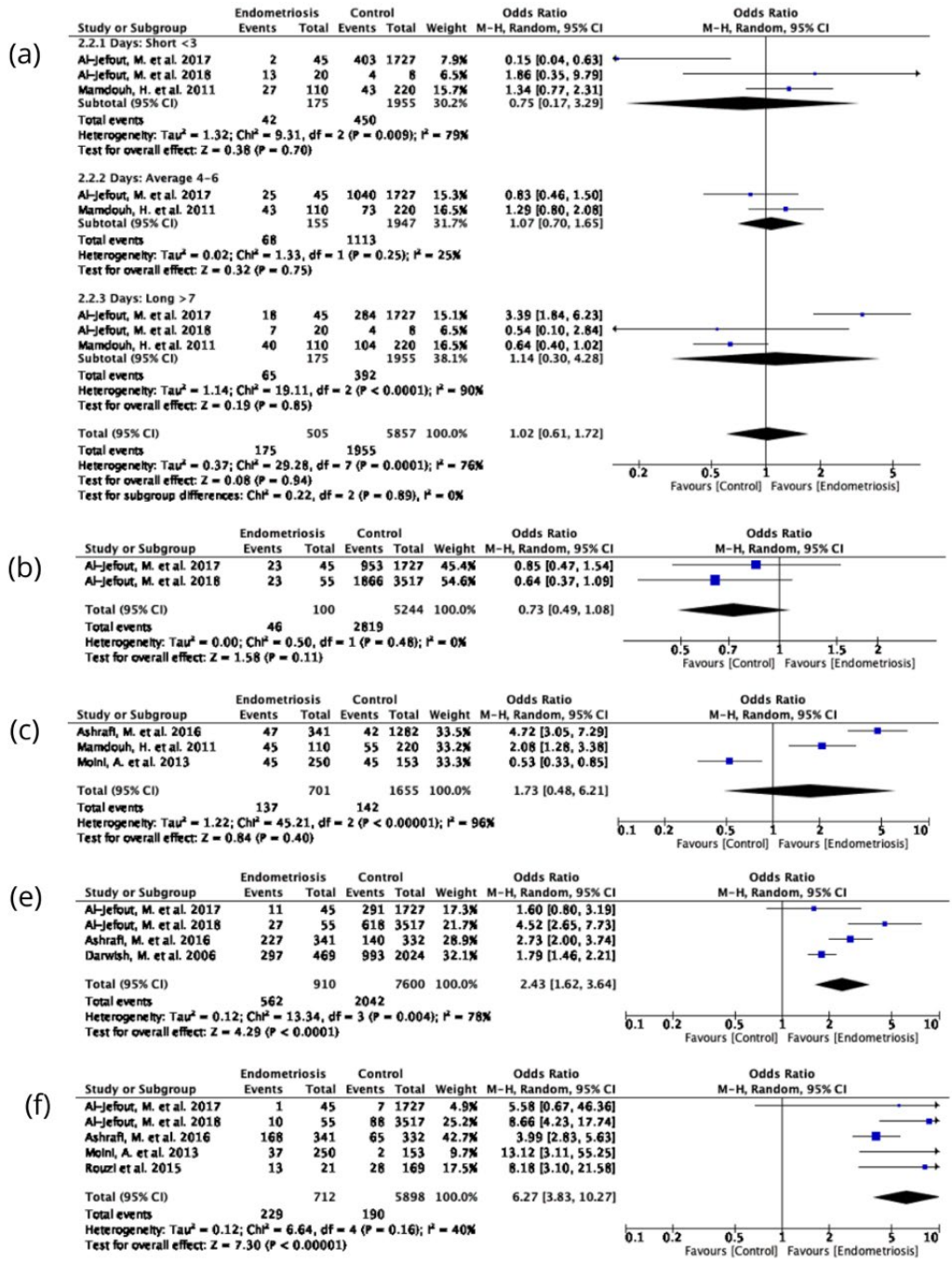


Figure 1.1. Forest plot of symptomatology of endometriosis, outcome: (a) length of menses, (b) menstrual cramps, (c) irregularity of menstrual cramps, (d) dysmenorrhea, (e) chronic pelvic pain.

The pooled prevalence of endometriosis in women presenting with ovarian cancer was 10.9% (95% CI: 2.01, 25.5), with the increased association to endometrioid carcinoma (OR: 4.48 (1.75, 11.48)) and clear cell carcinoma (OR: 8.65 (4.69, 15.95)) (Figure 1.2a)[299,303,304]. In addition, use of contraception (Figure 1.2b) and family history demonstrated a significant association endometriosis.

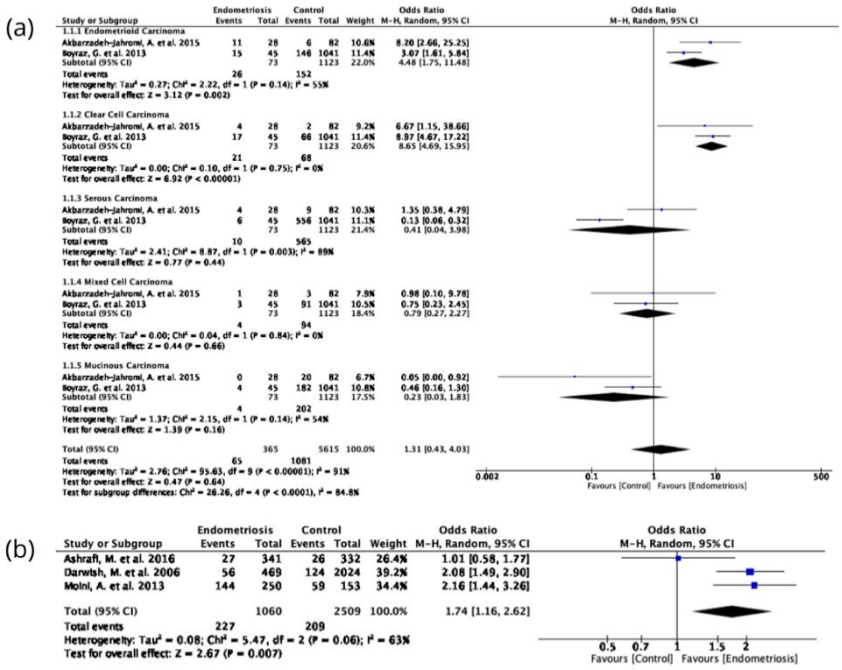


Figure 1.2. Forest plot of symptomatology of endometriosis, outcome: (a) subtypes of ovarian cancer, (b) use of oral contraceptives.

Women with a prior pelvic surgery, ovarian cystectomy and abnormal pap smear were associated with endometriosis (Table 3). Conflicting findings were demonstrated for comorbidities, such as asthma, ovarian cyst, uterine fibroid, hypertension, migraines, and galactorrhoea, as only two studies with high heterogeneity were presented (Table 3). The reliance on surgical confirmation of endometriosis, access to clinics that is mostly limited to married women, and consequent selection biases affect these estimates, as is demonstrated by the heterogeneity in our meta-analyses. The direction of the effects of symptomatology and risk factors associated with endometriosis were like other populations, however sample sizes and study designs limited meaningful interpretation. High heterogeneity was present due to inter study variability in

sample size, ascertainment method, age of participants and control selection. An important feature of this review is that it highlights the significance of investigating gynaecological health in the Middle East, and the need for representative population studies. Potential sources of bias were identified, and significant clinical and statistical heterogeneity were discussed to indicate considerable variability in the data due to residual confounding and study design.

Table 1.3. Symptomatology, risk factor and co-morbidity associated with surgically confirmed endometriosis.

Variable	No. of Studies	No. of Endometriosis Cases: Controls	Effect Estimate: Odds Ratio, (95% Ci)	Heterogeneity: I^2 (%)	Forest Plot	Reference
A. Symptomatology						
Menstrual Cycle Length						
<21	1	45: 1727	194.5 (60.58 to 624.6)	N/A	N/A	305
21-34	1	45: 1727	0.26 (0.14 to 0.48)	N/A	N/A	305
>34	1	45: 1727	0.75 (0.31 to 1.78)	N/A	N/A	305
Menstrual Flow Duration						
Short <4 Days	3	210: 5464	0.84 (0.32 to 2.19)	79.0	Figure 1.1a	296,305,306
Average 4-6 Days	3	210: 5464	0.85 (0.51 to 1.41)	64.0	Figure 1.1a	296,305,306
Long >6 Days	3	210: 5464	1.50 (0.55 to 4.04)	89.0	Figure 1.1a	296,305,306
Menstrual Cramps	2	100: 5244	0.73 (0.49 to 1.08)	0.00	Figure 1.1b	305,306
Menstrual Irregularity of Cycle	3	701:1655	1.73 (0.48 to 6.21)	95.5	Figure 1.1c	296,298,300
Dysmenorrhea	4	910: 7600	2.43 (1.62 to 3.64)	78.0	Figure 1.1d	297,300,305,306
Chronic Pelvic Pain	5	712: 5898	6.27 (3.83 to 10.27)	40.0	Figure 1.1e	298,300,302,305,306
Dyspareunia	2	591: 1,435	2.23 (1.71 to 2.91)	0.00	N/A	298,300
Cold Intolerance	1	20: 8	7.00 (1.08 to 45.1)	N/A	N/A	301
Infertility	2	100: 5244	14.74 (6.88 to 31.5)	0.00	N/A	305,306
Dysuria	1	55: 3517	7.01 (3.44 to 14.29)	N/A	N/A	306
Diarrhoea	1	341: 1282	26.19 (3.53 to 194.41)	N/A	N/A	300
Abnormal Uterine Bleeding	2	100: 5244	3.78 (2.07 to 6.89)	67.0	N/A	305,306
B. Risk Factors Comorbidities						
Asthma	2	100: 5244	1.85 (0.68 to 5.04)	29.0	N/A	305,306
Ovarian Cyst	2	100: 5244	5.32 (2.23 to 12.7)	71.0	N/A	305,306
Ovarian Cancer	2	73: 1123	1.31 (0.43 to 4.03)	84.8	Figure 1.2a	299,303
Ovarian Cystectomy	2	100: 5244	36.7 (21.6 to 62.7)	0.00	N/A	305,306
Hypertension	2	100: 5244	2.67 (0.82 to 8.70)	0.00	N/A	305,306
Prior Pelvic Surgery	2	810: 2356	1.71 (1.39 to 2.10)	0.00	N/A	297,300
Uterine Fibroids	2	100: 5244	9.98 (2.48 to 40.19)	61.0	N/A	305,306
Migraine	2	100: 5244	2.24 (0.78 to 6.44)	27.0	N/A	305,306
Galactorrhoea	1	341: 332	2.19 (1.44 to 3.33)	N/A	N/A	300
Abnormal Pap Smear	2	100: 5244	25.5 (1.51 to 431.7)	66.0	N/A	305,306
Use of Contraception	3	1060: 2509	1.74 (1.16 to 2.62)	63.0	Figure 1.2b	297,298,300
Family History	2	451: 552	3.50 (1.92 to 6.40)	0.00	N/A	296,300

Based on a study that investigated the global architecture of endometriosis research and public health efforts, there is a large gap of research activity in the Middle East, Asia, and African countries[307]. Research disparity in endometriosis exists and an intensification of collaborative research efforts is needed to battle pressing challenges on a global scale, especially that this enigmatic disease affects female health in a global

context, in women of all ethnicities. This will improve the development of novel non-invasive diagnostic tests and treatment approaches to improve disease management for millions of women, worldwide.

1.4 Aims of the thesis

The findings presented in this thesis are based on the analyses of data from a case-control study of Arab ancestry women living in the United Arab Emirates, 'the Middle Eastern Women Research Association: the MAR'A project', of which I am the principal investigator.

The MAR'A project is the largest epidemiological study on women's health conditions in the Middle East to date that aims to develop a better understanding of cultural and regional gynaecological health patterns using evidence-based, standardized questionnaires and anthropometric measurements, and additional collection of saliva samples for DNA extraction. The study addresses the absence of epidemiological data in the Middle East on common, benign gynaecological conditions, such as endometriosis, polycystic ovary syndrome (PCOS), uterine fibroids and related comorbidities among Arab women. The health statistics generated from the study will inform health authorities about prevalence and distribution of certain women's health issues that can be used in the development of data-driven health strategies in the region. In addition to data, saliva samples were collected to allow preliminary candidate gene association study (in this thesis), as well as future genome-wide association and sequencing studies.

A particular focus of this thesis was to conduct epidemiological investigations of endometriosis in Arab women to evaluate whether there are ethnic differences in clinical presentation, risk factors, quality of life, and diagnostic delay. This will provide a clearer understanding of the epidemiological determinants of endometriosis, inform preventive efforts, and draw attention to the public health importance of endometriosis. To achieve these goals, we collected standardized clinical, epidemiological, environmental, and surgical data with corresponding biological samples. We utilised multiple standardized, validated questionnaires including research instruments by the World Endometriosis Research Foundation's (WERF) Endometriosis Phenome and Biobanking Harmonization Project (EPHect) translated in the Arabic language. Methods employed in the MAR'A project are described in **Chapter 2**.

This thesis addresses the following objectives:

- To investigate the detailed symptomatology, risk factors, phenotypic profile, and comorbidities associated with endometriosis in women of Arab ancestry. This included pain, menstrual history and hormone use, infertility and reproductive history, comorbidities, family history, and adiposity and sociodemographic history. The results of these analyses are described in **Chapter 3**.
- To investigate the impact of endometriosis, and associated symptomatology, on health-related quality of life, work productivity, activity impairment, physical activity, diagnostic delay, and prevalence of psychological co-morbidities in Arab ancestry women. The results of these analyses are described in **Chapter 4**.
- To conduct a candidate gene association study on known endometriosis-associated genetic risk loci identified in European ancestry populations, for replication in women of Arab ancestry, and to investigate their relative effects in relation to detailed phenotypic information. The focus here was on variants in wingless-type MMTV integration site family member 4 (*WNT4*)[75,308–310] and the Vezatin (*VEZT*)[75,168,309,311]. These results are described in **Chapter 5**.

Chapter 2. Methodology

2.1 Introduction

This chapter gives a detailed description of the MAR'A project, its representation and generalizability to the Middle Eastern population, and rationale behind the study design. An inclusive description that detailed the target population, methods used to select the cases and multiple control groups, and recruitment of participants is described in detail. This section also includes information on the data collection tools, outcome measures and subsequent analysis plan. Copies of the data collection tools, including the questionnaires, consent form and participant information sheet, can be found in appendix 3-4.

2.2 Study design

The objective of this study is to investigate the association of symptomatology, risk factors and clinical variables on Arab ancestry women with endometriosis. The MAR'A project is a case-control study with multiple recruitment sites across the United Arab Emirates (UAE) to obtain information from Arab women representative of the general population. Pre-menopausal Arab women aged 18-50 years were enrolled from four geographically defined hospitals and clinics, and six population-based sites in the same catchment area. Women under the age of 18 were not selected due to the: (1) anticipated complications in obtaining parental consent; and (2) difficulty of obtaining ethical approval in the UAE due to the sensitivity of introducing the topic of women's health (menstruation, pain, reproductive factors, sexual factors) to the adolescent population. Women of reproductive age are considered the most relevant target group because endometriosis is an oestrogen-dependent disease, and its incidence rises after puberty. Post-menopausal women rarely exhibit continued symptoms of endometriosis, and their risk-factors for doing so (e.g., hormonal replacement therapy use) are markedly different from those of pre-menopausal women.

A case-control study is an efficient way to obtain a reliable estimate of odds ratio if case and control selection are clearly defined[312]. The advantage of the case-control design is that we are able to investigate a wide range of risk factors and test hypotheses that does not entail a long period of follow-up[313]. Case selection does not allow the need to wait for development of disease as subjects ascertained based on disease

status. In addition, incident cases were collected to minimize the chance that an observed effect of an environmental risk factor is the result of diagnosis and arrive at risk estimates that are comparable to that of a cohort study. As such, the case-control study design may present an appropriate strategy for the generation of refined hypotheses to be tested in future prospective cohort study design, which is the "gold standard" of observational research (i.e. it most closely approximates an experiment)[314].

Potential limitations of a case-control study are selection biases, when cases and controls are not sampled from the same source population and thus are not comparable in terms of exposures; recall bias where the cases are likely to recall their exposure history differently than controls; and information bias where exposure status may be ascertained after disease has already occurred[315–318]. All these need to be considered both in the design and the analysis of the study. The next section details: (1) endometriosis cases definition (section 2.3.1.1 and section 2.3.3); (2) the strategy for control selection to be representative of the sampling population (section 2.3.1.2 and section 2.3.3); and (3) adjustment for confounding factors in the analysis (section 2.6.1).

It is important to ensure precision (minimising random error in estimation through a sufficiently large sample size; section 2.6.2), internal validity (validity of inference of results for all women aged 18-50 in the study sample; section 2.3.3), and external validity (validity of inference of results that can be extrapolated to all Arab women aged 18-50; section 2.3.3) of the results. In the present chapter, I will demonstrate how we have selected a representative source population (section 2.2.1 and section 2.2.2) and how we implemented maximum efforts to reduce various biases (section 2.3.3) in the recruitment process (section 2.2.2).

It should be noted that while all Middle Eastern nationalities of the Arab women were included in this study sample (Levant region, Arabian Peninsula region, North Africa region), the data may not be generalisable to women who reside in countries that have been exposed to war (Iraq, Palestine, Syria, Lebanon, Yemen) due to the lack of access to healthcare, low standard of care, low accessibility to adequate medical supplies,

lack of qualified medical staff, mental health impact and the lack of attention for women's health due to high mortality and morbidity directly due to war and conflict.

Cases comprised women scheduled to undergo a diagnostic and/or therapeutic laparoscopy or laparotomy for any indication (pelvic pain, subfertility, pelvic mass, adnexal torsion, infection or to be sterilized) and diagnosed with endometriosis. The case group were newly diagnosed incident cases that were recruited from the recruitment sites, during the period of the study to allow for unbiased exposure information and accurate approximation of relative risk by the odds ratio. If prevalent cases were studied, any association found between endometriosis and the exposure would not refer to the exposure itself but to its interaction with an observed effect of a risk factor[145,319]. The interval between risk-factor exposure and onset of disease is largely unknown, especially in the Middle Eastern population, hence, the use of incident cases allowed us to extrapolate the direct factors.

The controls comprised three distinct groups: (1) hospital controls who had undergone laparoscopic surgery showing that they were endometriosis free; (2) clinic controls who were screened using therapeutic/diagnostic tests; and (3) population controls recruited during organized public seminars on women health issues. Details of the study population, and case/control selection are provided below.

The case-control analyses included a descriptive analysis of the study population to assess the association of symptomatology and the distribution of clinical variables in the study population across disease outcome categories based on the following comparisons: (1) ascertainment criteria (endometriosis cases vs. hospital controls; and endometriosis cases vs. population controls); and (2) symptomatic criteria (endometriosis cases vs. symptomatic controls; and endometriosis cases vs. asymptomatic controls). Several epidemiologic studies have investigated risk factors for endometriosis with highly variably results and inconsistent findings, mainly due to the variations in comparison group selection. This thesis will provide an opportunity to assess risk factors for endometriosis using both hospital and population-based control groups, with further stratification on symptomatic criteria, to evaluate issues related to this aspect of study design that might affect results and their interpretation.

More specifically, the frequency of the following symptoms was evaluated: (1) dysmenorrhea; (2) noncyclical pelvic pain; (3) dyschezia; (4) dysuria; and (5) infertility. The following groups of putative clinical variables and risk factors were measured for their association with endometriosis in the study population: (1) quality of life characteristics, including work productivity and activity impairment, physical assessment, and diagnostic delay; (2) socio-demographic and personal characteristics, including age, education, anthropometric measurement (BMI, waist-high ratio), consanguinity, and war exposure; (3) menstrual history and hormone use, including menstrual cycle characteristics, age at menarche, and use of hormone and contraception; (4) reproductive health factors, including parity history, fertility history, and pregnancy-related characteristics; and (5) comorbidities, including past medical and surgical history, and family history.

2.2.1 Representativeness of the sample

2.2.1.1 Geographic distribution

The Middle East is a transcontinental region that represents 6.8% of the world's population, compromising 24 countries and hold geopolitical importance, wealth of history, cultural heritage, and constitute more than 25 ethnic groups due to intercontinental migration[246,247]. The Middle Eastern population represent a distinctive population structure that consists of the Arabian Peninsula Region (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates, Yemen), the Levant region (Cyprus, Iraq, Israel, Jordan, Lebanon, Palestine, Syria, Turkey), the North African region (Algeria, Djibouti, Egypt, Libya, Morocco, Somalia, Sudan, Tunisia), and the Persian region (Iran)[320,321]. Arabs constitute the majority ethnic group in the region, with 19 out of the 24 Middle Eastern countries known as part of the Arab world. Even though Arabs practice different religions, they are unified by common cultural practices, social linguistic influences and traditional norms[237,241–243]. The focus of this study is on Arab women.

The UAE is located at the south eastern corner of the Arabian Peninsula, at the coastline of the Arabian Gulf and at the crossroads of African, European and Asian regions[322,323]. Due to its pivotal geographic location, economic growth, and political stability, a multidirectional flow of Arabs from the Middle East to

the UAE have contributed to shaping the unique composition of the population[257,322]. Genetic studies that have investigated the patterns of migration to the UAE have demonstrated that the ancestry of its contemporary population is representative of the Arabs in the region, in terms of admixture and subpopulation centrality[238,324]. Hence, the participants that were recruited from the UAE are representative of the Middle Eastern countries due to its geographical distribution.

The UAE is a rapidly developing country composed of a multinational population with varying religious beliefs and cultural practices with a population of 9.54 million. Females constitute of only 28% (2.65 million) of the total population, and of those 70% (1.87 million) are women of reproductive age (ages 14-54)[322]. There are no published data on the distribution of females across the UAE, or their ethnicities. Since the target population of this audience are reproductive-aged women of Arab ancestry, hospitals and population sites were strategically selected across the UAE to maximise the potential of participants to be representative of the population. These sites were selected alongside the Ministry of Health and Prevention in the UAE, based on location, insurance coverage, treatment provided, and high referrals of the target population.

2.2.1.2 Representativeness of the recruitment sites

The hospitals and clinics that were selected in this study are located across five of the seven cities in the UAE and consisted of both public and private entities to capture residents of different sociodemographic classes. The hospitals targeted variable urban, suburban, and rural areas across the country that included two public, government-owned hospitals that accept all medical insurance categories in the country, in addition to private funding, and charity/federal government funding for those that are unable to afford medical care, whereas the other two hospitals targeted the private sector which also included a range of health insurance (Figure 2.1). These four sites are among the most popular referral sites for women with gynaecological disorders due to the accessibility of highly trained surgeons and medical professions, hence it serves most cases originating in the UAE.

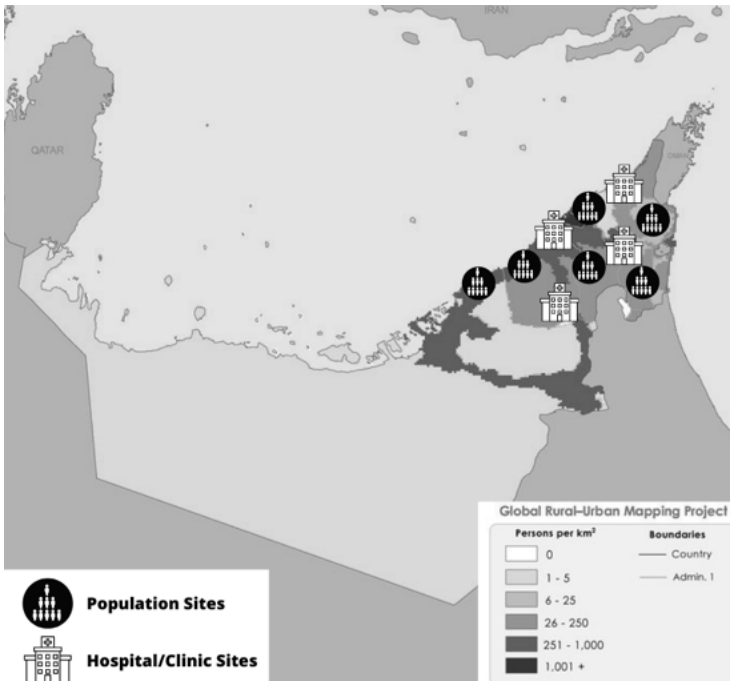


Figure 2.1. This figure demonstrates the population density in the UAE. The population density measures the number of persons per square kilometer of land area. The figure was obtained from the Socioeconomic Data and Application Center and Center for International.

In addition, since endometriosis is diagnosed and treated conventionally in a hospital, and all the selected hospitals define the disease based on a uniform, objective criteria with internationally standard techniques with no evident selection for hospitalization (such as ethnic or socioeconomic factors present), they were appropriate for epidemiological study. The population sites are within the same geographic catchment areas as the participating clinical and surgical centres, and census data for these defined areas were available to compare the sociodemographic status of participants on the database to national figures. It should be noted all Arab nationals (Levant region, Arabian Peninsula region, North Africa region) had access to public and private hospitals with similar insurance coverage. The representativeness of the sample population is further explored in this chapter.

It should also be noted that there are no national registries in the UAE to facilitate longitudinal population-based studies permitting the analysis of the magnitude and trends in occurrence of specific diseases. In addition, access to household data, area codes, and telephone directly listings were not publicly available,

and the local Ethics Committee did not approve of random digit dialling, postal surveys or contacting friends/relatives/neighbours of cases. Hence, the recruitment sites that were selected for population-based recruitment were collected from the public seminars organized for the women in the UAE. The public seminars were held in the same neighbourhood as the hospital controls to match age, marital status, occupation, and socio-economic status. These seminars are held bi-quarterly and hold 150 to 200 women. To measure the influence of external validity a post-hoc analysis on sociodemographic factor distribution (specifically age, BMI, marital status, employment status, and educational level) of the study sample were compared with the most recent census published in the UAE to demonstrate the representativeness of the source population (Chapter 3.4.1-3.4.3). Heterogeneity analysis of the sociodemographic factors using a non-parametric analysis via Mann Whitney U test to quantify the hidden bias was conducted for the control group (hospital-based and population-based control group; Chapter 3.4.2-3.1.3) and for the hospital ascertainment (private and public hospitals; Chapter 3.4.2-3.1.3). The representativeness of the population controls is explored in section 2.3.1.2.

2.2.2 Recruitment

Recruitment was conducted for one year, from August 1, 2018, to August 1, 2019. Two research assistants were employed to assist in data collection. The research assistants and I approached participants in the waiting room in the hospital and clinics, or at the end of the public seminars, and asked if they were interested in learning more about this research study. Participants who met the inclusion criteria were invited to participate in the study and given the consent form and participant information sheet in their preferred language (English or Arabic), which had been professionally translated using the forward/backward method and approved by the ethics committee. A poster introducing the study was also available in the waiting rooms and distributed in the public seminars. The participant information sheet detailed the rationale of the study to provide potential participants with the necessary understanding of the purpose, methods, risks and benefits of the research and the planned use of the data to be collected to make an informed decision as to whether they would like to participate in the research project. It also provided

potential participants with details of sources of further information to answer any further questions that they might have. The participants read the participant information sheet in the waiting room and were given the time to discuss it with the research assistants for more information, or family and friends. The research assistants emphasized that participation was optional and would not influence their healthcare. Once the participant agreed to participate in the study, the participant signed the consent form, which was witnessed and collected by the research assistant at the study site, prior to any study related study procedures began. The participant was given their unique participant ID, a copy of the signed consent form, participation information sheet and the research assistant's business card to answer any questions that she may have throughout the study.

Those women who agreed to participate were asked to complete a paper or online questionnaire in their preferred language (English or Arabic). Women were given the questionnaires to complete in private, without their husbands or family member around, and participants had the opportunity to ask questions and discuss any concerns. All study participants were instructed to answer questions based upon their current level of understanding and familiarity of the subject content. Questionnaires had to be completed before surgery. If the participant did not complete the questionnaire in the waiting room, she was given the opportunity to complete it at home and submit it to the research assistant before the scheduled surgery. After the scheduled laparoscopic procedure, the surgeon was requested to complete the surgical questionnaire. From a subset of consenting women (N=200) who completed the questionnaire and consent for genetic testing, a saliva sample was collected for DNA extraction. Figure 2.2 outlines the path of participant recruitment, eligibility criteria and time points in which each of the data collection tools were provided/collected from the participant/surgeon.

I kept an anonymized electronic log of women who fulfilled the eligibility criteria which includes, women who are invited to participate in the study, women recruited and women who left the trial early. Reasons for non-recruitment (not eligible and refusal to participate) were recorded. During the study, every effort was made to collect all reasons why someone would withdraw from the study.

2.2.3 Ethical considerations and funding

Ethical approval was obtained from the research ethics committee within the University of Oxford (OXTREC: 25-18) and the Ministry of Health in the UAE (MOHAP: MOHAP/DXB-REC-25/2018).

The study followed the guidelines established in the Declaration of Helsinki, General Data Protection Regulation and Good Clinical Practice, and adult participants provided written consent to participate in the study after reading the participant information sheet. The protocol, consent form, participant information sheet, all advertising material and data collection tools were submitted to OxTREC and MOHAP for written approval. The study staff ensured participants anonymity was maintained by complying with the Data Protection Act, where all participants were identified with a unique participant ID number (a six-digit number starting from 000001), and utilized in all questionnaires, baselines assessment data, and on the saliva kit collection tube.

This study was funded by a Doctoral Grant (MR-8180) awarded by The Sheikh Saud Bin Saqr Al Qasimi Foundation and an Internal Research Award by Khalifa University.

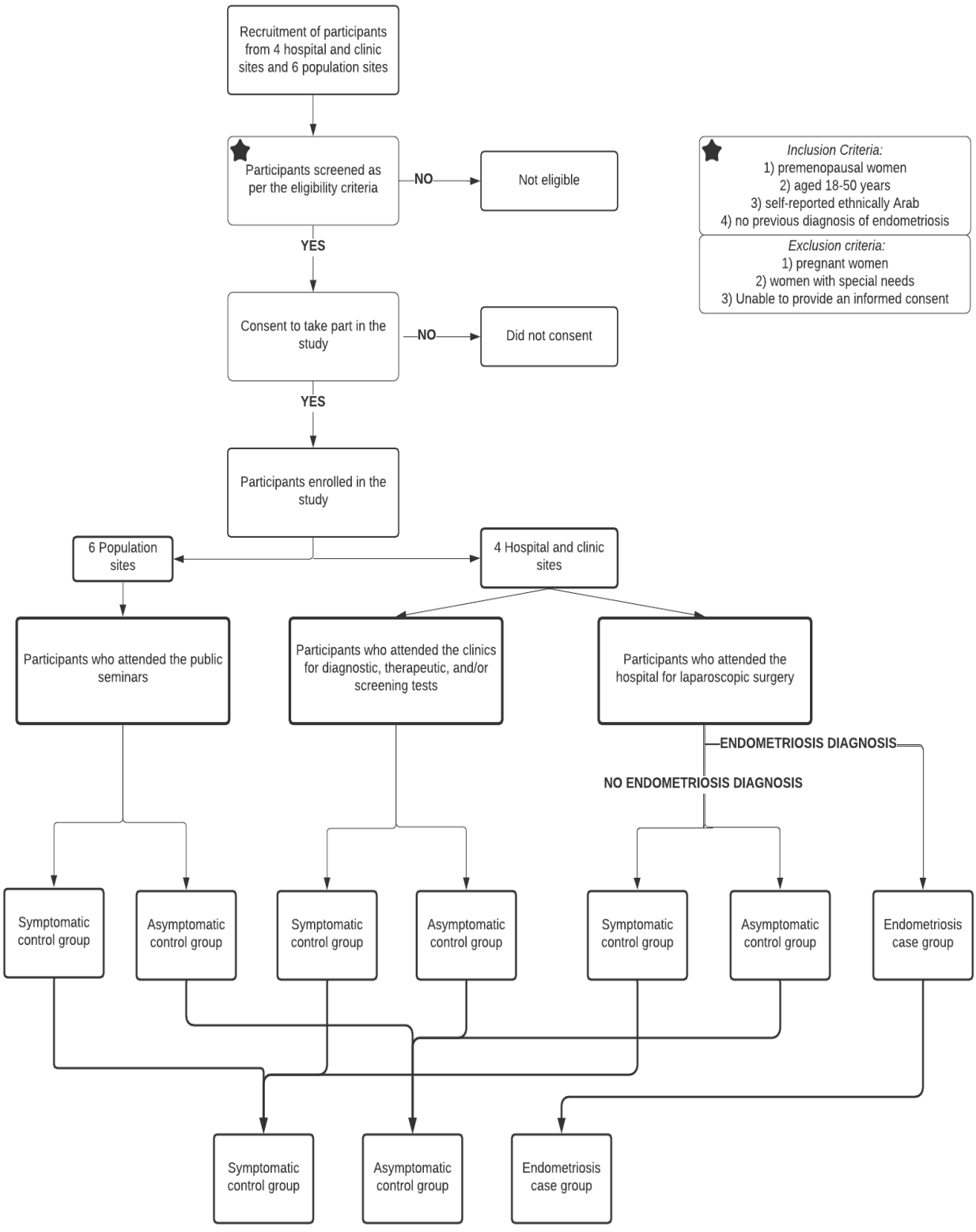


Figure 2.2. Recruitment flow chart of the study.

2.3 Study population

2.3.1 Definitions of cases and controls

2.3.1.1 Case group

Definition

Endometriosis is defined as the presence of endometrial tissue (glands and stroma) found at sites outside the uterus, mainly within the pelvic cavity, including the ovaries, ligaments, and peritoneal surfaces, as well as the bowel and bladder. The presentation of these endometrial lesions varies from superficial peritoneal and serosa lesions, to cysts (endometriomas) and deep endometriotic nodules (>5mm deep), and may be accompanied with fibrosis and adhesions[6].

Diagnosis

Diagnosis of endometriosis is established through visualization during pelvic surgery, most commonly through laparoscopic or laparotomy surgery with histopathologic diagnosis[7]. All endometriosis patients were assigned a surgical stage, based on extent of the disease in the pelvic cavity and pelvic pathology staging using the revised classification system of the American Society for Reproductive Medicine (rASRM): minimal (Stage I), mild (Stage II), moderate (Stage III), and severe (Stage IV) endometriosis, as well as a histological confirmation of the disease[16]. Indications for surgery, sometimes more than one per patient, included: I) pelvic pain, defined as the presence for at least 6 months of dysmenorrhea and/or chronic pelvic pain and/or dyspareunia and/or dyschezia and/or dysuria of moderate to severe intensity[325]; II) infertility defined as at least 12 months of unprotected intercourse not resulting in pregnancy[326]; III) others: pelvic mass (benign ovarian mass, uterine myoma, etc.); IV) others: uterine bleeding, request for tubal ligation, adnexal torsion, infection, etcetera. This provided me with further information of the phenotypic profile, symptomatology, and comorbidities of endometriosis.

Selection Criteria

The case group included pre-menopausal women aged 18 to 50 years, scheduled to undergo a diagnostic and/or therapeutic laparoscopy or laparotomy, regardless of clinical indication, at one of the participating surgical centres in the UAE. Only women who were self-reported ethnically Arab were recruited. Women with a history of previously surgical-confirmed endometriosis or presence of a malignancy found at laparoscopy were excluded.

Source and recruitment of case group

The case group were newly diagnosed incident cases that were recruited from the recruitment sites, during the period of the study. Clinical and risk factor information was collected retrospectively, but with careful attention to potential recall bias[327,328]. The use of incident cases reduced the magnitude of misclassification and minimized the chance that an observed effect of an environmental risk factor is the result of diagnosis. Even though this may be difficult to implement with endometriosis, as there is a substantial delay between symptom onset and diagnosis, and we do not know the pathological changes that cause the onset of the disease, incident cases are known as newly diagnosed cases to determine environmental exposures prior to any accurate diagnosis.

The need for an invasive procedure to establish the diagnosis of endometriosis diagnosis, without magnetic resonance imaging (MRI) or ultrasound imaging, is a potential limitation to case selection. It may be possible that only those of higher socioeconomic class and with severe disease diagnosis will undergo laparoscopy, causing selection bias compared to cases in the general population[319]. In addition, due to the cultural and traditional norms, women are more likely to seek gynaecological care for fertility issues, as opposed to chronic pain or menstrual irregularities. Hence, the case group may be limited to women going through surgical assessment due to their symptom of subfertility and may under sample those with pelvic pain or other symptoms. Diagnosis by MRI and ultrasound imaging is limited to ovarian endometriomas and deep nodules, and access to imaging may similarly be impacted by differential access in the population. The heterogeneous forms of endometriosis that may represent different underlying etiopathogeneses can

only be accurately visualized and diagnosed through surgery. Bearing these important issues in mind, the design of this study allowed collection of varying rASRM staging and endometriotic lesions of this heterogenous condition, to stratify based on the phenotypic profile and understand the association to different risk factors and symptoms. By limiting the case definition to those with laparoscopic confirmation of disease, this decreased misclassification bias of endometriosis[187]. The inclusion of the laparoscopy-negative control group and stratification of endometriosis case group by infertility and pain phenotype allowed me to investigate the sensitivity of my results to potential selection biases. In addition, since women with endometriosis exhibit significant pain phenotypic variability, this allowed us to classify patients into phenotypic groups, dependent on the endometriosis lesion characteristics and comorbid pelvic pain generators. Cases were selected from multiple hospitals and clinics across the UAE to strengthen generalizability of the study findings.

While asymptomatic women with endometriosis undergoing laparoscopy for other reasons (e.g., sterilization) would be included as cases, the frequency of this diagnostic opportunity is very low due to UAE laws and regulations. As per the UAE Federal law[329], a married woman can seek sterilization if she has a disease that would threaten her life should she become pregnant. If the pregnancy or labour poses a definite risk to the mother's life, the married woman should seek written approval from a medical specialty committee comprising of at least three physicians, written consent from the husband, and a written approval from the Ministry of Health and Prevention. It is very rare for single women to seek sterilization, and she is only given approval if she had a disease that would threaten her life. Therefore, the case selection in this study was primarily related to symptomatic cases.

2.3.1.2 Control group

In case-control studies for endometriosis, appropriate control selection is difficult, because there are many potential selection biases operating in the case identification. Owing to the need for surgery to diagnose endometriosis, most investigators employ controls from women undergoing other pelvic surgery such as hysterectomy or laparoscopy for reasons unrelated to endometriosis. Such controls are a highly selected

population and often do not represent the exposure distributions of the populations from which the cases are drawn. Furthermore, detection bias may complicate control selection of symptomatic women undergoing investigative laparoscopy because women with gynaecological symptoms or infertility are likely to receive heightened medical care, therefore underestimate the size of the effect.

Clinic controls undergo similar diagnostic procedures as cases to screen out the disease of interest in clinic settings and eliminate the possibility of case under-ascertainment, whereas this selection procedure is generally lacking for population controls. Clinic-based controls are better matched to cases on various potential confounding factors that impact on the opportunity for a diagnosis to be established, such as health care seeking pattern, as well as comparability in terms of recall. However, they may not be representative of the exposure distribution in the general population, due to selection bias and misguided effort to reduce misclassification of endometriosis cases by excluding suspected "cases in progress," This will lead to over-matching and attenuation of the relative risks for some exposures, and may constitute a non-random subset of the underlying population and as such may introduce bias[11].

While it is perceived that the control group should be a group of "normal" (i.e., disease-free) women, this conceptualization of the case-control design is inconsistent with the actual group of the control group selection, which is to provide a representative sample of the risk factor distribution among the population at risk. This concept of there being no 'perfect' control group for endometriosis cases was discussed in detail in an editorial by Zondervan et al[11]. The most appropriate solution is to select multiple control groups to enable investigation of sensitivity of the results to control selection.

Thus, I selected three control groups for the purpose of investigating heterogeneity in exposure distributions and results between clinic-based and population-based controls[330]: (1) hospital controls who had undergone laparoscopic surgery showing that they were endometriosis free; (2) clinic controls who were screened using therapeutic/diagnostic tests; and (3) population controls recruited during public seminars on women health issues, which I organised.

Hospital controls – women undergoing laparoscopic surgery

The hospital control group comprised symptomatic and asymptomatic women who were screened for endometriosis via laparoscopy with histopathologic diagnosis, with no presence of the disease found. Women with a history of surgical confirmation of endometriosis were excluded. Indications for surgery for the symptomatic control group, sometimes multiple per patient, were benign ovarian cysts, myomas, pelvic pain, infertility, lesions, adhesions, and others. Please refer to Section 3.4.3.2 for the heterogeneous diagnosed conditions for this group. Asymptomatic women underwent laparoscopy for sterilization purposes. Where my results indicated differences according to control group used, I investigated the contribution of pathologies to these differences.

Clinic controls – women attending clinic for screening therapeutic/diagnostic tests

This clinic control group included symptomatic and asymptomatic women who had undergone screening therapeutic/diagnostic tests at the study sites. Symptomatic women presented to the clinic for diagnosis and treatment of gynaecological conditions, bowel and bladder conditions, and infertility. Asymptomatic women visited the centre for pre-marital screening, reproductive/breast cancer screening, infectious disease screening, ovulatory monitoring, menopausal screening, gynaecological health check-up, cosmetic gynaecology, and post-natal care. Where my results showed differences according to control group used, this allowed me to investigate sensitivity of results to presence or absence of symptoms.

Population controls – women attending public seminars

Population controls were collected from public seminars organized for the women in the UAE. The public seminars were held in the same neighbourhood as the hospital controls to allow for closer matching on demographic factors. These seminars were held bi-quarterly and attract 150 to 200 women. The seminar is organized by the Sheikh Saud Bin Saqr Al Qasimi Foundation and myself. They focus on providing information including on the social determinants of health, availability of screening tests, and the contribution of certain risk factors to rates of common gynaecological diseases. The population controls

selected were women frequency matched to hospital and clinic controls, as well as cases, on key demographic variables such as neighbourhood, age, marital status, and socio-economic status. These population controls included asymptomatic or symptomatic women, and may have contained undiagnosed cases, which would decrease effect sizes towards the null hypothesis of there being no difference between cases and controls. However, it is a control population that may be most representative of exposures in the general population. As described above, my analyses allowed me to test sensitivity of my results to contrasts with this population-recruited vs. clinic-recruited controls.

Impact of control group selection on risk factor strength

Multiple controls groups would evaluate the endometriosis risk factors and investigate differences related to comparison group selection. The analyses included a descriptive analysis of the study population to assess the association of symptomatology and the distribution of clinical variables in the study population across disease outcome categories. Several epidemiologic studies have investigated risk factors for endometriosis with highly variably results and inconsistent findings, mainly due to the variations in comparison group selection. This thesis will provide an opportunity to assess risk factors for endometriosis using both hospital and population-based control groups, with further stratification on symptomatic criteria, to evaluate issues related to this aspect of study design that might affect results and their interpretation.

For comparison, the association of risk factors of endometriosis was investigated based on the following two groups:

(1) Ascertainment criteria:
    a. Endometriosis cases vs. hospital controls
    b. Endometriosis cases vs. population controls
(2) Symptomatic criteria:
    a. Endometriosis cases vs. symptomatic controls
    b. Endometriosis cases vs. asymptomatic controls

Selection of controls based on: Ascertainment criteria

The selection of controls from the hospitals are very common to use in endometriosis epidemiological studies, as they enable the assessment of predictors of endometriosis within a subset of the population, specifically women with pelvic symptoms or infertility, severe enough to warrant operative evaluation and treatment. Hospital-based controls may therefore underestimate the risk estimates for the variables; however, it would be able to offer advantages of economy and comparability with cases in terms of recall, and they have a document absence of endometriosis.

The selection of controls who are representative of the underlying population, in terms of exposure of interest, is a foundation of population-based and offers the advantage of a comparison group that is representative of the population giving rise to cases. However, even though population-based controls will not be 100% disease free because they are unlikely to have undergone a surgical evaluation to rule out the presence of endometriosis, undiagnosed symptomatic endometriosis is present only to a small degree in a population control group, making it unlikely that study results are affected appreciably by the inadvertent inclusion of these women as controls.

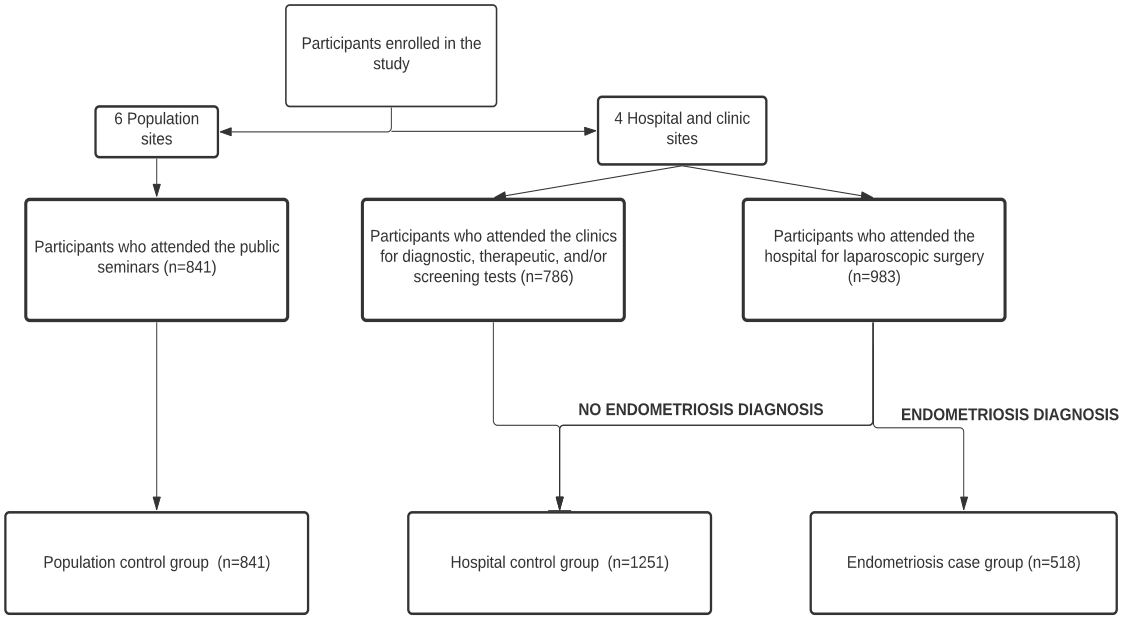


Figure 2.3. Selection of controls based on ascertainment criteria.

Selection of controls based on: Symptomatic criteria

Symptomatic controls were stratified into: (1) women who experienced chronic pelvic pain, dysmenorrhea, dyspareunia, dyschezia, dysuria for at least six months' duration, with a numerical rating scale (NRS)[331,332] score greater than 4[333]; and/or (2) women who were infertile defined as having had unprotected intercourse in the fertile phase of the menstrual cycles for at least 12 months[334]. Women who did not report one or more of the above symptoms were categorized into the asymptomatic control group.

The control groups were sub-divided into symptomatic and asymptomatic controls, to explore sensitivity of results to control definition. This allowed us to investigate whether the risk factors and clinical variables were driven by the endometriosis-related symptoms or endometriosis *per se*. The symptomatic control group allowed us to investigate whether observed associations relate to endometriosis *per se*, and not the presence of symptoms. The asymptomatic control group allowed investigation of factors associated with symptoms with or without endometriosis

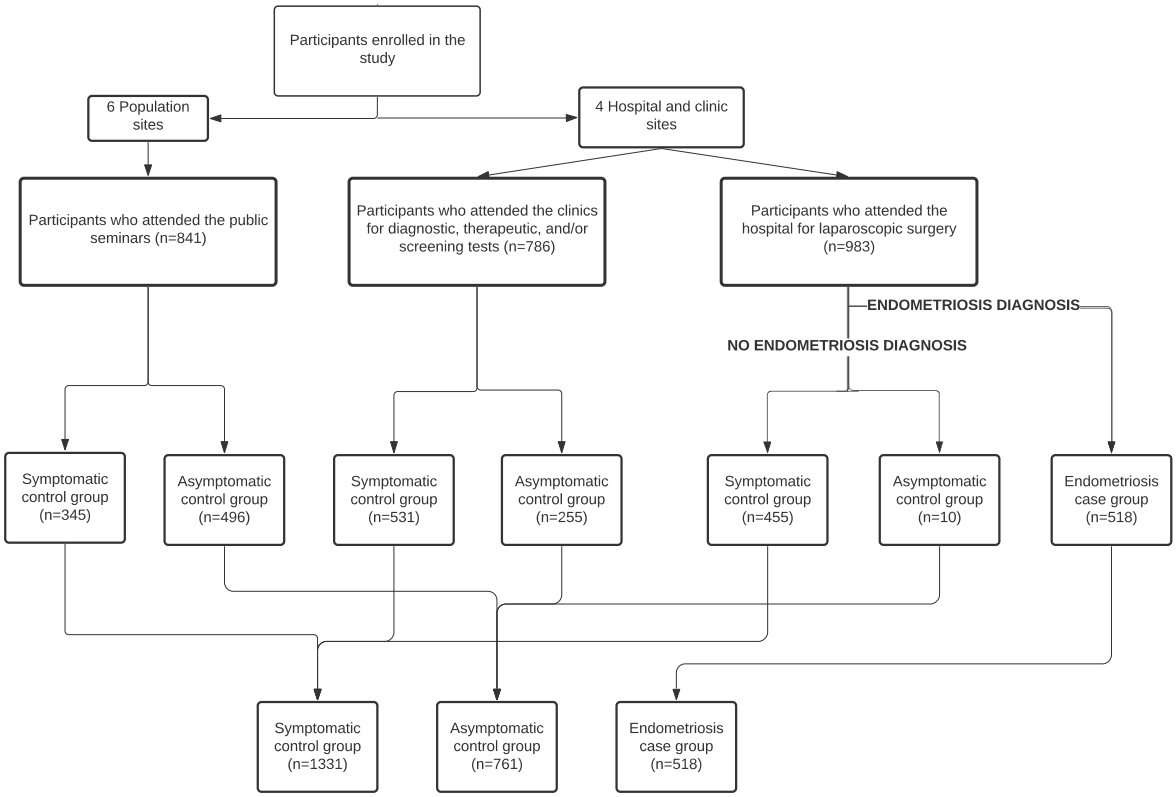


Figure 2.4. Selection of controls based on symptomatic criteria.

Sample selection for the candidate gene association study

Case Selection

For the candidate gene association study (CGAS) study, I selected a subset (n=100) of consenting women who completed the questionnaire, had undergone laparoscopic surgery, and had been diagnosed with endometriosis. A saliva sample was collected post-procedure for DNA extraction. Saliva samples were only collected for more severe disease stages (rASRM Stage III, IV endometriosis)[16], as the effect sizes of genetic loci are increased for more severe disease stages, consistent with the observation that this case subtype has a greater genetic burden[168]. Women with a diagnosis of adenomyosis, uterine fibroids, migraine, and presence of a malignancy were excluded due to the potential association of selected candidate genes with these comorbidities.

Control Selection

For the control group (n=100), women were selected who had been screened for endometriosis via laparoscopy, with no diagnosis of endometriosis, and asked to donate a saliva sample. I chose clinic-based controls that had undergone laparoscopy for my genetic study, as this group did not include women with endometriosis and therefore enabled me to obtain more accurate effect sizes. Furthermore, I investigated the sensitivity of the effect size estimation to control composition[335]. Selection of candidate single nucleotide polymorphisms is further explained in the respective genetic chapter (chapter 5).

In a genetic association study, bias due to environmental factors is not generally a problem; the primary potential confounding bias is related to any differential ethnic origin of cases and controls, termed population stratification. Population stratification is minimized when controls are matched to cases on ethnicity, often ascertained through self-report[336], although more subtle population stratification can only be adjusted for using genome-wide genetic data. The control population was selected to match to the case group on age within the geographic catchment areas for the participating surgical centres. Women matched by age group were chosen instead of younger women to maximize the probability that they were unaffected

by endometriosis. Women with a diagnosis of adenomyosis, uterine fibroids, migraine, and presence of a malignancy were excluded due to the potential association of selected candidate genes with these comorbidities.

2.3.2 Selection criteria for the study

The study with case-control evaluations is based on baseline (pre-surgical) data collected on women participating in the study. Between August 2018 and August 2019, we recruited 2,610 participants, using the following criteria: 1) premenopausal women, 2) aged 18-50 years, 3) self-reported ethnically Arab, and 4) no previous diagnosis of endometriosis. Exclusion criteria were: 1) pregnant women, 2) women with special needs, and 3) women who were illiterate, and were unable to comprehend and provide informed consent.

2.3.3 Rationale for choice of study population

To investigate whether the sample population was representative of the target population and source population, we needed to ensure that selection bias was avoided, and response rate was balanced across the sample population groups[312]. The target population for the study was the general population of premenopausal Arab women, aged 18-50, across the Middle East, to whom the findings would be generalized or applied. The source population represented the specific population of women attending the participating collection sites and meeting the eligibility criteria. None of the participant centres selected across the UAE were known to attract patients with demographic profiles that would be highly different from the general population of premenopausal women across the country: both private and public facilities were chosen that included a range of medical insurance coverages and served the population within the geographical reach. This strategy maximised the opportunity that the source population was representative of the generation population, and for women in the source population to have similar opportunity to be part of the sample population.

As described before, to minimize selection bias and temporal bias, incident cases were selected from a clearly defined source population during a specified period, as opposed to prevalent cases. The ideal control group were hospital and population-based controls, representative of that source-population, rather than only hospital-based controls[337]. The benefit of selecting multiple control groups is that it enabled me to investigate the sensitivity of the results to control selection for a disease for which no 'perfect' control group exists due to the different selection biases that operate, such as the likelihood of seeking medical advice, and being offering a laparoscopic investigation, both related to many personal, demographic, sociological and cultural factors[11,319]. While there are concerns those undiagnosed cases would be included in the control group, thereby diluting the risk factor effects, the community prevalence of severe stages of endometriosis is estimated at <2%. Therefore, to select a representative control population of the source population of cases, in terms of exposure of interest, hospital, clinic and populations controls were selected[11]. In addition, recall bias is reduced by keeping the study members blinded to the hypotheses of the project to ensure that both cases and controls have similar incentives to remember past events.

Observer bias did not occur because the research assistants were blinded to case/control status during data collection. To reduce the magnitude of misclassification from self-reported or symptom-based diagnosis in this study, endometriosis exposure was restricted to those women with surgical confirmation. Confounding bias was dealt with vigorously in the design stage, where controls were recruited in the same catchment area as cases, and in the analysis stage with analytical techniques that adjusts for these confounding factors, such as the Mantel-Haenszel method based on stratification, and mathematical modelling (regression methods) as demonstrated in Section 2.4.4[315].

2.4 Data collection

2.4.1 Data collection tools: questionnaires and forms

The WERF EPHect Working Group is a global, harmonization initiative that have developed and reached a consensus on standardized, evidenced-based data collection tools and guidelines that include: endometriosis participant questionnaire standard (EPQ-S) and minimum (EPQ-M)[338], surgical form

standard (SF-S) and minimum (SF-M)[339], and standard operating procedures (SOPs) for collection, processing and long-term storage of biological samples from women with endometriosis[340,341]. These tools were generated to standardize the collection of clinical and epidemiological data across global sites, and facilitate large-scale, international collaborations and epidemiologically robust research. Translations to the Arabic language, validated using the forward-backward translation method (see below), of the standardized, validated questionnaires were utilized. In this study, I have used the EPQ-M, SF-M and the SOP for collection, processing, and storage of saliva samples.

As highlighted above, only standardized instruments were incorporated into the questionnaire in English and Arabic languages. The EPQ-M questionnaire includes the following validated tools: short form McGill pain questionnaire[342], visual analogue scale for pain measurement[343], numerical rating scale for pain score[332], and pain catastrophizing scale[344]. In addition to these tools, the short form-36 version 2 questionnaire[345–348] and the work productivity and activity impairment tool[349] were included in the participant questionnaire. All the questionnaires have been assessed for internal consistency reliability of its dimensions, as well as its construct validity in community samples in the Middle East population.

2.4.1.1 Participant questionnaire

Endometriosis participant questionnaire minimum (EPQ-M)

The EPHect EPQ-M captures nonsurgical clinical information from endometriosis cases and controls that include key topics associated to symptomatology, risk factors and phenomic data, such as pain, subfertility and reproductive history, menstrual history and hormone use, medical and surgical history, medication use and personal information.

Cross-cultural adaption and translation to Arabic was conducted on the WERF EPHect EPQ-M, as per the recommended guidelines[338]. To do so, the WERF EPHect EPQ-M was carefully reviewed by two gynaecologists and two scientists to ensure that the questions were culturally appropriate for Arab women, and modifications were noted on questions that were culturally insensitive or not appropriate to ask. The

following questions were removed during this process: alcohol-related questions (Question F13 in the EPHect EPQ-M), gamete donation-related questions (Question B4), and termination (abortion)-related questions (Question B1). The following ancestries were added in Question F4: Arab, Baloch and Persian. Question F3, which asked if the participant considers themselves Hispanic/Latina, was removed because it was not relevant to the population. In Question F12, the question was changed to "Have you smoked more than 100 cigarettes *(1-hour consecutive shisha/hookah smoking session)* during your lifetime?" A statement was added before dyspareunia-related questions (Question C15-C26), due to cultural sensitivities, that stated: "If you are married, or have ever been married, please answer questions C15-C26. If you are single, please skip to C27." This allowed single women to not be exposed to sensitive questions that may be culturally inappropriate to introduce to unmarried women. Minor changes were made to Question E1 and E2, which included common medications that are marketed under different names with generic equivalents.

There are no standardized, validated questionnaires to assess the presence and severity of chemical and environmental exposure in a war zone. Hence, I included the questionnaire that is being utilized in the Gulf War Veteran Cohort[286], which is one bivariate qualitative war exposure assessment (yes/no). This was added at the 'Personal Information and Lifestyle' section, in which participants were asked if they were exposed to war, including smoke and oil cloud, chemical warfare agents including nerve gas and mustard gas, wearing chemical protective clothing, depleted uranium, and smoke from burned excrement and exhaust fumes. Questions that are impossible or difficult to answer (type, length and frequency of exposure), and questions asking for subjective evaluation (intensity and extent of exposure) were not included, as per the guidelines[286], due to exposure recall bias, non-differential exposure misclassification, and long questions on the details of the events that may trigger psychological stressors, such as post-traumatic stress disorder. Hence, the questions were limited to qualitative assessments. Questions relating to consanguinity (first or second cousin) were also included to assess parental consanguinity and consanguinity relationship of a woman with their husband, if married.

After the questionnaire was altered accordingly, a forward translation was carried out by two independent professional translators who were native speakers of Arabic and English. An expert panel of gynaecologists (n=2), an internist (n=1), and scientists (n=2) compared the two versions, and a final version was generated. The final version was back-translated to English, after which the expert panel compared this version to the original EPHect EPQ-M English version for errors and inconsistencies. Once the expert panel reviewed and finalized the Arabic translated version of the EPHect EPQ-M, a pilot study was conducted on 40 participants of variable age groups (18-30; 30-40; 40-50) and education levels (primary school diploma; secondary school diploma; university degree). Comments from the participants on any unclear questions were also addressed in the final version. The only comment that was raised by the participants was the inclusion of both the US and UK metric system (e.g., miles and kilometres) for exercise-related questions. For the Arabic validated and published versions of the questionnaire, scales were identified and incorporated into the questionnaire, explained in detail in the next section.

Short Form McGill pain questionnaire

The short form McGill pain questionnaire (sf-MPQ) measures the qualitative aspect and evaluation of pain phenotype. The pain rating index has 2 subscales that consists of 15 descriptors of pain, where 11 descriptors are categorized as sensory subscale (throbbing, shooting, stabbing, sharp, cramping, gnawing, hot-burning, aching, heavy, tender, and splitting) and 4 from affective subscale (tiring-exhausting, sickening, fearful, and punishing-cruel). Each descriptor was rated on an intensity scale as 0=none, 1=mild, 2=moderate and 3=severe. Three pain scores were derived from the sum of the intensity scores, calculated for sensory, affective, and total descriptors. A validated, Arabic translated version was utilized for this study[350].

Visual analogue scale

The visual analogue scale (VAS)[343] is a measurement tool that measures pain intensity experienced by individuals through a psychometric response scale. Scores are recorded by making a handwritten mark on

a 10-cm line that represents a continuum between “no pain” and “worst pain.” A validated, Arabic translated version was utilized for this study[351].

Numerical rating scale

The numerical rating scale (NRS)[332] is a subjective measure in which individuals rate their pain on an eleven-point numerical scale. The scale is composed of 0 (no pain at all) to 10 (worst imaginable pain). It has been developed to assess the extent of an individual's pain and improve communication regarding pain with health care professionals. A validated, Arabic translated version was utilized for this study[351].

Pain catastrophizing scale

The pain catastrophizing scale[344] includes 13 items that assesses the rumination (4 items), magnification (3 items) and helplessness (6 items) of the presence of pain. It helps quantify an individual's pain experience, asking about how they feel and what they think about when they are in pain. It is well documented that catastrophic thinking heightens the pain and distress experienced by the catastrophizer. Catastrophizing is defined as a negative mental state that is experienced during an actual or anticipated painful episode. It has been used to describe a tendency of the participants to expect the worse and to ruminate on the pain. A validated, Arabic translated version was utilized for this study[352].

Short form-36 version 2 (SF36v2) questionnaire

The Short form-36 version 2 (SF36v2)[345–348] questionnaire was used to measure HRQoL and is constructed to measure concepts relating to functional health, well-being, relative burden of the disease, objective and subjective ratings, and self-evaluation of general health status[348]. It is a multi-purpose, generic health survey that includes one unscaled transition question and 35 questions on quality of life. The SF-36 eight dimensions are physical functioning, role limitation-physical, bodily pain, general health, vitality, social functioning, role limitation-emotional, and mental health. These dimensions consist of functional health and well-being scores that fall into two psychometrically-based summary measures – the Physical

Component Summary (PCS) and the Mental Component Summary (MCS). The PCS correlates with physical functioning, role-physical and bodily pain, and the MCS correlates with mental health, role-emotional, and social function. Vitality, general health, and social functioning correlate with both components. Due to the lack of Middle Eastern normative values scores for the general population, the USA population normative values were utilized in this study as a reference population, to allow a meaningful comparison of the general health status and quality of life when conducting cross-cultural comparisons[345,347,353–355]. A validated, Arabic translated version was utilized for this study[356].

Work Productivity and Activity Impairment (WPAI) questionnaire

The Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH)[349] is a validated instrument that measures the effect of symptoms and disease on work productivity and daily tasks. The impact of the symptoms is measured by absenteeism (hours of missed work), presenteeism (perceived impairment of work tasks), work productivity loss (perceived loss in productivity levels) and activity impairment (impairment of patient's daily life activities). It aims to elicit the impact of the condition on impairment and work loss and whether the interventions reduce the number of impairment days and days lost to work. The six questions of the WPAI questionnaire refer to work and activity in the previous seven days. Although the recall period in all WPAI validation studies is 7 days, a 4-week recall period was employed to better capture the information.

2.4.1.2 Surgical questionnaire

Participating clinicians at the collaborating centres were highly trained and experienced laparoscopic surgeons. Consistent with the observational design, surgeons were not asked to change their practice in any way but were encouraged to obtain specimens for histology. Surgeons completed a standardized operative report (EPHect SF-M[357]) immediately after surgery to capture gynaecologic and pelvic pathology staging using the revised classification system of the American Society for Reproductive Medicine (rASRM): stage I (minimal), stage II (mild), stage III (moderate) or stage IV (severe). Surgeons were asked to stage using a categorical variable, from this questionnaire. This included information on the presence and position of

endometriomas or endometriotic nodules during pre-operative ultrasound scans, as well as staging of any endometriotic lesions found. If the surgeon did not complete the surgical form, the research assistant did so with the use of the operation notes, and the document was cross-checked with the surgeon. The EPHect SF-M was then collected by the research assistant after each procedure.

2.4.2 Anthropometric measurements

Basic anthropometric measurements were documented from consenting women including: (1) weight and height using calibrated digital scaling instruments; and (2) waist and hip circumference using the WHO guidelines[358]. Each measurement was taken twice, and an average was recorded for each measurement; where there was a significant difference between the two measurements, the two measurements were taken twice.

2.4.3 Saliva sample collection

Saliva samples specimens were obtained from a subset of the women post procedure, depending on their diagnosis, for DNA extraction for genotyping. Saliva samples are collected using the ORAGENE-DNA Saliva kits, which is the gold standard to collecting high quality DNA via a non-invasive method. The saliva collection kit preserves the DNA stable at room temperature up to 8 years. A total of 2ml of saliva sample is collected from each participant[359,360]. The SOP that comes with the saliva collection kit is followed by each participant and overseen by the research assistant. The research assistant recorded whether the patient has fasted (and number of hours), last exposure to toothpaste, gum, cigarettes, alcohol, meal, medication. Samples must be collected at least 1 hour after eating a meal and brushing teeth. Participants were asked to rinse their mouth before collection. The sample collection tube was labelled with the unique identified of the participant and the date/time of sample collection.

2.4.4 Outcome measures

The measures chosen to assess the impact of endometriosis, in association to symptomatology, risk factors, phenotypic profile and comorbid are elaborated below. All data was self-reported and obtained from the questionnaire.

Demographic factors and personal information

Demographic factors, such as age, education status, marital status, current employment status, ethnicity, basic anthropometric measurements (BMI, height, weight, waist-hip ratio), family history of endometriosis, war exposure, consanguinity and smoking were studied to understand whether these factors are associated with endometriosis. Anthropometric measurements were collected from the participant by the research assistant, and the rest of the data was extrapolated from the EPQ-M questionnaire (Question G1-15).

Quality of life, work productivity and activity impairment, diagnostic delay

I investigated the association between endometriosis and the physical, mental, and emotional health of the participants, by collecting the information on psychological state and health-related quality of life. These data were collected from the SF36v2 questionnaire (Question A1-A9). Work productivity and activity impairment was also measured using the WPAI tool (Question G19-G24), and physical activity was assessed using a validated measure from the EPQ-M (Question G16-G18). Age of first visit to gynaecologist and diagnostic delay of endometriosis was also calculated from the EPQ-M (Question E12-E13) – age at symptom onset.

Pain phenotypes

The frequency of the variable pain phenotypes (dysmenorrhea, noncyclical pelvic pain, dyspareunia, dyschezia and dysuria) among women with endometriosis was compared to symptomatic control group using bivariate (yes/no) analysis. The pain phenotypes were defined as women who experienced one or more of the pain symptoms for: (1) at least six months' duration; and (2) a NRS[331,332] score greater than 4[333]. The NRS and VAS scales allowed me to investigate the pain intensity and severity, the sf-MPQ

(Question D1-D30) allowed for subcategorization of pain symptoms based on two separate domains (sensory and affective pain), and the pain catastrophizing scale was used to understand the rumination, magnification, and helplessness of the presence of pain in women with endometriosis, in comparison to control group.

Menstrual history and oral contraceptive use

Menstrual history, such as age at menarche and menstrual cycle characteristics (regularity, frequency, duration, and heaviness of menstrual flow), was derived from the EPQ-M questionnaire (Question B1-B6), to understand the early life menstrual characteristics and their change over time to further comprehend the aetiology of endometriosis. In addition, by understanding the use of hormone and life-time contraceptive use was collected as this can affect biomarker profiles and treatment strategies. Participants were asked to indicate what type of contraceptive method was used, the reason of use, age at first use and time since they last used this method.

Subfertility and reproductive history

The association between infertility and endometriosis may have a common origin, as suggested by evidence linking in-utero exposures with endometriosis[156]. Infertility was defined as unprotected intercourse in the fertile phase of the menstrual cycles for 12 months[334]. Other reproductive factors that were extracted from the EPQ-M questionnaire (Question C1-C4) were: parity (nulliparous, parous), pregnancy history (multiple gestation, complications such as gestational diabetes, ectopic pregnancy, miscarriage, pre-eclampsia, pre-term birth and pregnancy related high blood pressure), type of delivery (vaginal delivery, emergency caesarean section) as well as the type of fertility treatment used (no treatment/natural conception, assisted reproduction, ovarian stimulation procedures).

Past medical and surgical history

Participants were asked if they have been medically diagnosed with a condition to investigate whether a condition is comorbid with endometriosis. Questions regarding diagnosis received were asked in relation

to a woman's lifetime, as this information was likely to be more accurately remembered. A checklist of possible diagnoses was provided, with the opportunity to add diagnoses that were not listed. This helped us understand if these conditions share a mechanistic pathway, risk factors, genetic markers, and/or immune-related factors that are associated with endometriosis, to better understand the pathophysiology of the disease. I focused on the association of endometriosis to the following comorbid conditions: anxiety, depression, asthma, eczema, diabetes mellitus type 1 and type 2, cardiovascular disorder, hypertension, uterine fibroids, and polycystic ovary syndrome. These data were collected from the EPQ-M questionnaire (Question E1-E15).

2.5 Data management

2.5.1 Administration of questionnaire

A custom-made cloud-based survey platform, Research Electronic Data Capture (REDCap)[361], with servers housed on a secure HIPAA compliant server at the University of Oxford, was utilized in this study to build and administer the questionnaire. As per the guidelines, I built the questionnaire algorithm by custom coding all variables, setting up branching matrix and formatting options to create a customized instrument to facilitate data collection. Only IRB-approved research team members had access to the REDCap data platform, to maintain data security and confidentiality. REDCap also serves as an integrated database for collecting and storing data through traditional methods, such as direct data entry from paper-based questionnaires. This software was not compatible with the Arabic language, so all paper-based questionnaires that were completed in Arabic, were entered into the system in English. On the Thursday of every week, I uploaded the paper-based questionnaires unto REDCAP, with 10% of the questionnaires entered by two independent data processers to find discrepancies. Possible data-entry errors were separated into 'correctable' (wrongly coded data that would be noticed in frequency tabulations and consistency checks) and 'not correctable' (wrongly coded data that would go unnoticed unless entered a second time). The maximum accepted not correctable error rate was set at 1 error per 100 questions. If the data-entry

errors exceeded the maximum accepted error rate, then all the questions were cross-checked to ensure accuracy and precision.

At the end of the project, REDCap software was used to enable easy export of all the selected data directly into a variety of statistical packages. All devices that were used to facilitate the data collection and analyses were ensured through encrypted transmissions and firewall protection. The survey was active between 1st August 2018 and 1st August 2019. A password protected and encrypted master list spreadsheet was kept on a secured shared drive that linked the unique research number to the patient medical record number, as per standard research practice.

2.5.2 Missing values

Exclusions occurred either on an a-priori basis (for example women who did not meet the eligibility criteria) or due to incomplete or missing data. The exact numbers of women excluded can be found in the methods sections of the relevant data analysis chapters (3.3.4, 4.3.4.1). Several options were considered for dealing with variables with missing data including complete case analysis, multiple imputation, or - where missingness involved a confounding variable - dropping this variable in the multivariate analysis. Depending on the tool/questionnaire utilized, the variables were imputed as per the developer's guideline. Pairwise deletion was utilized for variables where data were not missing at random; where reliability of data could not be confirmed by participant, the variable was dropped from the multivariable analysis to minimize the risk of bias.

2.5.3 Data cleaning

Data were checked for duplicate entries, inconsistencies such as more than one mutually exclusive outcome recorded, and any outliers which were not biologically plausible. After cleaning the datasets, variables of interest were created from the raw data in preparation for analysis. Variables were checked for impossible values by looking at frequency distributions and consistency checks were run between answers to related questions. Unlikely or conflicting information was always checked by going back to the questionnaires.

Thus, all correctable errors were rectified. If information given in the questionnaires was inconsistent and rendered the information uninterpretable, these women were excluded from all data analyses. Questionnaires with data inaccuracies such as abnormal data entry and missing response values were systematically excluded from the data analysis (demonstrated in Chapter 3.3.4 and 4.3.4.1).

2.6 Methods of analysis

2.6.1 Selection of confounders

For adjusted analyses, two a-priori variables were selected to be included in all models because of their robust relevance to endometriosis disease risk estimation: participant age at the reference date and BMI. This study recruited women aged 18 to 50 years, however, endometriosis is a condition that typically affects women of reproductive age with a peak observed between 25-29 years. Hence, age is a strong factor in risk of endometriosis diagnosis, and is also associated with most of the exposures of interest investigated, such as menstrual history, parity, and presence of comorbidity[10,362]. BMI is an important confounder related to endometriosis as women with endometriosis have repeated been shown to have a lower BMI than women without endometriosis[10,363], and is also associated with many exposures and factors of interest. BMI obtained at recruitment was adjusted for, as a categorical variable (underweight, ≤18.5; normal, 18.5-24.9; overweight, 25-29.9; obese ≥ 30). Additional confounders were first determined through crude, unadjusted analyses of association with outcome (endometriosis yes/no) and exposure; where both were nominally associated ($p<0.1$), the effect of addition of the variable to the model was checked (using the criterion of a change of >10% in the beta coefficient from the logistic regression model)[10]. If a factor was identified as a confounder of any estimated main effect, it was kept in all models related to the specific association tested. All covariates were represented as categorical variables, except for age, which was treated as a continuous variable.

2.6.2 Sample size estimation

The calculation of power and required sample sizes to detect the frequency of symptoms and association of risk factors and clinical variables with endometriosis involved assumptions for (1) the frequency of symptoms in cases and controls; (2) the effect sizes to be detected; (3) the significance level of the effect size to be detected; and (4) minimum and maximum sample sizes likely to be achieved. I used G*Power software (version 3.1.3) to determine the appropriate study sample size.[364] The sample size required for the intended analyses was computed, assuming an overall alpha Type I error probability of 0.05, power of 0.80 (1-β error probability), to detect effects with ORs from 1.20 to 4.00, and a minimum frequency of exposure of 10% was 434 cases and 1,302 controls. I increased the sample size by 15% to make allowance for adjustment for confounding variables[365]. Thus, my aim was to recruit N=500 cases, N=500 symptomatic clinic controls, N=500 asymptomatic clinic controls, and N=500 population controls, totalling a sample size of 2,000 women.

2.6.3 Tests for heterogeneity

Additional analysis of sensitivity of the results to control definition were conducted, which included: 3) clinic-based vs. population-based controls, to test for selection biases inherent to the likelihood for women to seek health care; and (4) public vs. private hospitals/clinics, to test for selection bias. To quantify hidden bias, such as the possibility of undiagnosed endometriosis cases in the control group, sensitivity analysis was conducted between demographic variables for the symptomatic controls with surgical confirmation vs. symptomatic controls with no surgical confirmation. Tests for heterogeneity were calculated with a Wald statistic referred to a chi-squared distribution with 1 degree of freedom or a Pearson chi-square when comparing to the UAE census data[366].

2.6.4 Statistical methods

The response rate was calculated as the proportion of eligible invited women who agreed to participate. Reasons for non-participation were explored and documented by the research assistant with the invitees

who declined participation. The proportions of completed questionnaires were assessed to give an indication of how participants have completed the questionnaires.

Descriptive statistics, univariate and multivariate logistic regression were applied to investigate the association between endometriosis and symptomatology, risk factors and comorbidities. To evaluate risk factors for endometriosis, univariate, and multivariate adjusted logistic regression (odds ratio (ORs) and corresponding 95% confidence intervals (CIs)), were calculated comparing cases with the following two control groups: (1) Ascertainment criteria (Endometriosis cases vs. hospital controls; Endometriosis cases vs. population controls), and (2) Symptomatic criteria (Endometriosis cases vs. symptomatic controls; Endometriosis cases vs. asymptomatic controls). The data was analysed using Statistical Package for Social Science (SPSS) version 20 (SPSS Inc., Chicago, IL), R (Version 3.4.1), and PLINK[367] (Version 1.9). The statistical methods utilized are detailed in each chapter.

2.7 Summary

The MAR'A project is a case-control study of Arab ancestry women living in the United Arab Emirates, that consists of an epidemiological and genetic epidemiological component. With the use of evidence-based, standardized questionnaires and CGAS analysis, the study aimed to investigate risk factors and clinical variables in association to endometriosis, with data collection adapted and respectful to religious beliefs, cultural norms, and traditional expectations in the community. This will ensure that results obtained will allow medical professionals to provide culturally sensitive, comprehensive care. Such understanding will allow policymakers, stakeholders, and medical physician to improve management and develop targeted health education awareness campaigns for Arab women that struggle with endometriosis, which will differ from the current, more western-centric approaches.

The next three chapters (3, 4 and 5) focus on epidemiological factors, HRQoL, and genetic factors with endometriosis, respectively. Any methods specific to the chapter which have not been described above are detailed in the respective chapters.

Chapter 3. Epidemiology of endometriosis in women of Arab ancestry

3.1 Introduction

Clinical presentation and risk factors of endometriosis have been investigated in studies mainly arising from European ancestry populations. Cross-cultural studies are valuable because they expose cultural and regional differences in symptom presentation and risk factors of women with endometriosis. In this chapter, I am investigating the symptom presentation, risk factors and phenotypic profile associated with endometriosis in women of Arab ancestry. Specifically, the association of various demographics, anthropometric, lifestyle, menstrual, reproductive factors and co-morbidities are investigated in women of Arab ancestry.

Among the most consistent associations with endometriosis reported in the literature are several demographics, anthropometric, and lifestyle factors that have been identified, including higher educational level and work status. There is an inverse association between endometriosis and a women's current body mass index (BMI) and waist-to-hip ratio adjusted for BMI (WHRadjBMI)[6,164,172,173]. Given that >70% of Arab women are obese and overweight[255,368], it is important to investigate whether regional variables and dietary factors influence the relation between endometriosis and BMI among Arab women. The risk for endometriosis in first degree relatives of endometriosis patients is four to seven fold compared to the normal population[58,62], and the severity of endometriosis is higher among patients with a positive family history[369]. Studies have suggested that Middle Eastern and Asian women are at higher risk of endometriosis compared with Caucasian women, with a lower risk among African American women[154,156–158,160]. While studies have demonstrated a potential link between smoking and endometriosis, smoking is not common among Arab women due to the cultural stigma associated with it[362,363]. Stressful life events, such as exposure to war, leave evident scars on all aspects of life including the prevalence of diseases[284,286]. The impact of war exposure on endometriosis has not been investigated to date.

Women with endometriosis present with a single or a combination of pain symptoms of variable intensity, including dysmenorrhea, dyspareunia, dysuria, dyschezia and chronic pelvic pain. Approximately, 40-80%

of women with endometriosis experience pelvic pain[6,7,10]. However, a clear characterization of pain typology and severity in Arab populations with endometriosis have not been investigated. In addition, a comparison between pain typology and severity, in comparison to women with other gynaecological pathology, is lacking. Understanding the precise nature of the relationship between pain and endometriosis is important for the clinical management of affected women to prevent delay of diagnosis. Pelvic pain with endometriosis has a complex pathophysiology through a network of interacting mechanisms likely involving inflammatory, nociceptive, neuropathic and centralised pain[81–87]. It can also explain the coexistence of these pain conditions in patients with endometriosis that are sensed in a nearby structure through crossing neurons along the pain signal pathway. Women with endometriosis often have other pain phenotypes including back pain, leg pain, ovulation pain and migraine. Common genetic influences on the co-occurrence of migraine and endometriosis have been identified[203,204]. Hence, it is important to assess the type and severity of pelvic pain, and pain beyond the pelvis, that is experienced among endometriosis women, to provide a more effective method for medical and surgical management.

Menstrual cycle characteristics, such as early age at menarche, shorter menstrual cycle length, and heavy menstruation, have been identified to be associated with endometriosis[10,161–166]. These risk factors influence endometriosis risk because they reflect the frequency of exposure to menstruation or volume of menstrual reflux. The increase of frequency and duration of retrograde menstruation lead to tissue degeneration that plays a central role in the inflammatory response, with the subsequent development of endometriosis, as described using Sampson's theory[24,161,370]. No studies have investigated the association of menstrual characteristics in Arab women to endometriosis, and how this differentiates to the general population.

Infertility is another symptom commonly associated with endometriosis, through mechanisms that are largely unknown. Approximately, 20-50% of women with endometriosis experience infertility[6,7,10]. Endometriosis has been associated with adverse pregnancy outcomes through many hypothesized mechanisms. Increased progression of the disease can result in anatomical distortion of the pelvic cavity, which may lower the pregnancy rate, leading to infertility, miscarriages and ectopic pregnancy[191]. The

increased presence of inflammatory cells in the peritoneal fluid, endometrial resistance to endometrial progesterone, and inadequate uterine contractility may compromise embryonic development, pregnancy implantation and maternity outcomes associated with endometriosis[110,113,125,192]. Such disturbances in the peri-implantation period could perpetuate throughout the later stages in pregnancy, and influence risk of gestational diabetes, pre-eclampsia, pre-term birth and emergency caesarean section[192,193]. In the Middle East, childlessness strongly influences marital life, and unfortunately may lead to divorce, or becoming a second wife in a polygamous marriage[281,282]. Hence, infertility has a significant impact on the mental health components in our study because women in Middle Eastern societies are often blamed when conception does not occur[371]. I am investigating fertility and reproductive risk factors in the context of endometriosis for the first time in women in an Arab population.

There is increasing evidence of a higher prevalence of a range of comorbidities with endometriosis, including immunological and inflammatory disorders (asthma, eczema, diabetes mellitus type 1), metabolic and cardiovascular disorders (diabetes mellitus type 2, hypertension), and gynaecology disorder (uterine fibroids, polycystic ovary syndrome and Mullerian anomalies)[86,179,374,375,199–202,207,223,372,373]. Immune and inflammatory conditions have been associated with endometriosis and postulated to be linked to immunological abnormalities (high T, B, and natural killer cell counts but decreased activity, high IgG/IgA/IgM autoantibodies and anti-endometrial antibodies) and hormonal factors (oestrogens and prolactin)[195–197]. Metabolic and cardiovascular disorders are also associated with endometriosis. Reason for this are unknown, but hypotheses include that atherosclerotic plaque and the peritoneal fluid of female patients with endometriosis have an abundance of inflammatory cytokines, chemokines and growth factors that are involved in the generation of localized inflammation and that may persist to increase risk of other inflammatory conditions[207]. Endometriosis, polycystic ovary syndrome and uterine fibroids involve altered functioning of the female hypothalamic-pituitary-gonadal (HPG) axis, hormonal factors, biological factors (menstrual cycle factors, pain, infertility) with a possible shared genetic variant[216,217,219]. There is a need to

examine the associations between endometriosis and a broad set of co-occurring conditions in an Arab population.

The current study was designed to address the gap in knowledge of endometriosis-associated symptomatology and prevalence of comorbidities in the Arab population. Women of various ethnicities may have different presenting symptoms of endometriosis and express different treatment preferences. To investigate the clinical presentation and symptomatology of endometriosis among Arab women, we will investigate the pain phenotype (typology, severity, alleviation to conventional medical therapy) and infertility (frequency of type of infertility and subfertility). To add further understanding of the association of endometriosis to modifiable and unmodifiable risk factors, the following factors will be investigated among Arab women: sociodemographic factors, anthropometry, menstrual characteristics, and reproductive history. Comorbidities and long-term disease risk will also be investigated to improve the management and care of women with endometriosis, and further understand the complex aetiology of the disorder. The following comorbidities will be investigated: immunological and inflammatory disorders (asthma, eczema, diabetes mellitus type 1), metabolic and cardiovascular disorders (diabetes mellitus type 2, hypertension), and gynaecology disorder (uterine fibroids, polycystic ovary syndrome and Mullerian anomalies). This study will provide a novel understanding of symptomatology and risk factors among Arab women, using validated and culturally sensitive patient outcome measures.

3.2 Objective

The findings presented in this chapter are based on the analyses of data from a case-control study (518 cases: 2093 controls) of Arab ancestry women living in the United Arab Emirates. As explained in the previous chapter, I addressed the objectives of my study in 'the Middle Eastern Women Research Association: the MAR'A project,' adopting the use of evidence-based, standardized questionnaires.

Firstly, I will present the representativeness of the sample control group by comparing it with the general population figures in terms of sociodemographic factors using the UAE census data for the same year as data collection (2018)[376]. I will also conduct sensitivity analyses to quantify hidden bias on hospital control

group vs. population control group, private medical facility vs. public medical facility, and total control group vs. UAE census data.

After presenting the sample population, in this Chapter, I aimed to answer the following questions:

1. Are the sociodemographic factors, such as age, BMI, WHRadjBMI, educational level, work status, parental consanguinity, war exposure and family history, associated with endometriosis risk?
2. What are the pain characteristics among women with endometriosis, in comparison to symptomatic and asymptomatic controls?
    a. What is the frequency, duration, and severity of the pain phenotypes?
    b. Does conventional medical therapy assist with pain alleviation?
    c. Is the rASRM staging of endometriosis correlated with the presence and severity of pain?
    d. Does parity influence the presence and severity of pain, regardless of clinical indication?
3. What is the role of menstrual history and symptoms in the risk of endometriosis, with particular emphasis on the timing of potential causal exposures?
    a. What is the age at menarche, regularity of menstrual cycle, duration of menstrual phase, menstrual cycle length and intensity of menstrual flow in women of endometriosis?
4. Are women with endometriosis more likely to have adverse pregnancy outcomes when compared to endometriosis?
    a. What are the fertility characteristics among endometriosis women compared with controls?
    b. What is the frequency of miscarriage, ectopic pregnancy, preeclampsia, pregnancy-induced hypertension, emergency caesarean section, and preterm birth in women with endometriosis, compared to the control group?
5. What comorbidities are associated with endometriosis, in comparison to symptomatic and asymptomatic controls?

a. Are immune and inflammatory conditions (asthma, eczema, diabetes mellitus type 1) associated with endometriosis?

b. Are metabolic disorders (diabetes mellitus type 2, cardiovascular disorder, hypertension) associated with endometriosis?

c. Are gynaecology disorders (uterine fibroids, polycystic ovary syndrome and structural problem) associated with endometriosis?

3.3 Methodology

3.3.1 Study population

Endometriosis cases and symptomatic and asymptomatic controls were defined as described in Chapter 2.3. Briefly, 2,610 participants were recruited from multiple sites across the UAE (four hospitals and clinics, and six population-based sites in the same catchment area), using the following inclusion criteria: 1) premenopausal women, 2) aged 18-50 years, 3) self-reported ethnically Arab, 4) no previous diagnosis of endometriosis, and 5) willing to give an informed consent form for participation. Exclusion criteria were: 1) previous diagnosis of endometriosis, 2) pregnant women, and 3) women who were illiterate, and were unable to comprehend and provide informed consent.

Incident cases of endometriosis were diagnosed among women scheduled to undergo a diagnostic and/or therapeutic laparoscopy or laparotomy for any indication by visual confirmation as is the current golden standard[19,377], and classified into four grades, based on the revised American Society for Reproductive Medicine (rASRM).[16] The control group comprised three distinct groups: (1) hospital controls who had undergone laparoscopic surgery showing that they were endometriosis-free, (2) clinic controls who were screened using therapeutic/diagnostic tests, (3) population controls recruited during organized public seminars on women health issues.

For comparison, the case-control analyses included a descriptive analysis of the study population to assess the association of symptomatology and the distribution of clinical variables in the study population across

disease outcome categories based on the following comparisons: (1) ascertainment criteria (endometriosis cases vs. hospital controls; and endometriosis cases vs. population controls); and (2) symptomatic criteria (endometriosis cases vs. symptomatic controls; and endometriosis cases vs. asymptomatic controls). The ascertainment criteria will enable the assessment of a representative control group of the underlying population, in terms of exposure of interest (population controls), versus the assessment of predictors of endometriosis within a subset of the population with comparable socioeconomic factors and recall bias (hospital controls). The symptomatic criteria will explore sensitivity of results to control definition by investigating whether the risk factors and clinical variables were driven by the endometriosis-related symptoms (asymptomatic controls) or endometriosis *per se* (symptomatic controls).

3.3.2 Questionnaire and data collection tool

Validated, English and Arabic versions of the standardized World Endometriosis Research Foundation EPHect minimum clinical questionnaire (EPQ-M) version[338] were utilized (described in Chapter 2.4). Translations into the Arabic language validated using the forward-backward translation method, of the questionnaires were utilized. The WERF-EPHect questionnaire included four pain measurement tools: Short Form McGill pain questionnaire[342], visual analogue scale for pain measurement[343], numerical rating scale for pain score[332], and pain catastrophizing scale[344]. Data were collected and entered into a web-based research electronic data capture (REDCap)[361] database, with 10% of the questionnaires inputted by two independent data processers to find discrepancies. The following basic anthropometric measurements were collected: 1) weight and height using calibrated digital scaling instruments, and 2) waist and hip circumference using the WHO guidelines[358]. After data checking and validation, 2,610 questionnaires were used for data analyses in this study.

3.3.3 Assessment of outcomes

Detailed information on sociodemographic factors, pain characteristics, menstrual factors and reproductive factors were obtained from all participants. All data were self-reported and derived from the EPQ-M questionnaire. The following information was collected:

Sociodemographic factors

Participants were asked their age, date of birth, civil status (single, married, divorced, widowed), work status (employed, self-employed, not employed), educational level (primary level, secondary level, high school level, bachelors, masters, and doctorate), and residential status (Abu Dhabi, Dubai, Sharjah, Ajman, Umm al Quwain, Ras al Khaimah, Fujairah). Weight and height were reported on the baseline questionnaire. BMI was calculated as weight in kilograms over height in meters squared (kg/m^2). BMI was categorized based on the World Health Organization classification into underweight ($\leq$18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2) and obese ($\geq$30 kg/m^2). Participants were asked about gynaecologic diseases in all first-degree relatives (mothers, sisters, and daughters), as well as second- and third-degree relatives (aunts, cousins). The maternal and paternal lines of relatives were evaluated separately. War exposure (yes/no) and first relative parental consanguinity (yes/no) were documented from all participants. Women were classified as smokers if they had smoked at least 100 cigarettes or one-hour of consecutive shisha smoking.

Pain characteristics

Data was collected on four pain phenotypes: dysmenorrhea, chronic pelvic pain, dyschezia and dysuria. The EPQ-M questionnaire included four pain measurement tools: Short Form McGill pain questionnaire (sf-MPQ)[342], visual analogue scale (VAS) for pain measurement[343], numerical rating scale (NRS) for pain score[332], and pain catastrophizing scale (PCS)[344]. The NRS and VAS scales allowed me to investigate the pain intensity and severity, the sf-MPQ allowed for subcategorization of pain symptoms based on two separate domains (sensory and affective pain), and the PCS tool was used to understand the rumination, magnification, and helplessness of the presence of pain in women with endometriosis, in comparison to controls. The age of symptom onset, and age of worst symptom onset was noted. The typical severity of pain was measured as: the average severity of pain in the last 6 months, the worst severity of pain in lifetime, and the average severity of pain in the last month. In addition, for all types of pain, severity was measured on a NRS and VAS. Use of medications (over the counter pills and hormones) for pelvic pain was noted,

and participants were asked if their pain was alleviated (yes/no). The association between the presence and severity of pain was investigated in relation to rASRM staging of endometriosis (rASRM stage 1-4) and parity (nulliparous/parous).

The following definitions were utilized for each pain phenotype:

- Dysmenorrhea: pain just before menstrual period, level of cramps with period, pain after period has finished.
- Chronic pelvic pain: constant or intermittent pelvic pain not exclusively associated with a menstrual episode or sexual intercourse.
- Dyschezia: pain with bowel emptying.
- Dysuria: pain with urination.

The pain phenotypes were classified as a bivariate (yes/no) analysis in women who experienced one or more of the pain symptoms for:

- At least six months' duration
- Numerical rating scale (NRS)[44,45] score greater than 4[46].

Menstrual history

Age at menarche (open ended question), regularity of menstrual cycle (regular, irregular), duration of menstrual phase (number of days noted in open ended question), menstrual cycle length (≤24, 25-31, ≥32) and intensity of menstrual flow (light, average, heavy) was derived from the EPQ-M questionnaire.

Subfertility and reproductive history

Fertility and reproductive characteristics were only measured in women who were ever married (married, divorced, widowed), as single women are prohibited from seeking fertility services in the UAE and majority of Middle Eastern countries. The following definitions were utilized for each fertility:

- Infertility: Women who were infertile defined as unprotected intercourse in the fertile phase of the menstrual cycles for 12-24 months or >24 months
    - Primary Infertility: Infertile couples who have never become pregnant before after having unprotected intercourse
    - Secondary Infertility: Infertile couples who have been able to get pregnant at least once, but are now unable to after having unprotected intercourse

Other reproductive factors that were extracted from the EPQ-M questionnaire were parity (nulliparous, parous) and pregnancy history. Pregnancy history included miscarriage (spontaneous pregnancy loss <24 weeks), ectopic pregnancy (pregnancy outside the uterine cavity), hypertensive disorders of pregnancy (preeclampsia, eclampsia, and pregnancy-induced hypertension), mode of delivery (spontaneous vaginal, instrumental delivery or emergency caesarean section), and preterm birth (delivery <37 weeks of gestation).

Past medical and surgical history

Participants were asked if they were clinically diagnosed with the following comorbid conditions: immunological and inflammatory disorders (asthma, eczema, diabetes mellitus type 1), metabolic and cardiovascular disorders (diabetes mellitus type 2, hypertension, cardiovascular disease (any condition affecting the heart or blood vessels including myocardial infarction, coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis)), and gynaecology disorder (uterine fibroids, polycystic ovary syndrome and Mullerian anomalies).

3.3.4 Missing values

In general, missing values for a variable were excluded from analyses involving that variable. For most variables, the frequency of missing values ranged between 0.5-1.3%. The maximum frequency of missing values in the models was 5%, and if a variable exceeded it, this was noted in the tables. Dyspareunia related

variables had 96% missing variables; hence this variable was excluded from multivariate modelling. In view of the conservative social values and cultural beliefs in the region, reluctance among women to report sexual problems was anticipated. In the following instances, missing values were imputed as per the guidelines:

- McGill pain scale[342]: 6% of women did not indicate the severity of pain for all the 15 descriptors. For those that were missing, the values were scored as none.
- Pain catastrophizing scale[344]: 8% of women did not indicate the severity of each pain dimension. For those that were missing, the values were scored as none.
- Past medical history: 19% of women had a missing value for presence of a past medical or surgical history. Missing values were treated as negative answers.

3.3.5 Assessment of covariates

A priori covariates were age (continuous) and BMI (categorical: underweight (≤18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2) and obese (≥30 kg/m^2)) (methods 2.5). We considered other possible risk factors for endometriosis as potential confounders if addition of that variable to the model changed the rate ratio by 10 percent or more (see Chapter 2.6.1). If a factor was identified as a confounder of any estimated main effect, it was kept in all models. Additional confounders of endometriosis included parity (nulliparous, 1, 2, ≥3 pregnancies), infertility history (yes/no), oral contraceptive use (never, past, current), age at menarche (continuous), smoking history (yes, no, past), physical activity (yes, no) and educational level (primary, pre-secondary, secondary, post-secondary, university, and post-doc). The potential risk factors for endometriosis were explored as both continuous and categorical variables. All the covariates listed as potential risk factors for endometriosis were separately evaluated as a potential model-based confounding factors (using the criterion of a change of >10% in the beta coefficient from the logistic regression model) of the association between endometriosis and individual hypothesized risk factors. For each model, the confounders are listed in the respective table.

3.3.6 Statistical methods

Descriptive statistics (frequencies and percentages; mean, standard deviation (SD); median interquartile range (IQR) as appropriate) were used to summarise socio-demographic characteristics in the endometriosis and the control groups. Statistical analysis was performed in SPSS 15.0.1 (SPSS Inc, 1989-2006). Sensitivity analysis was assessed using a non-parametric Mann Whitney U Test to quantify hidden bias.

Contingency tables and chi-square analysis were used to compare between groups. Comparisons between proportions were made using the Pearson chi squared test, and trends in proportions were assessed for statistical significance using the Mantel Haenszel chi squared test for trend. Differences in means between two groups were assessed using the t-test; difference between the means of more than two groups were assessed using analysis of variance (ANOVA). Correlations between pain severity scores and cumulative CPP duration were investigated by calculating Spearman correlation coefficients. In the regression models, endometriosis was modelled as the dependent variable and the exposure variables were modelled as independent variables. Binary and multivariate logistic regression models were used as appropriate to evaluate association of endometriosis with the independent variables. Crude and adjusted odds ratios (OR) with 95% confidence intervals (95% CI) were obtained. An asterisk was placed as a footnote of each table of the variables that were adjusted for in that model. A p-value of <0.05 was deemed statistically significant.

3.4 Results

3.4.1 Response and data completeness

The recruitment statistics of the study sample is outlined in Table 3.1. Given that epidemiological studies are not common in the Middle East, we estimated a 50% recruitment rate, hence aimed to recruit 3000 participants. A total of 3062 eligible women were approached, and 2660 (86.9%) agreed to participate. Fifty questionnaires (1.63%) had more than 50% missing data, leaving complete data for 2610 women. Of the 2610 women that returned a completed questionnaire, 2062 (79%) stated that they would like to participate in future studies.

Table 3.1. Recruitment and response rate of the study sample.

	Total Participants Targeted	Total Participants Recruited
Approached	3000	3062
Agreed to Participate*		2660
Refused to Participate		402
Participants with >50% Missing Data		50
Total Participants**	1500	2610
Endometriosis Cases	500	518
Symptomatic Controls	500	1331
Asymptomatic Controls	500	762

*Total Recruitment Rate: 86.9% (2660/3062)
** Total Response Rate: 85.2% (2610/3062)

Questionnaire data for the 2,610 women who responded were entered into the REDCap system and then extracted to Microsoft excel and the SPSS system. The language of completed questionnaires were 57.9% (n=1,511) in the English language, and 42.1% (n=1,099) in the Arabic language. A total of 51.9% (n=1,355) of the questionnaires were completed electronically, with 48.1% (n=1,255) questionnaires completed by paper. To check the accuracy of single data entry, the data from 10% sample (261 women) were entered a second time. As explained in chapter 2.5.1, possible data-entry errors were separated into correctable and not correctable, with a maximum accepted correctable error rate set at 1 error per 100 questions. For this study, the frequencies of correctable errors were 1 per 822. Since this is below the maximum accepted rate, the data for the remaining 2,349 women were not entered a second time.

3.4.2 Internal and external validity

An important problem that may compromise the internal and external validity of study results is selection bias. To investigate this, the sociodemographic factors of the control groups of the study sample were compared with the general population figures, using the UAE census data for the same year as data collection (2018)[376]. To investigate the heterogeneity of the control group (population-based control sample vs. hospital-based control sample) a Pearson chi-square was conducted to quantify hidden bias (Table 3.2).

There were no statistically significant differences between the total control sample and the UAE census. Compared to the census data, the total control sample was of slightly younger age. There was a slight difference in BMI, where the census data had a greater proportion of obese women, as opposed to our study sample. This could be due to the slightly younger age group of our study sample. Women in the study

sample were slightly more educated (frequency of doctorate degree); however, this is expected for epidemiological studies. Employment rate and proportion of residential status was like the census data. Women in the study sample were more likely to be single, as opposed to the census data, however this could be because the study sample was of younger age.

Table 3.2. Comparison of the control sample to the 2018 UAE census health data

	Population-Based Control Sample	Hospital-Based Control Sample	*p*-value	Total Control Sample	UAE Census Data	*p*-value*
Age						
18-27	245 (29.1%)	303 (24.2%)		548 (24.8%)	835 (21.3%)	
28-36	237 (28.2%)	377 (30.1%)	0.053	614 (29.3%)	1479 (37.9%)	0.419
37-50	359 (42.7%)	571 (45.6%)		930 (44.5%)	1588 (40.7%)	
BMI						
≤18.5	11 (1.3%)	26 (2.1%)		37 (1.8%)	90 (1.1%)	
>18.5 to ≤ 24.9	352 (41.9%)	473 (37.8%)	0.142	825 (39.4%)	2784 (34.0%)	0.664
>24.9 to ≤ 29.9	291 (34.6%)	439 (35.1%)		730 (34.9%)	2808 (34.3%)	
>29.9	187 (22.2%)	313 (25.0%)		500 (23.9%)	2505 (30.6%)	
Education Level						
Primary**	10 (1.2%)	18 (1.4%)		28 (1.3%)	238 (5.9%)	
Pre-Secondary	29 (3.4%)	45 (3.6%)		74 (3.5%)	187 (4.6%)	
Secondary	198 (23.5%)	285 (22.8%)	0.657	483 (23.1%)	885 (21.8%)	0.201
Post-Secondary	112 (13.3%)	138 (11.0%)		250 (12.0%)	475 (11.7%)	
Bachelors	445 (52.9%)	696 (55.6%)		1141 (54.5%)	2214 (54.7%)	
Doctorate	47 (5.6%)	69 (5.5%)		116 (5.5%)	45 (1.1%)	
Employment						
Employed	406 (48.3%)	572 (45.7%)		978 (46.7%)	1774 (43.8%)	NA
Self-Employed	129 (15.3%)	237 (18.9%)	0.101	366 (17.5%)	NR	
Not Employed	306 (36.4%)	442 (35.3%)		748 (35.8%)	NR	
Marital Status						
Single	115 (13.7%)	199 (15.9%)		314 (15.0%)	399 (9.9%)	
Married	681 (81.0%)	992 (79.3%)	0.398	1673 (80.0%)	3460 (85.5%)	0.657
Divorced	14 (1.7%)	23 (1.8%)		68 (3.3%)	63 (1.6%)	
Widowed	31 (3.7%)	37 (3.10%)		37 (1.8%)	123 (3.0%)	
Residential Status						
Abu Dhabi	224 (26.6%)	295 (23.6%)		519 (24.8%)	4999 (34.0%)	
Dubai	236 (28.1%)	376 (30.1%)		612 (29.3%)	5472 (37.3%)	
Sharjah	175 (20.8%)	265 (21.2%)		440 (21.0%)	2319 (15.8%)	
Ajman	57 (6.8%)	87 (7.0%)	0.790	144 (6.9%)	797 (5.4%)	0.207
Umm Al-Quwain	21 (2.5%)	30 (2.4%)		51 (2.4%)	161 (1.1%)	
Ras Al Khaimah	106 (12.6%)	169 (13.5%)		275 (13.1%)	578 (3.9%)	
Fujairah	22 (2.6%)	29 (2.3%)		51 (2.4%)	358 (2.4%)	

NR: Not Reported; NA: Not Applicable

*Sample weighting was carried out to investigate differences between total control sample and UAE census data.

**While the participants did not have schooling, there were literate to provide consent and complete the questionnaire. These participants are often older women from the Bedouin populations. However, they were well versed in the Arabic language, as it is the language of their religion.

Sensitivity analysis was assessed to quantify hidden bias from using the following two groups: hospital control group vs. the population control group in the same catchment area, and the public medical institution vs. private medical institution (Table 3.3). This demonstrates that there was no unmeasured or uncontrolled confounding that may affect the extent to which an unmeasured variable would have to affect the exposure and outcome as solely to confounding. In addition, given that there was no statistically significant

magnitude of effect between the groups for sociodemographic factors, this suggests that the potential presence of undiagnosed cases in our symptomatic control group, regardless of their ascertainment, had little impact on the results of the analyses we present.

Table 3.3. Non-parametric analysis to quantify hidden bias between hospital controls vs. population controls, and public vs. private medical institution.

	Z-score	***p*-value**
Hospital controls vs. Population controls		
Residency	-0.986	0.324
Age	-1.991	0.053
BMI	-1.552	0.121
Marriage	-1.435	0.151
School level	-0.739	0.460
Work Status	-0.455	0.649
Public medical institution vs. Private medical institution		
Residency	-1.898	0.058
Age	-0.085	0.932
BMI	-0.840	0.401
Marriage	-1.474	0.140
School level	-0.897	0.370
Work Status	-0.160	0.109
Sensitivity analysis was assessed using a non-parametric Mann Whitney U Test to quantify hidden bias		

3.4.3 Characteristics of the study sample

In total there were 32.2% (n=841) of participants recruited from the population-based setting (public seminar), 30.1% (n=786) of participants recruited from the clinic setting (participants who were screened using therapeutic/diagnostic tests (such as monitoring for other gynaecological conditions or pre-marital screening, ovulation monitoring, cosmetic gynaecology, reproductive cancer screening and/or gynaecological health check-up), and 37.7% (n=983) of participants recruited from the hospital setting (participants who have attended the hospital to undergo laparoscopic surgery).

The case-control analyses included a descriptive analysis of the study population to assess the association of symptomatology and the distribution of clinical variables in the study population across disease outcome categories based on the following comparisons: (1) ascertainment criteria (endometriosis cases vs. hospital controls; and endometriosis cases vs. population controls); and (2) symptomatic criteria (endometriosis cases vs. symptomatic controls; and endometriosis cases vs. asymptomatic controls).

3.4.3.1 Characteristics of cases

A total of 518 endometriosis cases (Table 3.4), surgically confirmed via laparoscopy, were classified into four grades, based on the revised American Society for Reproductive Medicine (rASRM).[16] As explained in Chapter 2.3.1.1, the rASRM classification system is based on intraoperative disease findings, and it takes into account peritoneal endometriosis, ovarian endometriosis, posterior cul-de-sac obliteration, ovarian adhesions and tubal adhesions. Scores are assigned depending on lesion size, location, and presence of adhesions or obliterations. The assigned points are summed, and a value is obtained, classifying the disease in one of four stages: Stage 1 (Minimal Endometriosis; 1-5 points), Stage 2 (Mild Endometriosis; 6-15 points), Stage 3 (Moderate Endometriosis; 16-40 points), and Stage 4 (Severe Endometriosis; >40 points). Table 3.4 characterises the endometriosis cases based on the rASRM staging system and reason for surgical investigation. The primary reason for women to seek surgical confirmation of endometriosis was due to fertility-related (61.8%) symptoms than pain-related symptom (36.8%).

Table 3.4. Characteristics of the endometriosis case group (n=518).

Variable	Study Population % (n=518)
Endometriosis rASRM Staging	
Stage I	24.9% (129)
Stage II	36.8% (191)
Stage III	21.0% (109)
Stage IV	17.2% (89)
Reason for Surgical Investigation	
Infertility	61.8% (320)
Pain	36.8% (191)
No Symptoms (Tubal ligation/Sterilization)	1.4% (7)

3.4.3.2 Characteristics of controls

As detailed, two comparison groups were used to evaluate endometriosis risk factors and investigate differences related to comparison group selection.

Ascertainment criteria

The control group was stratified based on its ascertainment criteria (hospital controls (n=1251) and population controls (n=841)).

The ascertainment criteria will enable the assessment of a representative control group of the underlying population, in terms of exposure of interest (population controls), versus the assessment of predictors of endometriosis within a subset of the population with comparable socioeconomic factors and recall bias (hospital controls).

Symptomatic criteria

The symptomatic criteria will explore sensitivity of results to control definition by investigating whether the risk factors and clinical variables were driven by the endometriosis-related symptoms (asymptomatic controls) or endometriosis *per se* (symptomatic controls).

To determine the numerical cut-offs for mild, moderate, and severe categories of pelvic pain, the participants rated their pelvic pain symptoms (dysmenorrhea, chronic pelvic pain, dyschezia, dysuria) both on a 0-10 NRS and a categorical scale (no pain to severe pain) separately so that these could be compared. Data were collected and optimal cut-offs relating the NRS to the categorical scale determined statistically using Cohen's kappa test. The cut−offs identified were: 1−4 for mild, 5−7 for moderate and 8−10 for severe pain (κ=0.510−0.596, $p<0.001$) for all types of pain investigated.

As explained previously, the control groups were sub-divided into symptomatic and asymptomatic controls, to explore sensitivity of results to control definition. Symptomatic controls were defined as: 1) women who experienced chronic pelvic pain, dysmenorrhea, dyspareunia, dyschezia, dysuria for at least six months duration with a NRS[331,332] score greater than 4[333], and/or 2) women who were infertile defined as

unprotected intercourse in the fertile phase of the menstrual cycles for 12 months[334]. Women who did not report the above symptoms were categorized into the asymptomatic control group. Table 3.5 and 3.6 demonstrates the self-reported clinical characteristics of the symptomatic and asymptomatic control groups, respectively.

Table 3.5. Clinical characteristics of the symptomatic control group (n=1331).

Variable	Study Population % (n=1331)*
Infertility	40.8% (543)
Ovarian Cyst	16.8% (224)
Pregnancy Complications	16.6% (223)
PCOS	15.6% (207)
Urinary Tract Infection	14.8% (143)
Urine Incontinence	14.2% (189)
Uterine Fibroids	12.8% (170)
Uterine Polyps	11.5% (153)
Pelvic Inflammatory Disease	9.9% (132)
Adenomyosis	8.5% (113)
Irritable Bowel Syndrome	5.2% (69)
Adhesions	4.6% (61)
Interstitial Cystitis	3.8% (50)
Inflammatory Bowel Disease	1.3% (17)

*Numbers do not always add up to the total amount because participants may present with more than one condition.

Table 3.6. Clinical characteristics of the asymptomatic control group (n=761).

Variable	Study Population % (n=761)*
Family Planning	22.9% (174)
Menstrual Irregularities	20.0% (152)
Ovulation Monitoring	18.3% (139)
Gynaecological Health Check-up	16.9% (128)
Pre-marital Screening	16.2% (123)
Cosmetic Gynaecology	8.2% (62)
Psychiatric Related	7.5% (57)
Tubal Ligation	1.3% (10)

*Numbers do not always add up to the total amount because participants may present with more than one condition.

3.4.4 Symptomatology

3.4.4.1 Pain typology

Frequency of pain phenotypes

To be able to assess the extent of presentation of pain phenotypes in endometriosis, in comparison to symptomatic controls, the control group was stratified into symptomatic controls in whom a surgical investigation had been conducted and symptomatic controls that had not received a surgical confirmation (Table 3.7). When comparing endometriosis cases with these two symptomatic control groups, women with endometriosis had a higher frequency of dysmenorrhea (OR: 1.80 (95% CI: 1.25, 2.61); p=0.002; OR: 1.96 (95% CI: 1.42, 2.69), p<0.001), chronic pelvic pain (OR: 1.32 (95% CI: 1.00, 1.75), p=0.049; OR: 1.53 (95% CI: 1.22, 1.93), p<0.001), dysuria (OR: 1.72 (95% CI: 1.26, 2.35), p=0.001; OR: 1.98 (95% CI: 1.51, 2.61), p<0.001), and dyschezia (OR: 1.98 (95% CI: 1.43, 2.74), p<0.001; OR: 1.99 (95% CI: 1.53, 2.61), p<0.001).

There were no clear differences in results when stratifying symptomatic controls into those with surgical investigation vs. no surgical investigation, suggesting that results were not dependent on definition of symptomatic control group. This demonstrates that the requirement of surgical visualization for the control group to confirm 'true' endometriosis diagnosis may not be necessary for future epidemiological studies. The inclusion of the possible undiagnosed cases may have only diluted the observed effects of risk factors to a marginal extent. Therefore, it is more beneficial to focus research efforts on defining a control population that is representative of the source population of cases, than to be overly concerned on obtaining a disease-free control group.

Table 3.7. Descriptive statistical analysis: frequency rates comparing endometriosis cases vs. controls (unadjusted analysis).

	Endometriosis Cases (n=518)	Symptomatic Controls Endometriosis-Free (Laparoscopy) (n=455)		Symptomatic Controls No Surgical Diagnosis (n=876)		Asymptomatic Controls (n=761)	
Variable	**% (n)**	**% (n)**	***p*-value**	**% (n)**	***p*-value**	**% (n)**	***p*-value**
Dysmenorrhea	88.2% (457)	79.3% (361)	**<0.001**	78.9% (691)	**<0.001**		
Chronic Pelvic Pain	67.0% (347)	56.5% (257)	**0.001**	56.5% (495)	**<0.001**		
Dyschezia	30.1% (156)	19.1% (87)	**<0.001**	18.6% (163)	**<0.001**		
Dysuria	27.0% (140)	16.7% (76)	**<0.001**	15.9% (139)	**<0.001**		
Back Pain	51.0% (264)	45.5% (207)	0.088	44.2% (387)	**0.014**	23.5% (179)	**<0.001**
Leg Pain	47.9% (248)	35.8% (163)	**<0.001**	33.9% (297)	**<0.001**	11.8% (90)	**<0.001**
Ovulation Pain	51.5% (267)	47.9% (218)	0.258	44.4% (389)	**0.010**	20.9% (159)	**<0.001**
Muscle Pain	39.2% (203)	31.9% (145)	**0.017**	34.5% (302)	0.077	28.9% (220)	**<0.001**
Migraine	33.4% (173)	25.9% (118)	**0.011**	20.1% (176)	**<0.001**	12.1% (92)	**<0.001**

Several comorbid pain conditions were commonly present. The frequency of leg pain (OR: 1.59 (95% CI: 1.22, 2.08), p=0.001; OR: 1.75 (95% CI: 1.39, 2.19), p<0.001) and migraine (OR: 1.47 (95% CI: 1.10, 1.96) p=0.008; OR: 1.94 (95% CI: 1.51, 2.49), p<0.001) was greater among women diagnosed with endometriosis compared to both symptomatic control groups. Back pain and ovulation pain were associated with endometriosis diagnosis, but only when compared to symptomatic controls with no surgical confirmation (p=0.020; p=0.027). Therefore, there were very few differences in results when stratifying symptomatic controls into surgical investigation vs. no surgical investigation (Table 3.7-3.8).

Table 3.8. Logistic multivariate regression analysis: adjusted risk of endometriosis according to pain type.

	Endometriosis vs. Symptomatic Control Endometriosis-Free (Laparoscopy)				**Endometriosis vs. Symptomatic Control No Surgical Diagnosis**				**Endometriosis vs. Asymptomatic Control**			
Variable	**Crude Odds Ratio (95% CI)**	***p*-value**	**Adjusted Odds Ratio (95% CI)**	***p*-value**	**Crude Odds Ratio (95% CI)**	***p*-value**	**Adjusted Odds Ratio (95% CI)**	***p*-value**	**Crude Odds Ratio (95% CI)**	***p*-value**	**Adjusted Odds Ratio (95% CI)**	***p*-value**
Dysmenorrhea	1.95 (1.37, 2.71)	<0.001	1.80 (1.25, 2.61)	**0.002**	2.01 (1.46, 2.74)	<0.001	1.96 (1.42, 2.69)	**<0.001**				
Chronic Pelvic Pain	1.56 (1.20, 2.02)	0.001	1.32 (1.00, 1.75)	**0.049**	1.56 (1.24, 1.95)	<0.001	1.53 (1.22, 1.93)	**<0.001**				
Dyschezia	1.82 (1.35, 2.46)	<0.001	1.72 (1.26, 2.35)	**0.001**	1.88 (1.46, 2.43)	<0.001	1.98 (1.51, 2.61)	**<0.001**				
Dysuria	1.84 (1.35, 2.52)	<0.001	1.98 (1.43, 2.74)	**<0.001**	1.96 (1.51, 2.56)	<0.001	1.99 (1.53, 2.61)	**<0.001**				
Back Pain	1.24 (0.96, 1.60)	0.089	1.16 (0.89, 1.51)	0.247	1.31 (1.05, 1.63)	0.014	1.30 (1.04, 1.62)	**0.020**	3.37 (2.65, 4.29)	**<0.001**	3.66 (2.79, 4.79)	**<0.001**
Leg Pain	1.64 (1.27, 2.12)	<0.001	1.59 (1.22, 2.08)	**0.001**	1.79 (1.43, 2.23)	<0.001	1.75 (1.39, 2.19)	**<0.001**	6.84 (5.17, 9.05)	**<0.001**	7.64 (5.57, 10.45)	**<0.001**
Ovulation Pain	1.15 (0.89, 1.50)	0.258	1.11 (0.85, 1.44)	0.437	1.33 (1.07, 1.65)	0.010	1.28 (1.03, 1.60)	**0.027**	4.02 (3.15, 5.15)	**<0.001**	4.16 (3.16, 5.47)	**<0.001**
Muscle Pain	1.37 (1.05, 1.79)	0.018	1.36 (1.03, 1.79)	**0.028**	1.22 (0.97, 1.53)	0.077	1.21 (0.96, 1.51)	0.109	1.58 (1.25, 2.00)	**<0.001**	1.56 (1.20, 2.04)	**0.001**
Migraine	1.43 (1.08, 1.89)	0.011	1.47 (1.10, 1.96)	**0.008**	1.99 (1.55, 2.55)	<0.001	1.94 (1.51, 2.49)	**<0.001**	3.64 (2.74, 4.86)	**<0.001**	3.74 (2.74, 5.12)	**<0.001**

CI: Confidence Interval.
Adjusted for Age, BMI, OC use, Parity

Severity and characteristics of the pain phenotypes

When conducting a more detailed investigation of women who experienced dysmenorrhea, women with endometriosis reported a greater NRS severity (8.21 vs. 7.47, p<0.001; 6.61 <0.001), a greater VAS (p=0.038; p<0.001), and earlier age of symptom onset (16.82 vs. 18.83, p<0.001; 19.37, p<0.001), in comparison to endometriosis-free controls and controls without surgical confirmation. There was no difference in the proportion of women with endometriosis taking over-the-counter painkillers for the pelvic pain (90.4% of endometriosis women; 88.9% endometriosis-free, p=0.678; 89.7% no surgical confirmation, p=0.408), however a difference was present among women taking hormonal medication (41.3% vs. 28.3 (p=0.002) and 23.7% (p<0.001), respectively). Endometriosis women had a lower rate (40.6%) of responding to conventional medical therapy for pelvic pain, in comparison to symptomatic controls (52.6-65.7%; p<0.001) (Table 3.9).

Table 3.9. Descriptive statistical analysis: frequency rates of the characteristics of dysmenorrhea comparing endometriosis cases vs. controls (unadjusted analysis).

	Endometriosis Cases (n=457)	**Symptomatic Control Endometriosis-Free (Laparoscopy) (n=361)**		**Symptomatic Control No Surgical Diagnosis (n=495)**	
Variable	**% (n)**	**% (n)**	***p*-value**	**% (n)**	***p*-value**
Severity of dysmenorrhea					
Worst Pain: NRS*, Mean (SD)	9.01 (1.84)	8.74 (1.75)	**0.037**	8.15 (2.08)	**<0.001**
General: NRS*, Mean (SD)	8.21 (2.13)	7.47 (2.24)	**<0.001**	6.61 (2.91)	**<0.001**
VAS staging					
Mild, % (n)	20.1% (92)	25.8% (93)	**0.038**	28.5% (197)	**<0.001**
Moderate, % (n)	39.8% (182)	42.1% (152)		41.1% (284)	
Severe, % (n)	40.0% (183)	32.1% (116)		30.4% (210)	
Age at first symptoms					
Symptom Onset, Years (SD)	16.82 (2.48)	18.83 (2.60)	**<0.001**	19.37 (2.98)	**<0.001**
Symptom Onset at Worse, Years (SD)	19.43 (3.05)	20.81 (2.62)	**<0.001**	23.81 (2.22)	**<0.001**
Use of medications**					
Over-the-Counter Painkillers, % (n)	90.4% (414)	89.7% (323)	0.678	88.9% (614)	0.406
Hormones, % (n)	41.3% (189)	28.3% (102)	**0.021**	23.7% (164)	**<0.001**
Pain Alleviated, % (n)	40.6% (186)	52.6% (276)	**0.001**	65.7% (454)	**<0.001**

Only participants with dysmenorrhea were included as denominators in this table
SD: Standard Deviation
*11-point numerical reporting scale with 0 being no pain and 10 being the most severe pain imaginable, women reported any pain in the last 6 months
**Pain medications taken on at least a monthly basis for any indication in the past 12 months

When considering chronic pelvic pain characteristics in more detail, women with endometriosis reported a greater NRS score (8.70 vs. 8.14, p<0.001; 8.08 p<0.001), with an earlier age of symptom onset (20.19 vs. 21.87, p<0.001; 23.26, p<0.001), in comparison to surgically confirmed endometriosis-free controls (laparoscopy) and symptomatic controls without surgical confirmation. All dimensions of pain intensity (continuous: p<0.001, p<0.001; intermittent: p=0.010, p<0.001; neuropathic: p<0.001, p<0.001; affective: p<0.001; overall: p<0.001, p<0.001) were significantly greater comparing endometriosis vs. the two control groups. In addition, women with endometriosis had a higher number of pain episodes experienced in the last month in comparison to symptomatic controls (p<0.001) (Table 3.10).

Table 3.10. Descriptive statistical analysis: frequency rates of characterises of chronic pelvic pain comparing endometriosis cases vs. controls (unadjusted analysis).

	Endometriosis Cases (n=457)	**Symptomatic Control Endometriosis-Free (Laparoscopy) (n=361)**		**Symptomatic Control No Surgical Diagnosis (n=495)**	
Variable	**% (n)**	**% (n)**	***p*-value**	**% (n)**	***p*-value**
Severity of chronic pelvic pain					
Worst Pain: NRS*, Mean (SD)	9.27 (1.01)	9.19 (1.30)	0.421	9.12 (1.29)	0.066
General: NRS*, Mean (SD)	8.70 (1.23)	8.14 (1.67)	**<0.001**	8.08 (1.56)	**<0.001**
Pelvic Pain Quality and Intensity**					
Continuous, PPI score (SD); %	11.37 (5.96); 65.3%	9.56 (6.44); 58.1%	**<0.001**	9.70 (7.09); 59.8%	**<0.001**
Intermittent, PPI score (SD); %	7.61 (3.82); 64.5%	6.82 (3.66); 56.1%	**0.010**	6.57 (4.21); 56.7%	**<0.001**
Neuropathic, PPI score (SD); %	4.25 (1.97); 72.2%	3.55 (2.08); 68.7%	**<0.001**	3.69 (2.32); 68.4%	**<0.001**
Affective, PPI score (SD); %	6.03 (3.24); 64.7%	4.93 (3.27); 56.6%	**<0.001**	4.72 (3.66); 55.1%	**<0.001**
Total, PPI score (SD)	29.27 (12.81)	24.85 (13.0541)	**<0.001**	24.70 (15.57)	**<0.001**
Age at first symptom onset, Years (SD)	20.19 (3.65)	21.87 (3.58)	**<0.001**	23.26 (3.08)	**<0.001**
Presence of pain per month**					
1 day, % (n)	3.2% (11)	12.5% (34)	**<0.001**	16.4% (81)	**<0.001**
2-3 days, % (n)	9.5% (33)	21.0% (57)		20.4% (101)	
1 day a week, % (n)	48.1% (167)	38.0% (103)		41.2% (204)	
More than 1 day a week, % (n)	32.3% (112)	24.0% (65)		20.4% (101)	
Every day, % (n)	6.9% (24)	4.4% (12)		1.6% (8)	

Only participants with chronic pelvic pain were included as denominators in this table (as demonstrated in Table 12).
SD: Standard Deviation
*11-point visual analogy scale with 0 being no pain and 10 being the most severe pain imaginable, women reported any pain in the last 6 months
**SF-McGill Questionnaire; Total score for each subscale is: 18 PPI for Continuous, 12 PPI for Intermittent, 6 PPI for Neuropathic, 9 PPI for Affective.

Pain catastrophizing scale

Higher levels of pain-related catastrophizing thoughts (Table 3.11) were found in women with endometriosis compared to symptomatic controls in whom a surgical investigation had been conducted and symptomatic controls that had not received a surgical confirmation (35.02 vs 30.81 and 28.79, p<0.001). No differences were observed in the pain catastrophizing scale score between stages I–II and III–IV patients (34.27 ± 15.63 vs 36.24 ± 17.19; p=0.179).

Table 3.11. Pain catastrophizing scale: comparing endometriosis cases vs. controls.

Variable	Endometriosis Cases (n=518)	Symptomatic Controls Endometriosis-Free (Laparoscopy) (n=455)		Symptomatic Controls No Surgical Diagnosis (n=876)	
	Mean (SD)	Mean (SD)	*p*-value	Mean (SD)	*p*-value
Rumination	10.57 (5.19)	9.24 (5.17)	**<0.001**	8.77 (5.28)	**<0.001**
Magnification	8.25 (3.99)	7.27 (3.99)	**<0.001**	6.87 (3.99)	**<0.001**
Helplessness	16.19 (7.58)	14.24 (7.87)	**<0.001**	13.15 (8.06)	**<0.001**
Overall	35.02 (16.26)	30.81 (16.62)	**<0.001**	28.79 (16.36)	**<0.001**

Association to pain typology and endometriosis phenotype

The frequency and severity of dysmenorrhea (p=0.775; p=0.429), chronic pelvic pain (p=0.463; p=0.679), dyschezia (p=0.124; p=0.170), and dysuria (p=0.657; p=0.469) were not associated with rASRM stage of endometriosis (Table 3.12).

Table 3.12. Descriptive statistical analysis: association of rASRM endometriosis stage and types of pain (unadjusted analysis)

Variable	Stage 1 (n=129)	Stage 2 (n=191)	Stage 3 (n=109)	Stage 4 (n=89)	*p*-value*
Dysmenorrhea, % (n)	87.6% (113)	89.5% (171)	89.0% (97)	85.4% (76)	0.775
Severity of Dysmenorrhea, NRS, Mean (SD)	8.07 (225)	7.96 (2.32)	8.49 (1.85)	8.57 (1.71)	0.429
Chronic Pelvic Pain, % (n)	65.1% (84)	65.4% (125)	73.4% (80)	65.2% (58)	0.463
Severity of Chronic Pelvic Pain, NRS, Mean (SD)	8.84 (1.18)	8.52 (1.44)	8.82 (0.99)	8.71 (1.07)	0.679
Dyschezia, % (n)	24.0% (31)	28.3% (54)	36.7% (40)	34.8% (31)	0.124
Severity of Dyschezia, NRS, Mean (SD)	6.12 (3.05)	5.83 (3.12)	6.87 (2.88)	7.03 (1.88)	0.170
Dysuria, % (n)	24.0% (31)	29.8% (57)	27.5% (30)	24.7% (22)	0.657
Severity of Dysuria, NRS, Mean (SD)	6.77 (1.56)	6.14 (2.27)	6.56 (2.28)	6.68 (1.32)	0.469

**p*-value for frequency (%) of pain type and endometriosis stage was measured using Pearson's χ^2; *p*-value for severity (NRS; Mean (SD)) of pain type and stage was measured using Kruskal-Wallis test

Pain phenotype and severity among parous women

Since there is a regression of endometriotic lesions during pregnancy, it is often hypothesized that parous women have a reduced symptom progression. Hence, the frequency of pain symptoms was compared between nulliparous and parous women in women with endometriosis and symptomatic controls. Ever married parous women had a lower likelihood of reporting dysmenorrhea (women with endometriosis: OR 0.52 (95% CI: 0.28, 0.93), p=0.010; symptomatic controls: OR 0.71 (95% CI: 0.52, 0.96), p=0.027) and dysuria (women with endometriosis: 0.64 (95% CI: 0.42, 0.97), p=0.010; symptomatic controls: OR 0.82 (95% CI: 0.65, 0.99), p=0.047), irrespective of type and presence of gynaecological condition. Chronic pelvic pain and dyschezia were not associated with parity (Table 3.13-3.14).

Table 3.13. Descriptive statistical analysis: frequency rates of pain types of endometriosis cases and controls stratified by nulliparous vs. parous (unadjusted analysis).

Variable	Endometriosis			Symptomatic Controls		
	Nulliparous (n=248) % (n)	**Parous (n=270) % (n)**	***p*-value**	**Nulliparous (n=504) % (n)**	**Parous (n=827) % (n)**	***p*-value**
Dysmenorrhea	91.9% (228/248)	84.8% (229/270)	**0.012**	81.0% (408/504)	77.9% (644/827)	0.180
Chronic Pelvic Pain	68.5% (170/248)	65.6% (177/270)	0.469	56.7% (286/504)	58.0% (480/827)	0.643
Dyschezia	33.5% (83/248)	27.0% (73/270)	0.111	19.6% (99/504)	18.3% (151/827)	0.531
Dysuria	30.6% (76/248)	23.7% (64/270)	0.076	15.5% (78/504)	16.6% (137/827)	0.600

Table 3.14. Logistic multivariate regression analysis: adjusted risk of pain type according to parity, among symptomatic women with and without endometriosis.

	Endometriosis				Symptomatic Controls			
Variable	**Crude Odds Ratio (95% CI)**	***p*-value**	**Adjusted Odds Ratio (95% CI)**	***p*-value**	**Crude Odds Ratio (95% CI)**	***p*-value**	**Adjusted Odds Ratio (95% CI)**	***p*-value**
Dysmenorrhea								
Nulliparous	1.00		1.00		1.00		1.00	
Parous	0.49 (0.28, 0.86)	**0.013**	0.52 (0.28, 0.93)	**0.010**	0.82 (0.63, 1.09)	0.181	0.71 (0.52, 0.96)	**0.027**
Chronic Pelvic Pain								
Nulligravida	1.00		1.00		1.00		1.00	
Parous	0.87 (0.61, 1.26)	0.469	0.89 (0.61, 1.32)	0.572	1.05 (0.84, 1.32)	0.643	0.88 (0.68, 1.14)	0.341
Dyschezia								
Nulligravida	1.00		1.00		1.00		1.00	
Parous	0.88 (0.61, 1.12)	0.484	0.71 (0.48, 1.05)	0.086	0.71 (0.60, 1.02)	0.051	0.77 (0.56, 1.05)	0.107
Dysuria								
Nulligravida	1.00		1.00		1.00		1.00	
Parous	0.64 (0.42, 0.97)	0.512	0.64 (0.42, 0.97)	**0.034**	0.79 (0.61, 0.92)	**0.042**	0.82 (0.65, 0.99)	**0.047**

Adjusted for age, OC use, parity

3.4.4.2 Infertility

When investigating fertility characteristics, only ever married women (married, widowed, divorced) were utilised as the denominator of the frequency because single women are not allowed to seek fertility care in the UAE.

When investigating the frequency of infertility on the study, 64.9% (281/433) of endometriosis cases and 55.2% (624/1130) of controls were infertile (<0.001). After adjustment to sociodemographic variables, age at menarche and OCP use, women with endometriosis were at a greater risk of being infertile than symptomatic controls (OR: 1.33 (95% CI: 1.05, 1.69); p=0.017). The frequency of infertility, with a duration of 12-24 months and >24 months, was not significantly different between the two groups (p=0.632).

When investigating the difference in frequency between primary and secondary infertility, women with endometriosis had a higher likelihood of being primary infertile (53.7%; OR: 1.40 (95% CI: 1.06, 1.86), p=0.020). However, after adjustment to sociodemographic variables, age at menarche and OCP use, there was no significant association between endometriosis and controls (Table 3.15).

Table 3.15. Descriptive statistical analysis: fertility characteristics comparing endometriosis cases vs. controls (unadjusted analysis).

Variable	Endometriosis % (n)	Symptomatic Controls % (n)	*p*-value
Infertility			
12-24 months	73.7% (207/281)	75.2% (469/624)	0.632
>24 months	26.3% (74/281)	24.8% (155/624)	
Type of Infertility			
Secondary Infertility	46.3% (130/281)	54.6% (341/624)	**0.019**
Primary Infertility	53.7% (151/281)	45.4% (283/624)	

Definitions:
Infertility: Women who were infertile defined as unprotected intercourse in the fertile phase of the menstrual cycles for more than 12 months
Secondary Infertility: Infertile couples who have been able to get pregnant at least once, but are now unable to after having unprotected intercourse
Primary Infertility: Infertile couples who have never become pregnant before, after having unprotected intercourse

3.4.5 Sociodemographic characteristics

Table 3.16, Table 3.17 and Table 3.18 demonstrate the unadjusted and adjusted comparison of sociodemographic factors between endometriosis cases compared to the following two comparisons: (1) impact of control selection based on ascertainment criteria (endometriosis cases vs. hospital controls; endometriosis cases vs. population controls), and impact of control selection based on symptomatic criteria (endometriosis cases vs. symptomatic controls; endometriosis cases vs. asymptomatic controls).

The endometriosis case group (mean age: 34.04 (SD: 4.81)) were slightly younger than the symptomatic control group (mean age: 35.36 (8.01); $p<0.001$), but older than the asymptomatic control group (mean age: 32.22 (8.54); $p<0.001$). However, when combining the control sample (age: 34.68 (8.97)); there was no significant difference between cases and controls ($p=0.344$). Additionally, there was no significant difference between endometriosis cases and hospital controls (mean age: 34.42 (SD: 8.01)) and population controls (mean age: 33.92 (SD: 8.83)).

Figure 3.1 demonstrates the multivariate logistic regression models of the two comparison groups (symptomatic criteria (1.1 symptomatic controls and 1.2 asymptomatic controls); ascertainment criteria (2.1 hospital controls and 2.2 population controls). Across the four control groups, marital status, smoking, and parental consanguinity were not associated to endometriosis.

While women with endometriosis had a greater risk of obtaining a higher educational level in comparison to asymptomatic control group ($p<0.001$) and population control group ($p=0.003$), endometriosis women had a significantly higher unemployment rate (asymptomatic control group ($p<0.001$); population control group ($p<0.001$)). However, in comparison to symptomatic controls and hospital controls, endometriosis women had no significant difference in educational level ($p=0.844$; $p=0.050$) or employment rate ($p=0.483$; $p=0.260$). This suggests that work employment status is mainly associated with symptom presence and severity, as opposed to endometriosis *per se*.

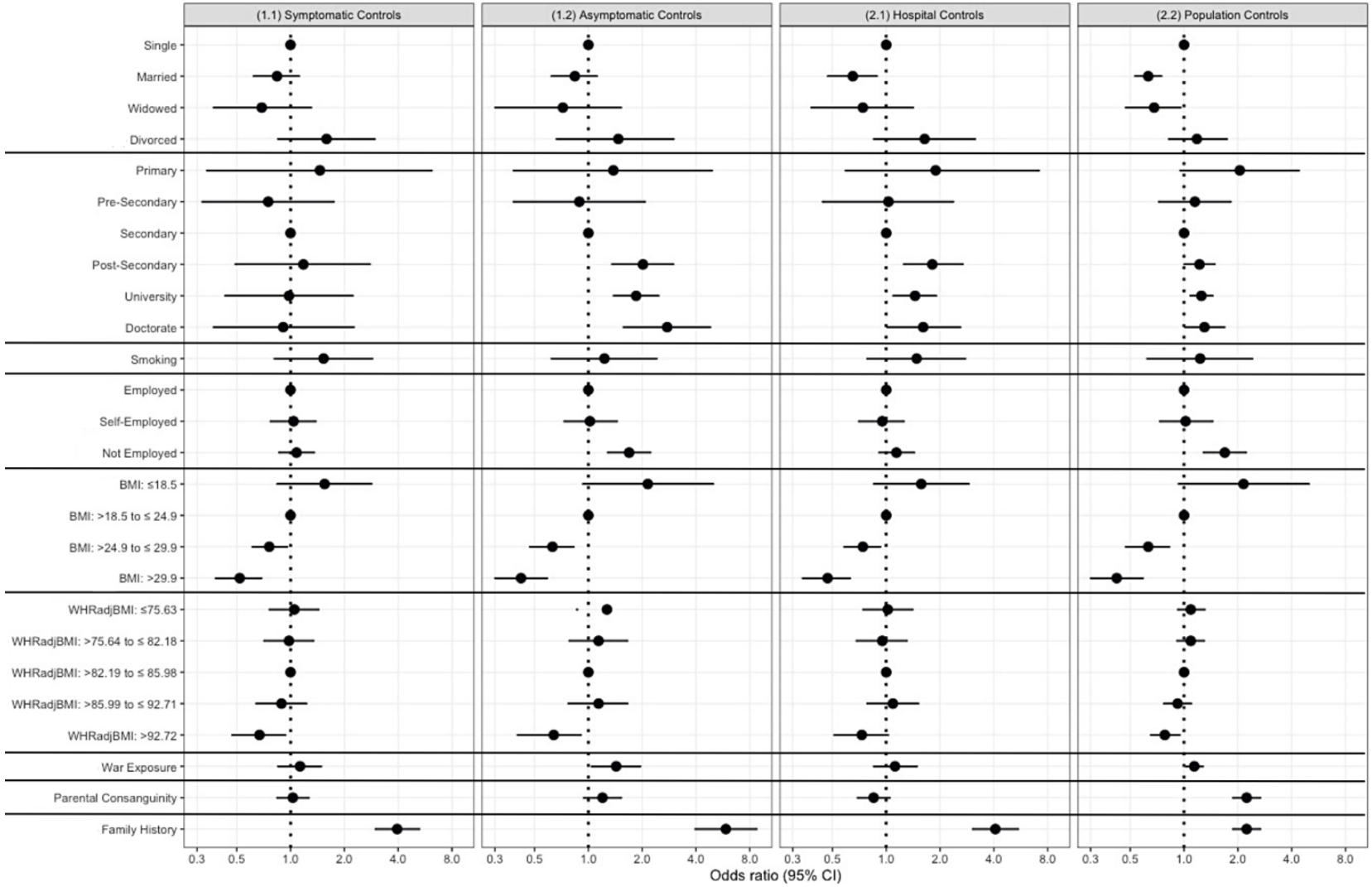


Figure 3.1. Forest plot of the multivariate logistic regression models: adjusted risk of endometriosis to four control groups (symptomatic criteria (1.1; 1.2) and ascertainment criteria (2.1; 2.2)) according to demographic characteristics.

Across all four control groups (symptomatic controls, asymptomatic controls, hospital controls and population controls), women with endometriosis had a lower BMI ($p=0.005$; $p<0.001$; $p<0.001$; $p=0.001$) and lower WHRadjBMI ($p=0.003$; $p=0.001$; $p=0.012$; $p<0.001$). After adjusting for age, education and ever pregnant, women with endometriosis had a lower odds of being obese (symptomatic controls: OR 0.52 (95% CI: 0.38, 0.69), $p<0.001$; asymptomatic controls: OR 0.42 (95% CI: 0.30, 0.59), $p<0.001$); hospital controls: OR 0.47 (95% CI: 0.34, 0.63), $p<0.001$; population controls: OR 0.42 (95% CI: 0.30, 0.59), and also a lower odds of being in the highest (>92.72) WHRadjBMI category (symptomatic controls: OR 0.67 (95% CI: 0.47, 0.94), $p=0.022$; asymptomatic controls: OR 0.64 (95% CI: 0.40, 0.91), $p=0.018$; population controls: OR 0.78 (95% CI: 0.65, 0.95), $p=0.012$).

There was no difference in war exposure comparing endometriosis cases with symptomatic controls ($p=0.407$) or with hospital controls ($p=0.420$), but an association was present in comparison to asymptomatic controls (OR: 1.43 (95% CI: 1.04, 1.96), $p=0.027$) and to population controls (OR 1.18 (95% CI: 1.01, 1.38), $p=0.039$) . Interestingly, this may suggest that war exposure plays a role in triggering symptoms of pain and infertility, as opposed to endometriosis *per se*, although more detailed studies would need to be conducted to relate these causally.

By pooling family history of endometriosis from all first-degree relatives, women with a family history had a higher risk of being diagnosed with endometriosis, in comparison to symptomatic (OR: 3.95, 95% CI: 2.98, 5.27; $p<0.001$), asymptomatic controls (OR: 5.88, 95% CI: 3.95-8.77; $p <0.001$), hospital controls (OR: 4.08 , 95% CI: 3.04, 5.49); $p<0.001$) and population controls (OR: 2.24 , 95% CI: 1.87, 2.68); $p<0.001$).

Table 3.16. Descriptive statistical analysis: demographic characteristics comparing endometriosis cases vs. controls (unadjusted analysis).

Variable	Endometriosis Cases (n=518) % (n)	Control Categorization: Symptomatic Criteria				Control Categorization: Ascertainment Criteria			
		Symptomatic Controls (n=1331) % (n)	*p*-value	Asymptomatic Controls (n=762) % (n)	*p*-value	Hospital Controls (n=1251) % (n)	*p*-value	Population Controls (n=841) % (n)	*p*-value
Age (y) [Mean (SD)]	34.04 (4.81)	35.36 (8.01)	**<0.001**	32.22 (8.54)	**<0.001**	34.42 (8.01)	0.310	33.92 (8.83)	0.769
Body mass index (kg/m^2) [mean (SD)]	26.07 (5.67)	27.08 (6.14)	**0.001**	27.48 (5.76)	**0.001**	27.42 (4.58)	**<0.001**	26.9 (5.29)	**0.003**
Use of Oral Contraception	28.6% (148)	21.4% (285)	**0.002**	10.5% (80)	**<0.001**	15.8% (198)	**<0.001**	19.9% (167)	**<0.001**
Marriage									
Single	16.4% (85)	15.0% (200)	0.096	13.9% (106)	**0.049**	15.9% (199)	**0.031**	13.7% (115)	**0.012**
Married	76.3% (395)	79.2% (1054)		81.3% (619)		79.3% (992)		81.0% (681)	
Widowed	3.1% (16)	3.5% (47)		2.8% (21)		3.0% (37)		3.7% (31)	
Divorced	4.2% (22)	2.3% (30)		2.0% (15)		1.8% (23)		1.7% (14)	
School level									
Primary	0.8% (4)	1.6% (21)	**0.019**	0.9% (7)	**<0.001**	1.4% (18)	**0.002**	1.2% (10)	**0.009**
Pre-Secondary	1.5% (8)	3.8% (51)		3.0% (23)		3.6% (45)		3.4% (29)	
Secondary	16.8% (87)	20.5% (273)		27.6% (210)		22.8% (285)		23.5% (198)	
Post-Secondary	14.7% (76)	12.2% (162)		11.6% (88)		11.0% (138)		13.3% (112)	
University	59.7% (309)	55.4% (737)		53.1% (404)		55.6% (696)		52.9% (445)	
Post-Doc	6.6% (34)	6.5% (87)		3.8% (29)		5.5% (69)		5.6% (47)	
Smoker									
No	96.9% (502)	97.8% (1302)	0.254	97.1% (739)	0.838	97.8% (1302)	0.254	97.1% (817)	0.803
Yes	3.1% (16)	2.2% (29)		2.9% (22)		2.2% (29)		2.9% (24)	
Work status									
Employed	44.0% (228)	44.9% (597)	0.925	50.1% (381)	**0.027**	44.9% (597)	0.925	48.3% (406)	0.305
Self-Employed	17.0% (88)	17.1% (228)		18.1% (138)		17.1% (228)		15.3% (129)	
Not Employed	39.0% (202)	38.0% (506)		31.8% (242)		38.0% (506)		36.4% (306)	
BMI									
≤18.5	3.9% (20)	2.0% (26)	**<0.001**	1.4% (11)	**<0.001**	2.1% (26)	**<0.001**	1.3% (11)	**<0.001**
>18.5 to ≤ 24.9	48.3% (250)	39.0% (519)		37.7% (287)		37.8% (473)		41.9% (352)	
>24.9 to ≤ 29.9	33.2% (172)	35.8% (476)		35.6% (271)		35.1% (439)		34.6% (291)	
>29.9	14.7% (76)	23.3% (310)		25.2% (192)		25.0% (313)		22.2% (187)	
Waist to Hip Ratio									
≤75.63	24.1% (125)	20.1% (267)	**0.011**	18.0% (137)	**0.001**	20.5% (256)	**0.022**	17.6% (148)	**<0.001**
>75.64 to ≤ 82.18	21.4% (111)	19.5% (259)		19.1% (145)		20.6% (258)		17.4% (146)	
>82.19 to ≤ 85.98	20.5% (110)	18.9% (252)		21.9% (167)		20.0% (250)		20.1% (169)	
>85.99 to ≤ 92.71	20.1% (104)	21.0% (279)		18.4% (140)		18.5% (231)		22.4% (188)	
>92.72	13.9% (72)	20.6% (274)		22.6% (172)		20.5% (256)		22.6% (190)	
War exposure									
No	83.2% (431)	84.0% (1131)	0.345	87.4% (665)	**0.036**	84.8% (1061)	0.397	87.4% (735)	**0.032**
Yes	16.8% (87)	15.0% (200)		12.6% (96)		15.2% (190)		12.6% (106)	
Parental Consanguinity									
No	48.4% (250)	47.7% (635)	0.803	51.0% (388)	0.356	44.4% (556)	0.133	55.5% (467)	**0.010**
Yes	51.6% (267)	52.3% (696)		49.0% (373)		55.6% (695)		44.5% (374)	
Family History									
No	75.7% (392)	92.6% (1232)	**<0.001**	94.9% (722)	**<0.001**	92.9% (1162)	**<0.001**	94.2% (792)	**<0.001**
Yes	24.3% (126)	7.4% (99)		5.1% (39)		7.1% (89)		5.8% (49)	

Table 3.17. Logistic multivariate regression analysis: adjusted risk of endometriosis vs. controls (symptomatic criteria) according to demographic characteristics

Variable	Endometriosis vs. Symptomatic Controls				Endometriosis vs. Asymptomatic Controls			
	Crude Odds Ratio (95% CI)	***p*-value**	**Adjusted Odds-Ratio (95% CI)**	***p*-value**	**Crude Odds Ratio (95% CI)**	***p*-value**	**Adjusted Odds-Ratio (95% CI)**	***p*-value**
Marriage								
Single	1.00		1.00		1.00		1.00	
Married	0.88 (0.66, 1.17)	0.377	0.84 (0.62, 1.12)	0.252	0. 79 (0.58, 1.08)	0.151	0.84 (0.62, 1.12)	0.252
Widowed	0.80 (0.43, 1.49)	0.484	0.69 (0.37, 1.31)	0.259	0.95 (0.47, 1.93)	0.484	0.72 (0.34, 1.53)	0.259
Divorced	1.72 (0.94, 3.16)	0.078	1.59 (0.85, 2.97)	0.149	1.83 (0.90, 3.74)	0.098	1.47 (0.62, 3.01)	0.430
School level								
Primary	1.21 (0.33, 4.47)	0.770	1.46 (0.34, 6.19)	0.603	1.33 (0.38, 4.84)	0.615	1.38 (0.38, 4.94)	0.620
Pre-Secondary	2.03 (0.93, 4.44)	0.076	0.75 (0.32, 1.75)	0.501	0.82 (0.36, 1.94)	0.684	0.89 (0.38, 2.08)	0.787
Secondary	1.00		1.00		1.00		1.00	
Post-Secondary	2.99 (1.35, 6.61)	**0.007**	1.18 (0.49, 2.79	0.705	2.09 (1.40, 2.44)	**<0.001**	2.02 (1.35, 3.00)	**<0.001**
University	2.67 (1.25, 5.69)	**0.011**	0.98 (0.43, 2.24)	0.956	1.85 (1.38, 2.48)	**<0.001**	1.85 (1.38, 2.48)	**<0.001**
Doctorate	2.49 (1.07, 5.79)	**0.034**	0.91 (0.37, 2.27)	0.844	2.88 (1.63, 4.93)	**<0.001**	2.76 (1.57, 4.83)	**<0.001**
Smoker								
No	1.00		1.00		1.00		1.00	0.548
Yes	1. 43 (0.77, 2.65)	0.257	1.53 (0.81, 2.88)	0.187	1.07 (0.56, 2.05)	0.838	1.23 (0.62, 2.42)	
Work status								
Employed	1.00		1.00		1.00		1.00	
Self-Employed	1.01 (0.75, 1.35)	0.943	1.04 (0.77, 1.39)	0.799	1.06 (0.77, 1.45)	0.691	1.02 (0.73, 1.45)	0.877
Not Employed	1.05 (0.83, 1.31)	0.697	1.08 (0.86, 1.36)	0.483	1.39 (1.08, 1.78)	**0.009**	1.69 (1.28, 2.23)	**<0.001**
BMI								
≤18.5	1.59 (0.87, 2.92)	0.128	1.55 (0.84, 2.85)	0.155	1.77 (0.98, 3.22)	0.059	2.15 (0.93, 5.01)	0.073
>18.5 to ≤ 24.9	1.00		1.00		1.00		1.00	
>24.9 to ≤ 29.9	0.75 (0.59, 0.95)	**0.015**	0.76 (0.61, 0.96)	**0.023**	0.88 (0.68, 1.16)	0.364	0. 63 (0.47, 0.83)	**0.001**
>29.9	0.51 (0. 38, 0.68)	**<0.001**	0.52 (0.38, 0.69)	**<0.001**	0.72 (0.50, 0.94)	**0.011**	0.42 (0.30, 0.59)	**<0.001**
p_{trend}				**0.005**				**<0.001**
Waist to Hip Ratio								
≤75.63	1.11 (0.81, 1.51)	0.500	1.05 (0.76, 1.44)	0.949	1.43 (1.02, 2.03)	0.038	1.27 (0.87, 1.86)	0.207
>75.64 to ≤ 82.18	1.02 (0.75, 1.40)	0.908	0.98 (0.71, 1.35)	0.901	1.21 (0.85, 1.71)	0.290	1.14 (0.78, 1.66)	0.492
>82.19 to ≤ 85.98	1.00		1.00		1.00		1.00	
>85.99 to ≤ 92.71	0.88 (0.65, 1.23)	0.459	0.89 (0.64, 1.23)	0.606	1.17 (0.82, 1.66)	0.381	1.14 (0.77, 1.66)	0.505
>92.72	0.63 (0.44, 0.88)	**0.007**	0.67 (0.47, 0.94)	**0.022**	0.66 (0.46, 0.95)	**0.026**	0.64 (0.40, 0.91)	**0.018**
p_{trend}				**0.003**				**0.001**
War exposure								
No	1.00		1.00		1.00		1.00	
Yes	1.14 (0.86, 1.50)	0.346	1.13 (0.85, 1.49)	0.407	1.38 (1.15, 1.64)	**0.009**	1.43 (1.04, 1.96)	**0.027**
Parental Consanguinity								
No	1.00		1.00		1.00		1.00	
Yes	1.02 (0.83, 1.25)	0.803	1.03 (0.84, 1.27)	0.729	1.20 (0.91, 1.69)	0.168	1.20 (0.94, 1.53)	0.142
Family History								
No	1.00		1..00	**<0.001**	1.00	**<0.001**	1.00	**<0.001**
Yes	4.00 (3.00, 5.32)	**<0.001**	3.95 (2.98, 5.27)		5.95 (4.07, 6.91)		5.88 (3.95, 8.77)	

Adjusted for Age, Education, Ever Pregnant; Waist to Hip Ratio adjusted for BMI, Age, Education, Ever Pregnant

Table 3.18. Logistic multivariate regression analysis: adjusted risk of endometriosis vs. controls (ascertainment criteria) according to demographic characteristics

Variable	Endometriosis vs. Hospital Controls				Endometriosis vs. Population Controls			
	Crude Odds Ratio (95% CI)	***p*-value**	**Adjusted Odds-Ratio (95% CI)**	***p*-value**	**Crude Odds Ratio (95% CI)**	***p*-value**	**Adjusted Odds-Ratio (95% CI)**	***p*-value**
Marriage								
Single	1.00		1.00		1.00		1.00	
Married	0.88 (0.66, 1.17)	0.377	0.65 (0.47, 0.89)	0.008	0. 89 (0.76, 1.03)	0.121	0.63 (0.53, 0.75)	<0.001
Widowed	0.80 (0.43, 1.49)	0.484	0.74 (0.38, 1.42)	0.364	0.84 (0.59, 1.17)	0.290	0.68 (0.47, 0.96)	0.027
Divorced	1.72 (0.94, 3.16)	0.078	1.64 (0.85, 3.15)	0.137	1.46 (1.01, 2.09)	0.042	1.18 (0.82, 1.744)	0.374
School level								
Primary	0.73 (0.24, 2.21)	0.770	1.89 (0.59, 7.19)	0.252	0.95 (0.53, 1.73)	0.877	2.05 (0.95, 4.41)	0.068
Pre-Secondary	0.58 (0.26, 1.28)	0.076	1.03 (0.44, 2.38)	0.949	0.79 (0.53, 1.19)	0.267	1.15 (0.72, 1.83)	0.552
Secondary	1.00		1.00		1.00		1.00	
Post-Secondary	1.80 (1.25, 2.61)	**0.002**	1.81 (1.25, 2.63)	**0.002**	1.24 (1.03, 1.51)	**0.027**	1.22 (1.00, 1.49)	**0.048**
University	1.45 (1.11, 1.92)	**0.008**	1.45 (1.09, 1.91)	**0.009**	1.25 (1.08, 1.45)	**0.002**	1.25 (1.08, 1.45)	**0.003**
Post-Doc	1.61 (1.01, 2.59)	**0.049**	1.61 (1.01, 2.61)	**0.050**	1.28 (0.99, 1.65)	**0.055**	1.30 (1.01, 1.69)	**0.045**
Smoker								
No	1.00		1.00		1.00		1.00	0.548
Yes	1.44 (0.77, 2.71)	0.250	1.48 (0.78, 2.78)	0.231	1.04 (0.76, 1.44)	0.803	1.23 (0.62, 2.42)	
Work status								
Employed	1.00		1.00		1.00		1.00	
Self-Employed	0.93 (0.70, 1.24)	0.630	0.95 (0.70, 1.26)	0.689	1.10 (0.94, 1.29)	0.227	1.02 (0.73, 1.45)	0.877
Not Employed	1.15 (0.91, 1.44)	0.237	1.14 (0.91, 1.44)	0.260	1.08 (0.96, 1.22)	**0.188**	1.69 (1.28, 2.23)	**<0.001**
BMI								
≤18.5	1.44 (0.78, 2.63)	0.237	1.57 (0.85, 2.91)	0.148	1.59 (1.09, 2.32)	**0.016**	2.15 (0.93, 5.01)	0.073
>18.5 to ≤ 24.9	1.00		1.00		1.00		1.00	
>24.9 to ≤ 29.9	0.72 (0.57, 0.91)	**0.006**	0.74 (0.58, 0.93)	**0.011**	0.89 (0.79, 1.02)	0.093	0. 63 (0.47, 0.83)	**0.001**
>29.9	0.45 (0. 33, 0.61)	**<0.001**	0.47 (0.34, 0.63)	**<0.001**	0.75 (0.64, 0.87)	**<0.001**	0.42 (0.30, 0.59)	**<0.001**
p_{trend}				**<0.001**				**0.001**
Waist to Hip Ratio								
≤75.63	1.15 (0.84, 1.57)	0.375	1.02 (0.74, 1.41)	0.863	1.16 (0.98, 1.38)	0.086	1.09 (0.92, 1.31)	0.319
>75.64 to ≤ 82.18	1.01 (0.74, 1.39)	0.928	0.95 (0.68, 1.31)	0.755	1.10 (0.93, 1.31)	0.276	1.09 (0.91, 1.30)	0.354
>82.19 to ≤ 85.98	1.00		1.00		1.00		1.00	
>85.99 to ≤ 92.71	1.06 (0.77, 1.47)	0.717	1.09 (0.78, 1.52)	0.592	0.94 (0.79, 1.11)	0.470	0.92 (0.77, 1.10)	0.381
>92.72	0.66 (0.46, 0.93)	**0.020**	0.73 (0.51, 1.03)	0.080	0.77 (0.65, 0.93)	**0.007**	0.78 (0.65, 0.95)	**0.012**
p_{trend}				**0.012**				**<0.001**
War exposure								
No	1.00		1.00		1.00		1.00	
Yes	1.13 (0.85, 1.48)	0.397	1.12 (0.85, 1.49)	0.420	1.18 (1.01, 1.38)	**0.032**	1.18 (1.01, 1.38)	**0.039**
Parental Consanguinity								
No	1.00		1.00		1.00		1.00	
Yes	0.85 (0.69, 1.05)	0.133	0.85 (0.69, 1.05)	0.133	1.15 (1.04, 1.29)	**0.010**	1.14 (1.02, 1.28)	**0.023**
Family History								
No	1.00		1..00	**<0.001**	1.00	**<0.001**	1.00	**<0.001**
Yes	4.19 (3.13, 5.63)	**<0.001**	4.08 (3.04, 5.49)		2.28 (1.92, 2.72)		2.24 (1.87, 2.68)	

Adjusted for Age, Education, Ever Pregnant; Waist to Hip Ratio adjusted for BMI, Age, Education, Ever Pregnant

3.4.6 Menstrual characteristics

Table 3.19, Table 3.20, and Table 3.21 displays the results of menstrual characteristics in relation to disease status. Women with endometriosis seem to be comparable to those without this disorder with respect to most menstrual characteristics, except for menstrual cycle irregularity.

The mean age of menarche for women with endometriosis was 13.12 (1.34), 13.56 (1.57) for symptomatic controls (p<0.001), 13.60 (1.96) for asymptomatic controls (p<0.001), 13.62 (1.47) for hospital controls (p<0.001) and 13.51 (1.39) for population controls (p<0.001). After adjustment for age, BMI, ever pregnant, OC use and education, endometriosis was associated with earlier age (≤12) at menarche when comparing the cases to symptomatic controls (OR: 1.23 95% CI: (1.01, 1.58); p=0.043), asymptomatic controls (OR: 1.52 95% CI: (1.12, 2.04); p=0.007) and population controls (OR: 1.24 95% CI: (1.08, 1.43); p=0.003).

Table 3.19. Descriptive statistical analysis: menstrual characteristics comparing endometriosis cases vs. controls (unadjusted analysis).

		Control Categorization: Symptomatic Criteria				**Control Categorization: Ascertainment Criteria**			
Variable	**Endometriosis Cases (n=518) % (n)**	**Symptomatic Controls (n=1331) % (n)**	***p*-value**	**Asymptomatic Controls (n=762) % (n)**	***p*-value**	**Hospital Controls (n=1251) % (n)**	***p*-value**	**Population Controls (n=841) % (n)**	***p*-value**
Age at Menarche									
≤12	29.0% (150)	21.7% (289)	**<0.001**	18.8% (143)	**<0.001**	22.0% (275)	**<0.001**	18.7% (157)	**<0.001**
13-14	51.2% (265)	50.6% (674)		56.6% (431)		49.6% (621)		57.6% (484)	
≥15	19.9% (103)	27.6% (368)		24.6% (187)		28.4% (355)		23.8% (200)	
Menstrual Cycle Length									
≤24	22.4% (116)	14.6% (194)	**0.001**	12.6% (96)	**<0.001**	14.7% (184)	**<0.001**	12.6% (106)	**<0.001**
25-32	65.6% (340)	69.8% (929)		73.3% (558)		69.1% (864)		74.1% (623)	
≥33	12.0% (62)	15.6% (208)		14.1% (107)		16.2% (203)		13.3% (112)	
Menstrual Cycle Irregularity									
No	68.7% (356)	72.8% (969)	0.081	80.0% (609)	**<0.001**	72.9% (912)	0.076	79.2% (666)	**<0.001**
Yes	31.3% (162)	27.2% (362)		20.0% (152)		27.1% (339)		20.8% (175)	
Intensity of Menstrual Flow									
Light	18.5% (96)	22.1% (294)	**<0.001**	20.0% (152)	**0.001**	22.3% (279)	**<0.001**	19.9% (167)	**<0.001**
Average	47.3% (245)	53.9% (718)		55.2% (420)		53.4% (668)		55.9% (470)	
Heavy	34.2% (177)	24.0% (319)		24.8% (189)		24.3% (304)		24.3% (204)	
Duration of Menstrual Phase									
≤4	22.4% (116)	28.5% (379)	**<0.001**	26.7% (203)	**<0.001**	29.7% (371)	**<0.001**	25.1% (211)	**0.001**
5-6	44.6% (231)	49.1% (653)		51.5% (392)		49.2% (616)		51.0% (429)	
≥7	33.0% (171)	22.5% (299)		21.8% (166)		21.1% (264)		23.9% (201)	

As demonstrated in Figure 3.2, across all four control groups (symptomatic controls; asymptomatic controls; hospital controls; population controls), women with endometriosis had a significant association with shorter (≤24) menstrual cycle length (p<0.001; p<0.001; p=0.047; p<0.001), heavy menstrual flow (p<0.001; p=0.011; p<0.001; p=0.003), and long (≥7) duration of menstrual phase (p<0.001; p<0.001; p<0.001; p<0.001), after adjustment for age, BMI, ever pregnant, OC use and education. The mean duration of menstrual phase was 5.76 (1.57) for women with endometriosis, 5.35 (1.40) for symptomatic controls (p<0.001), 5.51 (1.31) for asymptomatic controls (p=0.003), 5.33 (1.38) for hospital controls (p<0.001) and 5.52 (1.34) for population controls (p=0.004). Menstrual cycle irregularity was not associated with endometriosis in comparison to symptomatic controls (p=0.411) and hospital controls (p=0.363), however a significant association was present when comparing it to asymptomatic controls (p<0.001) and population controls (p=0.001). This could be because menstrual irregularity is associated to the symptoms, such as infertility, and not endometriosis *per se*.

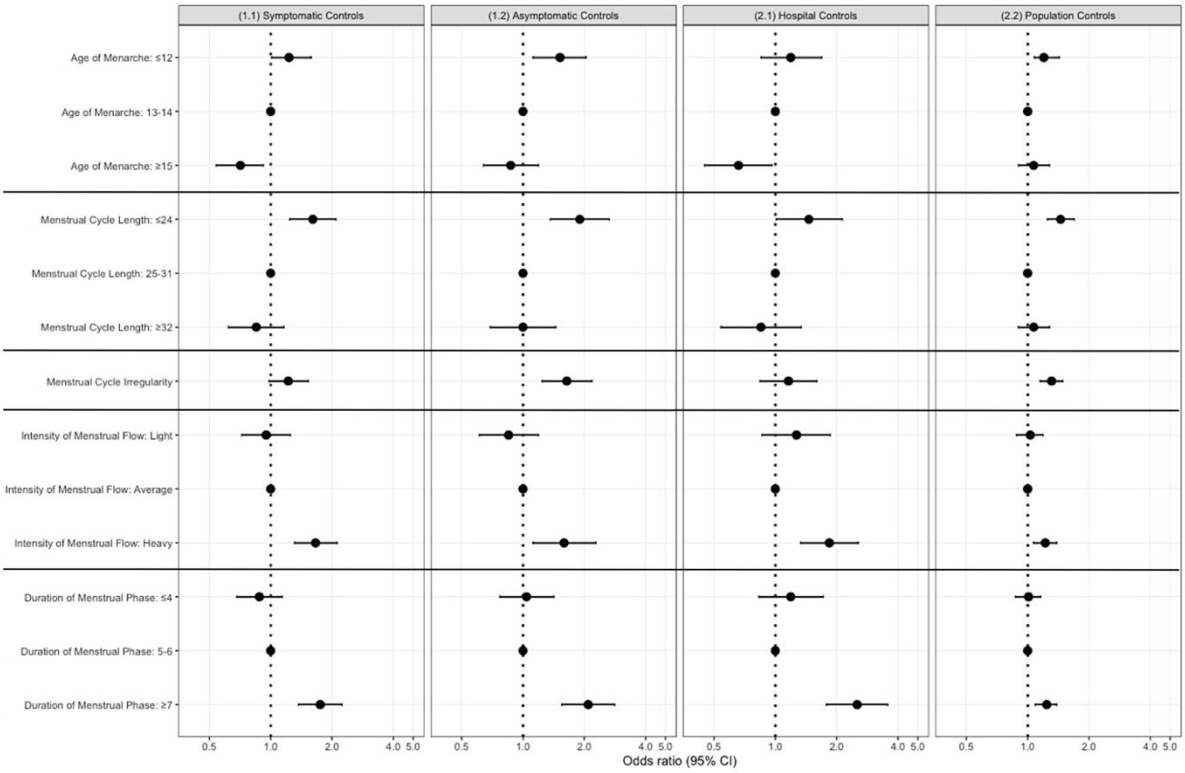


Figure 3.2. Forest plot of the multivariate logistic regression models: adjusted risk of endometriosis to four control groups (symptomatic criteria (1.1; 1.2) and ascertainment criteria (2.1; 2.2)) according to menstrual characteristics.

Table 3.20. Logistic multivariate regression analysis: adjusted risk of endometriosis vs. controls (symptomatic criteria) according to menstrual characteristics.

Variable	Endometriosis vs. Symptomatic Controls				Endometriosis vs. Asymptomatic Controls			
	Crude Odds Ratio (95% CI)	***p*-value**	**Adjusted Odds-Ratio (95% CI)**	***p*-value**	**Crude Odds Ratio (95% CI)**	***p*-value**	**Adjusted Odds-Ratio (95% CI)**	***p*-value**
Age of Menarche								
≤12	1.32 (1.04, 1.68)	**0.025**	1.23 (1.01, 1.58)	**0.043**	1.71 (1.29, 2.24)	**<0.001**	1.52 (1.12, 2.04)	**0.007**
13-14	1.00		1.00		1.00		1.00	
≥15	0.71 (0.55, 0.92)	**0.011**	0.71 (0. 54, 0.92)	**0.009**	0.89 (0.67, 1.19)	0.449	0.87 (0.64, 1.19)	0.878
Menstrual Cycle Length								
≤24	1.63 (1.26, 2.12)	**<0.001**	1.61 (1.24, 2.09)	**<0.001**	1.98 (1.46, 2.68)	**<0.001**	1.90 (1.36, 2.65)	**<0.001**
25-31	1.00		1.00		1.00		1.00	
≥32	0.81 (0.59, 1.11)	0.194	0.85 (0.62, 1.16)	0.292	0.95 (0.67, 1.34)	0.951	1.00 (0.69, 1.45)	0.992
Menstrual Cycle Irregularity								
No	1.00		1.00		1.00		1.00	
Yes	1.26 (0.97, 1.54)	0.081	1.22 (0.98, 1.53)	0.411	1.82 (1.41, 2.35)	**<0.001**	1.64 (1.24, 2.18)	**0.001**
Intensity of Menstrual Flow								
Light	0.96 (0.73, 1.27)	0.751	0.95 (0.72, 1.25)	0.719	1.08 (0.81, 1.46)	0.604	0.85 (0.61, 1.19)	0.334
Average	1.00		1.00		1.00		1.00	
Heavy	1.63 (1.28, 2.05)	**<0.001**	1.66 (1.31, 2.12)	**<0.001**	1.61 (1.24, 2.07)	**<0.001**	1.59 (1.12, 2.28)	**0.011**
Duration of Menstrual Phase								
≤4	0.86 (0.67, 1.18)	0.268	0.88 (0.68, 1.14)	0.078	0.97 (0.73, 1.28)	0.830	1.04 (0.77, 1.42)	0.778
5-6	1.00		1.00		1.00		1.00	
≥7	1.62 (1.27, 2.05)	**<0.001**	1.75 (1.37, 2.24)	**<0.001**	1.74 (1.33, 2.28)	**<0.001**	2.09 (1.55, 2.82)	**<0.001**

Adjusted for Age, BMI, Ever Pregnant, OC use, Education

Table 3.21. Logistic multivariate regression analysis: adjusted risk of endometriosis vs. controls (ascertainment criteria) according to menstrual characteristics.

Variable	Endometriosis vs. Hospital Controls				Endometriosis vs. Population Controls			
	Crude Odds Ratio (95% CI)	***p*-value**	**Adjusted Odds-Ratio (95% CI)**	***p*-value**	**Crude Odds Ratio (95% CI)**	***p*-value**	**Adjusted Odds-Ratio (95% CI)**	***p*-value**
Age of Menarche								
≤12	1.27 (1.00, 1.63)	**0.050**	1.19 (0.85, 1.68)	**0.310**	1.32 (1.15, 1.51)	**<0.001**	1.24 (1.08, 1.43)	**0.003**
13-14	1.00		1.00		1.00		1.00	
≥15	0.68 (0.52, 0.88)	**0.004**	0.66 (0.45, 0.96)	**0.029**	0.97 (0.84, 1.12)	0.669	0.96 (0.83, 1.11)	0.569
Menstrual Cycle Length								
≤24	1.60 (1.23, 2.08)	**<0.001**	1.46 (1.01, 2.13)	**0.047**	1.98 (1.46, 2.68)	**<0.001**	1.45 (1.25, 1.69)	**<0.001**
25-31	1.00		1.00		1.00		1.00	
≥32	0.77 (0.56, 1.05)	0.110	0.85 (0.54, 1.34)	0.503	0.95 (0.67, 1.34)	0.951	1.07 (0.90, 1.28)	0.419
Menstrual Cycle Irregularity								
No	1.00		1.00		1.00		1.00	
Yes	1.22 (0.97, 1.53)	0.076	1.16 (0.84, 1.60)	0.363	1.32 (1.16, 1.49)	**<0.001**	1.31 (1.15, 1.49)	**<0.001**
Intensity of Menstrual Flow								
Light	0.94 (0.71, 1.23)	0.648	1.27 (0.86, 1.86)	0.223	1.05 (0.91, 1.22)	0.515	1.03 (0.88, 1.19)	0.742
Average	1.00		1.00		1.00		1.00	
Heavy	1.58 (1.25, 2.01)	**<0.001**	1.84 (1.33, 2.55)	**<0.001**	1.29 (1.14, 1.47)	**<0.001**	1.22 (1.07, 1.39)	**0.003**
Duration of Menstrual Phase								
≤4	0.83 (0.64, 1.08)	0.167	1.19 (0.83, 1.72)	0.326	1.01 (0.88, 1.16)	0.883	1.01 (0.87, 1.16)	0.886
5-6	1.00		1.00		1.00		1.00	
≥7	1.73 (1.35, 2.21)	**<0.001**	2.52 (1.78, 3.56)	**<0.001**	1.26 (1.10, 1.43)	**<0.001**	1.24 (1.09, 1.43)	**<0.001**

Adjusted for Age, BMI, Ever Pregnant, OC use, Education

3.4.7 Reproductive characteristics

Endometriosis has been linked with fertility and pregnancy outcomes, possibly due to underlying chronic inflammation, hormonal factors, immune-related factors, and functional abnormalities. When investigating fertility characteristics, only ever married women (married, widowed, divorced) were utilised as the denominator of the frequency because single women are not allowed to seek fertility care in the UAE. In this study, average parity (number of children) among women with endometriosis was 2.08 (SD: 1.04), significantly less than among symptomatic controls 2.55 (SD: 1.57; p=0.003), asymptomatic controls 3.03 (SD: 2.21; p<0.001), hospital controls 2.25 (SD: 0.79; p=0.006), and population controls 2.23 (SD: 0.79; p=0.019).

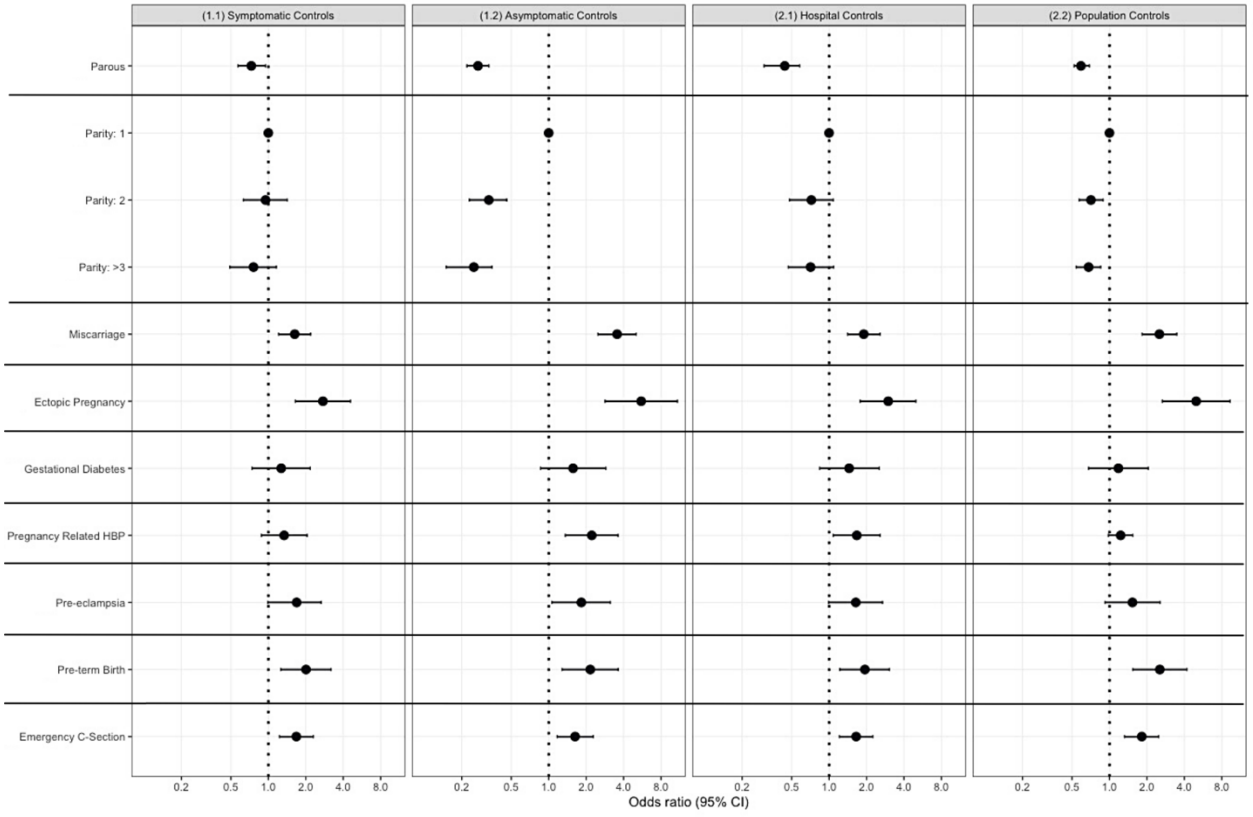


Figure 3.3. Forest plot of the multivariate logistic regression models: adjusted risk of endometriosis to four control groups (symptomatic criteria (1.1; 1.2) and ascertainment criteria (2.1; 2.2)) according to reproductive characteristics.

As demonstrated by Figure 3.3, women with endometriosis were more likely to be nulliparous in comparison to symptomatic controls ($p=0.017$), asymptomatic controls ($p<0.001$), hospital controls ($p=0.002$), and population controls ($p<0.001$). If the women were parous, women with endometriosis had a lower likelihood of having more than three live births, in comparison to asymptomatic controls ($p<0.001$) and population controls ($p<0.001$), however no association was present when comparing it to symptomatic controls ($p=0.198$) and hospital controls ($p=0.243$). This could be because parity is associated to the symptoms, such as infertility, and not endometriosis *per se*.

Across all four control groups, women with endometriosis had a higher risk of miscarriage (symptomatic controls ($p=0.001$), asymptomatic controls ($p<0.001$), hospital controls ($p<0.001$), and population controls ($p<0.001$), ectopic pregnancy (symptomatic controls (($p<0.001$), asymptomatic controls ($p<0.001$), hospital controls ($p<0.001$), and population controls ($p<0.001$), pre-term birth (symptomatic controls ($p=0.003$), asymptomatic controls ($p=0.003$), hospital controls ($p=0.005$), and population controls ($p<0.001$), and emergency caesarean section (symptomatic controls ($p=0.001$), asymptomatic controls ($p=0.004$), hospital controls ($p=0.001$), and population controls ($p<0.001$). Pregnancy-related high blood pressure, pre-eclampsia and gestational diabetes showed conflicting findings and no significant association with endometriosis, in comparison to the control groups (Table 3.22-3.24).

Table 3.22. Descriptive statistical analysis: reproductive characteristics comparing endometriosis cases vs. controls (unadjusted analysis).

		Control Categorization: Symptomatic Criteria				Control Categorization: Ascertainment Criteria			
Variable	**Endometriosis (n=518) % (n)**	**Symptomatic Controls (n=1331) % (n)**	***p*-value**	**Asymptomatic Controls (n=762) % (n)**	***p*-value**	**Hospital Controls (n=1331) % (n)**	***p*-value**	**Population Controls (n=762) % (n)**	***p*-value**
Parity									
Nulliparous	37.6% (163/433)	27.3% (309/1130)	**<0.001**	7.9% (51/648)	**<0.001**	20.6% (217/1052)	**0.002**	19.7% (143/726)	**<0.001**
Parous	62.4% (270/433)	72.7% (821/1130)		92.1% (597/648)		79.42% (835/1052)		80.3% (583/726)	
Parous									
1	29.3% (79/270)	22.8% (187/821)	**0.046**	21.9% (131/597)	**0.030**	22.0% (184/835)	**0.024**	23.0% (134/583)	0.075
2	31.9% (86/270)	30.8% (253/821)		31.2% (186/597)		31.0% (259/835)		30.9% (180/583)	
>3	38.9% (105/270)	46.4% (381/821)		46.9% (280/597)		46.9% (392/835)		46.1% (269/583)	
Miscarriage									
No	60.7% (164/270)	71.3% (585/821)	**0.001**	84.6% (505/597)	**<0.001**	74.9% (625/835)	**<0.001**	79.8% (465/583)	**<0.001**
Yes	39.3% (106/270)	28.7% (236/821)		15.4% (92/597)		25.1% (210/835)		20.2% (118/583)	
Ectopic Pregnancy									
No	87.4% (236/270)	95.2% (782/821)	**<0.001**	97.7% (583/597)	**<0.001**	95.6% (798/835)	**<0.001**	97.3% (567/583)	**<0.001**
Yes	12.6% (34/270)	4.8% (39/821)		2.3% (14/597)		4.4% (37/835)		2.7% (16/583)	
Gestational Diabetes									
No	91.9% (248/270)	93.2% (765/821)	0.463	94.8% (566/597)	0.093	94.6% (790/835)	0.099	92.8% (541/583)	0.626
Yes	8.1% (22/270)	6.8% (56/821)		5.2% (31/597)		5.4% (45/835)		7.2% (42/583)	
Pregnancy Related High Blood Pressure									
No	85.9% (232/270)	88.9% (730/821)	0.187	92.0% (549/597)	**0.006**	90.5% (756/835)	**0.032**	89.7% (523/583)	0.107
Yes	14.1% (38/270)	11.1% (91/821)		8.0% (48/597)		9.5% (79/835)		10.3% (60/583)	
Pre-eclampsia									
No	89.3% (241/270)	92.9% (763/821)	0.053	93.8% (560/597)	**0.020**	93.4% (780/835)	**0.025**	93.1% (543/583)	0.053
Yes	10.7% (29/270)	7.1% (58/821)		6.2% (37/597)		6.6% (55/835)		6.9% (40/583)	
Pre-term Birth									
No	86.3% (233/270)	92.9% (763/821)	**<0.001**	94.1% (562/597)	**<0.001**	92.9% (776/835)	**<0.001**	94.2% (549/583)	**<0.001**
Yes	13.7% (37/270)	7.1% (58/821)		5.9% (35/597)		7.1% (59/835)		5.8% (34/583)	
Emergency Caesarean Section									
No	63.7% (172/270)	75.6% (621/821)	**<0.001**	75.9% (453/597)	**<0.001**	75.9% (634/835)	**<0.001**	75.5% (440/583)	**<0.001**
Yes	36.3% (98/270)	24.4% (200/821)		24.1% (144/597)		24.1% (201/835)		24.5% (143/583)	

Table 3.23. Logistic multivariate regression analysis: adjusted risk of endometriosis vs. controls (symptomatic criteria)according to reproductive factors.

Variable	Endometriosis vs. Symptomatic Controls				Endometriosis vs. Asymptomatic Controls			
	Crude Odds Ratio (95% CI)	***p*-value**	**Adjusted Odds-Ratio (95% CI)**	***p*-value**	**Crude Odds Ratio (95% CI)**	***p*-value**	**Adjusted Odds-Ratio (95% CI)**	***p*-value**
Parity								
Nulliparous	1.00		1.00		1.00		1.00	
Parous	0.62 (0.49, 0.78)	**<0.001**	0.73 (0.57, 0.95)	**0.017**	0.41 (0.33, 0.57)	**<0.001**	0.27 (0.22, 0.33)	**<0.001**
Parous								
1	1.00		1.00		1.00		1.00	
2	0.81 (0.56, 1.15)	0.236	0.95 (0.63, 1.42)	0.792	0.75 (0.52, 1.09)	0.141	0.33 (0.23, 0.46)	**<0.001**
>3	0.65 (0.46, 0.92)	**0.014**	0.76 (0.49, 1.16)	0.198	0.62 (0.43, 0.88)	**0.008**	0.25 (0.15, 0.35)	**<0.001**
Miscarriage								
No	1.00		1.00		1.00		1.00	
Yes	1.60 (1.20, 2.13)	**0.001**	1.63 (1.21, 2.19)	**0.001**	3.55 (2.55, 4.95)	**<0.001**	3.55 (2.49, 5.05)	**<0.001**
Ectopic Pregnancy								
No	1.00		1.00		1.00		1.00	
Yes	2.89 (1.78, 4.67)	**<0.001**	2.75 (1.65, 4.58)	**<0.001**	6.01 (3.17, 11.40)	**<0.001**	5.54 (2.84, 10.84)	**<0.001**
Gestational Diabetes								
No	1.00		1.00		1.00		1.00	
Yes	1.21 (0.72, 2.03)	0.463	1.27 (0.74, 2.17)	0.396	1.62 (0.92, 2.86)	0.094	1.57 (0.86, 2.88)	0.136
Pregnancy Related High Blood Pressure								
No	1.00		1.00		1.00		1.00	
Yes	1.31 (0.88, 1.97)	0.188	1.34 (0.88, 2.05)	0.177	1.88 (1. 19, 2.95)	**0.006**	2.22 (1.36, 3.61)	**0.001**
Pre-eclampsia								
No	1.00		1.00		1.00		1.00	
Yes	1.58 (0.99, 2.53)	0.055	1.63 (0.99, 2.66)	0.052	1.82 (1.09, 3.04)	**0.021**	1.83 (1.06, 3.13)	**0.028**
Pre-term Birth								
No	1.00		1.00		1.00		1.00	
Yes	2.08 (1.35, 3.24)	**<0.001**	2.01 (1.26, 3.19)	**0.003**	2.55 (1.57, 4.15)	**<0.001**	2.16 (1.28, 3.62)	**0.003**
Emergency Caesarean Section								
No	1.00		1.00		1.00		1.00	
Yes	1.77 (1.32, 2.38)	**<0.001**	1.68 (1.23, 2.30)	**0.001**	1.79 (1.32, 2.45)	**<0.001**	1.63 (1.17, 2.28)	**0.004**

Adjusted for Age, BMI, Ever Pregnant, Parity, Education, Age at Menarche, OCP use, infertility

Table 3.24. Logistic multivariate regression analysis: adjusted risk of endometriosis vs. controls (ascertainment criteria) according to reproductive factors.

Variable	Endometriosis vs. Hospital Controls				Endometriosis vs. Population Controls			
	Crude Odds Ratio (95% CI)	***p*-value**	**Adjusted Odds-Ratio (95% CI)**	***p*-value**	**Crude Odds Ratio (95% CI)**	***p*-value**	**Adjusted Odds-Ratio (95% CI)**	***p*-value**
Parity								
Nulliparous	1.00		1.00		1.00		1.00	
Parous	0.77 (0.54, 1.11)	**0.002**	0.44 (0.34, 0.58)	**0.002**	0.64 (0.56, 0.72)	**<0.001**	0.59 (0.52, 0.69)	**<0.001**
Parous								
1	1.00		1.00		1.00		1.00	
2	0.77 (0.54, 1.11)	0.161	0.72 (0.48, 1.08)	0.607	0.90 (0.74, 1.09)	0.276	0.71 (0.57, 0.89)	0.002
>3	0.62 (0.44, 0.88)	**0.007**	0.71 (0.47, 1.09)	**0.243**	0.81 (0.68, 0.97)	**0.024**	0.68 (0.54, 0.85)	**<0.001**
Miscarriage								
No	1.00		1.00		1.00		1.00	
Yes	1.92 (1.44, 2.57)	**<0.001**	1.90 (1.41, 2.57)	**<0.001**	1.58 (1.18, 2.10)	**0.002**	2.52 (1.83, 3.48)	**<0.001**
Ectopic Pregnancy								
No	1.00		1.00		1.00		1.00	
Yes	3.11 (1.91, 5.06)	**<0.001**	2.99 (1.78, 4.99)	**<0.001**	3.62 (1.98, 6.63)	**<0.001**	4.98 (2.66, 9.32)	**<0.001**
Gestational Diabetes								
No	1.00		1.00		1.00		1.00	
Yes	1.56 (0.92, 2.64)	0.101	1.45 (0.84, 2.53)	0.184	0.84 (0.49, 1.43)	0.528	1.18 (0.68, 2.05)	0.558
Pregnancy Related High Blood Pressure								
No	1.00		1.00		1.00		1.00	
Yes	1.57 (1.04, 2.37)	**0.033**	1.67 (1.08, 2.57)	**0.020**	103 (0.67, 1.57)	0.889	1.23 (0.98, 1.54)	0.066
Pre-eclampsia								
No	1.00		1.00		1.00		1.00	
Yes	1.71 (1.06, 2.74)	**0.027**	1.64 (0.99, 2.69)	0.050	1.16 (0.71, 1.88)	0.558	1.53 (0.92, 2.55)	0.103
Pre-term Birth								
No	1.00		1.00		1.00		1.00	
Yes	2.09 (1.35, 3.23)	**<0.001**	1.94 (1.22, 3.06)	**0.005**	1.77 (1.10, 2.85)	**<0.001**	2.54 (1.54, 4.19)	**<0.001**
Emergency Caesarean Section								
No	1.00		1.00		1.00		1.00	
Yes	1.79 (1.34, 2.41)	**<0.001**	1.65 (1.21, 2.25)	**0.001**	1.14 (0.86, 1.52)	0.369	1.82 (1.32, 2.49)	**<0.001**

Adjusted for Age, BMI, Parity, Education, Age at Menarche, OCP use, infertility

3.4.8 Comorbid disorders

Comorbidities, if more prevalent among women with endometriosis than among those without, may provide an indication of shared environmental, genetic, and biological influences and of multifactorial pain contributors beyond the endometriosis lesions themselves. Figure 3.4, Tables 3.25, Table 3.26 and 3.27 show results for the conditions that have are more frequent among women with endometriosis: immune and inflammatory disorders (asthma, eczema, diabetes mellitus type 1), metabolic disorders (diabetes mellitus type 2, cardiovascular disorders, hypertension), and gynaecological disorders (uterine fibroids, polycystic ovary syndrome and structural problems).

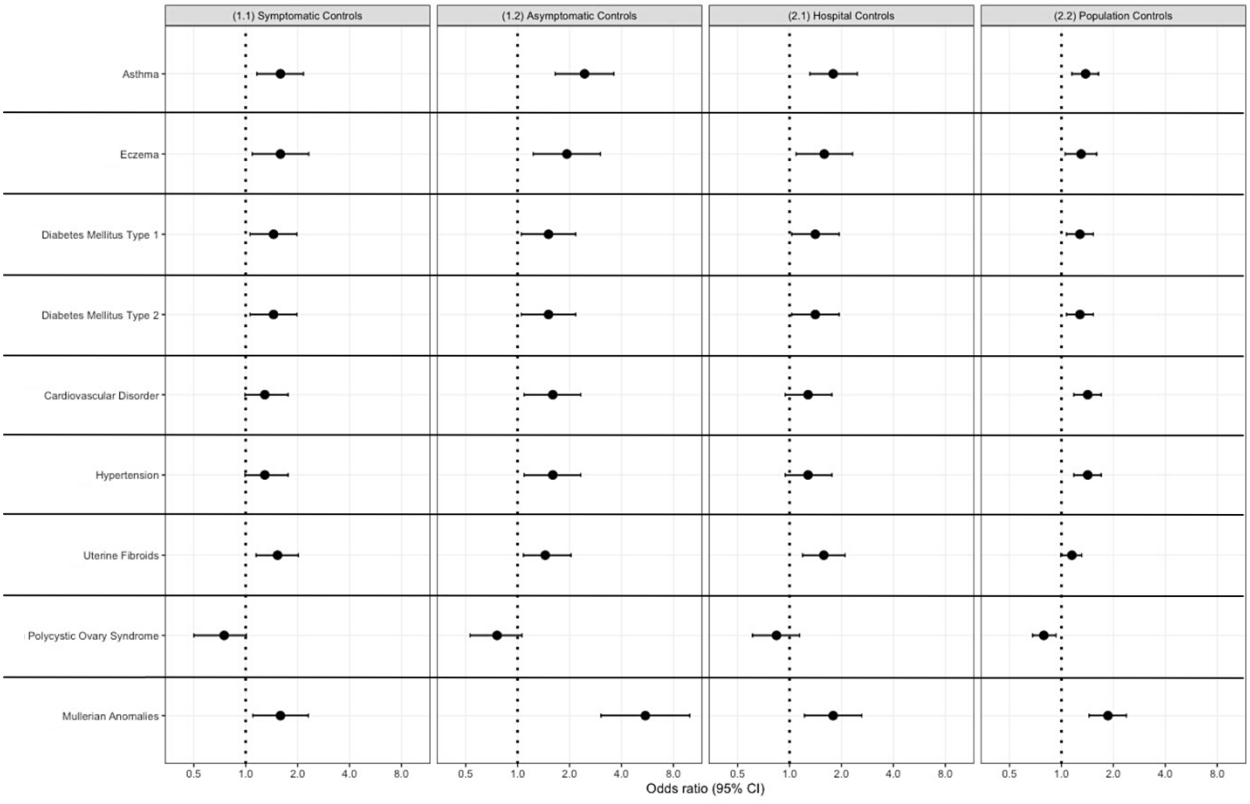


Figure 3.4. Forest plot of the multivariate logistic regression models: adjusted risk of endometriosis to four control groups (symptomatic criteria (1.1; 1.2) and ascertainment criteria (2.1; 2.2)) according to comorbid conditions.

Immune and inflammatory disorders

Participants were asked if they had received a medical diagnosis of asthma, eczema, and diabetes mellitus Type 1. Consistently across all four control groups, women with endometriosis had a higher frequency of asthma (symptomatic controls ($p=0.003$), asymptomatic controls ($p<0.001$), hospital controls ($p=0.003$), and population controls ($p<0.001$)), eczema (symptomatic controls ($p=0.015$), asymptomatic controls ($p=0.004$), hospital controls ($p=0.018$), and population controls ($p=0.015$)) and diabetes mellitus type 1 (symptomatic controls ($p=0.019$), asymptomatic controls ($p=0.024$), hospital controls ($p=0.031$), and population controls ($p=0.005$)), after adjusting for age, BMI, education, smoking history and physical activity.

Metabolic disorders

There was no significantly different frequency of diabetes mellitus type 2 and hypertension among women with endometriosis, in comparison to all four control groups. These results remained after adjustment. However, in comparison to asymptomatic controls and population controls, women with endometriosis had a higher frequency of being diagnosed with cardiovascular disorder (OR 1.60 (95% CI:1.09, 2.32), $p=0.015$; OR 1.42 (95% CI:1.18, 1.70), $p<0.001$). This association was not significant when comparing it to symptomatic controls ($p=0.111$) and hospital controls ($p=0.122$), demonstrating that this may be associated to the symptoms and not endometriosis *per se*.

Gynaecological disorders

After adjusting for age, BMI, education, smoking history and physical activity, women with endometriosis had a higher rate of uterine fibroids and Mullerian anomalies, compared with symptomatic controls ($p=0.003$; $p=0.012$), asymptomatic controls ($p=0.014$; $p<0.001$), hospital controls ($p=0.002$; $p=0.003$) and population controls ($p=0.051$; $p<0.001$). While there was a lower effect size and inverse relationship present between polycystic ovary syndrome and endometriosis, this was not significantly associated across all four control groups.

Table 3.25. Descriptive statistical analysis: comorbid conditions comparing endometriosis cases vs. controls (unadjusted analysis).

Variable		Control Categorization: Symptomatic Criteria				Control Categorization: Ascertainment Criteria			
	Endometriosis (n=518) % (n)	**Symptomatic Control (n=1331) % (n)**	***p*-value**	**Asymptomatic Control (n=762) % (n)**	***p*-value**	**Hospital Control (n=1331) % (n)**	***p*-value**	**Population Control (n=762) % (n)**	***p*-value**
Asthma									
No	85.5% (443)	90.7% (1207)	**0.001**	93.2% (709)	**<0.001**	91.4% (1144)	**<0.001**	91.8% (772)	**<0.001**
Yes	14.5% (75)	9.3% (124)		6.8% (52)		8.6% (107)		8.2% (69)	
Eczema									
No	90.5% (469)	93.6% (1246)	**0.022**	94.7% (721)	**0.004**	93.8% (1174)	**0.014**	94.3% (793)	**0.009**
Yes	9.5% (49)	6.4% (85)		5.3% (40)		6.2% (77)		5.7% (48)	
Diabetes Mellitus Type 1									
No	86.3% (447)	90.0% (1198)	**0.022**	90.5% (689)	**0.018**	89.6% (1121)	**0.046**	91.1% (766)	**0.006**
Yes	13.7% (71)	10.0% (133)		9.5% (72)		10.4% (130)		8.9% (75)	
Diabetes Mellitus Type 2									
No	85.9% (445)	82.6% (1099)	0.082	83.8% (638)	0.313	82.3% (1030)	0.066	84.1% (707)	0.359
Yes	14.1% (73)	17.4% (232)		16.2% (123)		17.7% (221)		15.9% (134)	
Cardiovascular Disorder									
No	87.6% (454)	89.9% (1197)	0.153	91.6% (697)	**0.021**	89.1% (1115)	0.176	92.6% (779)	**<0.001**
Yes	12.4% (64)	10.1% (134)		8.4% (64)		10.9% (136)		7.4% (62)	
Hypertension									
No	78.8% (408)	82.5% (1098)	0.064	82.7% (629)	0.081	83.0% (1038)	**0.037**	82.44% (693)	0.097
Yes	21.2% (110)	17.5% (233)		17.3% (132)		17.0% (213)		17.6% (148)	
Uterine Fibroids									
No	81.9% (424)	87.2% (1161)	**0.003**	87.0% (662)	**0.012**	87.4% (1093)	**0.003**	85.7% (721)	0.057
Yes	18.1% (94)	12.8% (170)		13.0% (99)		12.6% (158)		14.3% (120)	
Polycystic Ovary Syndrome									
No	88.0% (456)	84.4% (1124)	0.050	84.1% (640)	**0.049**	85.9% (1074)	0.222	82.0% (690)	**0.003**
Yes	12.0% (62)	15.6% (207)		15.9% (121)		14.1% (177)		18.0% (151)	
Mullerian Anomalies									
No	90.2% (467)	93.8% (1248)	**0.007**	97.9% (745)	**<0.001**	94.2% (1178)	**0.003**	96.9% (815)	**<0.001**
Yes	9.8% (51)	6.2% (83)		2.1% (16)		5.8% (73)		3.1% (26)	

Table 3.26. Logistic multivariate regression analysis: adjusted risk of endometriosis vs. controls (symptomatic criteria) according to comorbidity status.

Variable	Endometriosis vs. Symptomatic Controls				Endometriosis vs. Asymptomatic Controls			
	Crude Odds Ratio (95% CI)	***p*-value**	**Adjusted Odds-Ratio (95% CI)**	***p*-value**	**Crude Odds Ratio (95% CI)**	***p*-value**	**Adjusted Odds-Ratio (95% CI)**	***p*-value**
Asthma								
No	1.00		1.00		1.00		1.00	
Yes	1.65 (1.21, 2.23)	**0.001**	1.59 (1.16. 2.16)	**0.003**	2.31 (1.59, 3.35)	**<0.001**	2.44 (1.65, 3.61)	**<0.001**
Eczema								
No	1.00		1.00		1.00		1.00	
Yes	1.53 (1.06, 2.21)	**0.023**	1.59 (1.09, 2.32)	**0.015**	1.88 (1.22, 2.91)	**0.004**	1.93 (1.23, 3.02)	**0.004**
Diabetes Mellitus Type 1								
No	1.00		1.00		1.00		1.00	
Yes	1.43 (1.05, 1.95)	**0.023**	1.45 (1.06, 1.98)	**0.019**	1.52 (1.07, 2.15)	**0.019**	1.51 (1.05, 2.17)	**0.024**
Diabetes Mellitus Type 2								
No	1.00		1.00		1.00		1.00	
Yes	0.77 (0.58, 1.03)	0.083	0.76 (0.57, 1.02)	0.063	0.85 (0.62, 1.17)	0.313	0.84 (0.61, 1.16)	0.289
Cardiovascular Disorder								
No	1.00		1.00		1.00		1.00	
Yes	1.25 (0.92, 1.72)	0.154	1.29 (0.94, 1.79)	0.111	1.54 (1.06, 2.21)	**0.022**	1.60 (1.09, 2.32)	**0.015**
Hypertension								
No	1.00		1.00		1.00		1.00	
Yes	1.27 (0.98, 1.63)	0.064	1.28 (0.99, 1.66)	0.059	1.28 (0.97, 1.70)	0.082	1.35 (1.01, 1.81)	**0.045**
Uterine Fibroids								
No	1.00		1.00		1.00		1.00	
Yes	1.51 (1.15, 1.99)	**0.003**	1.53 (1.15, 2.02)	**0.003**	1.48 (1.09, 2.02)	**0.012**	1.46 (1.08, 2.04)	**0.014**
Polycystic Ovary Syndrome								
No	1.00		1.00		1.00		1.00	
Yes	0.74 (0.55, 1.00)	0.050	0.75 (0.54, 1.01)	0.055	0.71 (0.52, 0.99)	**0.049**	0.76 (0.53, 1.06)	0.104
Mullerian Anomalies								
No	1.00		1.00		1.00		1.00	
Yes	1.64 (1.14, 2.36)	**0.008**	1.59 (1.10, 2.31)	**0.012**	5.08 (2.86, 9.02)	**<0.001**	5.50 (3.04, 9.96)	**<0.001**

Adjusted for Age, BMI, Education, Smoking history, Physical Activity

Table 3.27. Logistic multivariate regression analysis: adjusted risk of endometriosis vs. controls (ascertainment criteria) according to comorbidity status

Variable	Endometriosis vs. Hospital Controls				Endometriosis vs. Population Controls			
	Crude Odds Ratio (95% CI)	***p*-value**	**Adjusted Odds-Ratio (95% CI)**	***p*-value**	**Crude Odds Ratio (95% CI)**	***p*-value**	**Adjusted Odds-Ratio (95% CI)**	***p*-value**
Asthma								
No	1.00		1.00		1.00		1.00	
Yes	1.65 (1.21, 2.23)	**0.001**	1.79 (1.31. 2.47)	**<0.001**	1.37 (1.15, 1.63)	**<0.001**	1.38 (1.15, 1.644)	**<0.001**
Eczema								
No	1.00		1.00		1.00		1.00	
Yes	1.53 (1.06, 2.21)	**0.023**	1.59 (1.09, 2.33)	**0.018**	1.31 (1.06, 1.62)	**0.010**	1.30 (1.05, 1.60)	**0.015**
Diabetes Mellitus Type 1								
No	1.00		1.00		1.00		1.00	
Yes	1.43 (1.05, 1.95)	**0.023**	1.41 (1.03, 1.94)	**0.031**	1.27 (1.07, 1.51)	**0.006**	1.28 (1.07, 1.53)	**0.005**
Diabetes Mellitus Type 2								
No	1.00		1.00		1.00		1.00	
Yes	0.77 (0.58, 1.03)	0.083	0.74 (0.56, 0.99)	**0.047**	0.93 (0.79, 1.09)	0.359	0.93 (0.79, 1.09)	0.363
Cardiovascular Disorder								
No	1.00		1.00		1.00		1.00	
Yes	1.25 (0.92, 1.72)	0.154	1.28 (0.94, 1.76)	0.122	1.38 (1.15, 1.65)	**<0.001**	1.42 (1.18, 1.70)	**<0.001**
Hypertension								
No	1.00		1.00		1.00		1.00	
Yes	1.27 (0.98, 1.63)	0.064	1.29 (0.99, 1.68)	0.051	1.12 (0.97, 1.29)	0.097	1.14 (0.98, 1.31)	0.073
Uterine Fibroids								
No	1.00		1.00		1.00		1.00	
Yes	1.51 (1.15, 1.99)	**0.003**	1.58 (1.19, 2.10)	**0.002**	1.15 (0.99, 1.34)	0.057	1.15 (0.99, 1.34)	0.061
Polycystic Ovary Syndrome								
No	1.00		1.00		1.00		1.00	
Yes	0.74 (0.55, 1.00)	0.050	0.84 (0.61, 1.14)	0.835	0.79 (0.67 0.92)	**0.003**	0.79 (0.68, 0.93)	**0.005**
Mullerian Anomalies								
No	1.00		1.00		1.00		1.00	
Yes	1.64 (1.14, 2.36)	**0.008**	1.79 (1.22, 2.62)	**0.003**	1.85 (1.45, 2.36)	**<0.001**	1.86 (1.45, 2.38)	**<0.001**

Adjusted for Age, BMI, Education, Smoking history, Physical Activity

3.5 Discussion

Endometriosis is a complex disease for which many aspects of aetiology are yet to be determined. Characterising risk and protective factors could help identify women at risk of endometriosis. Available data on this subject are scarce and lack methodological rigour, especially among Arab women. For the first time, this study provides novel data on patient symptomatology and disease experience among Arab women.

The selected potential risk factors for endometriosis were assessed using multiple control criteria (symptomatic criteria -symptomatic and asymptomatic- and ascertainment criteria -hospital-based and population-based). Our findings demonstrated that the results of studies of risk factors for endometriosis are likely to be affected by the control selection, and often the asymptomatic controls and population controls travel in the same direction of effect, and similarly with the symptomatic controls and hospital controls. Population-based controls may be more adequate to use when evaluating menstrual factors (steroid-related risk factors) and lifestyle factors (BMI; WHRadjBMI), given that women attending hospitals often have comorbidities that may influence their hormonal profile, menstrual characteristics, and body weight. In contrast, hospital controls may be a better comparison group choice when evaluating risk factors associated to reproductive factors, such as parity, adverse pregnancy outcomes and comorbidity conditions. Therefore, using both types of control groups collected from different ascertainment sites, and then further stratifying these groups based on symptomatic criteria, has provided us with the opportunity to objectively evaluate endometriosis risk factors using multiple control groups.

Across all four control groups (symptomatic controls, asymptomatic controls, hospital controls and population controls), women with endometriosis had a lower BMI ($p=0.005$; $p<0.001$; $p<0.001$; $p=0.001$) and lower WHRadjBMI ($p=0.003$; $p=0.001$; $p=0.012$; $p<0.001$) , and a higher frequency of family history of endometriosis ($p<0.001$; $p<0.001$; $p<0.001$; $p<0.001$). Our study replicated the inverse relationship found between endometriosis with BMI and WHRadjBMI, which has been reported in previous observational studies of different ethnicities[10,164,166,363,378–382]. While women with endometriosis had a greater risk of

obtaining a higher educational level in comparison to asymptomatic control group ($p<0.001$) and population control group ($p=0.003$), endometriosis women had a significantly higher unemployment rate (asymptomatic control group ($p<0.001$); population control group ($p<0.001$)). The association with higher educational level may reflect socioeconomic biases, such as access to medical care and importance placed on seeking such care, or it may be associated to delay in childbearing resulting in a higher rate of endometriosis diagnosis[383]. However, in comparison to symptomatic controls and hospital controls, endometriosis women had no significant difference in educational level ($p=0.844$; $p=0.050$) or employment rate ($p=0.483$; $p=0.260$). This indicated that these variables are associated with symptoms, or correlated factors such as health care seeking behaviour, and not endometriosis *per se*. These health care seeking factors include the ability to recognize symptoms and signs, perception of severity, social characteristics, availability of treatment resources, and competing needs[384]. The lower employment rate seen in both endometriosis women and symptomatic controls may be due to the significant impact of the debilitating symptoms on the quality of life, work productivity and activity impairment, as reported by others[14,129,142].

Across the four control groups, marital status, smoking, and parental consanguinity were not associated to endometriosis. While studies have demonstrated a potential link between smoking and endometriosis, no such association was identified in this study[181,378,385]. However, due to the cultural norms, it is frowned down upon for women to smoke, and hence the low frequency of smoking may have prevented testing this association in this population. Divorce rate was more common in endometriosis women vs. symptomatic controls, where there may be a cultural link. In the Middle East, childlessness strongly influences marital life, and unfortunately, may lead to divorce, or becoming a second wife in a polygamous marriage[281,282]. Strikingly, 88.2% of the divorced women in this study sample were from childless marriages.

There was no difference in war exposure comparing endometriosis cases with symptomatic controls ($p=0.407$) or with hospital controls ($p=0.420$), but an association was present in comparison to asymptomatic controls ($p=0.027$) and population controls ($p=0.039$). Interestingly, this may suggest that war exposure plays a role in triggering symptoms of pain and infertility, as opposed to endometriosis *per*

se. Environmental toxicants, including war exposure, may play a role in the development of endometriosis. Exposure to these chemicals may modulate the immunological response, giving a biological explanation for their potential effect in the pathogenesis of endometriosis[284,386]. However, the data showed that the frequency of this exposure was the same in women with endometriosis and symptomatic controls.

Characterising the frequency of multiple types of pain associated with endometriosis in diverse ethnic groups is important to optimise treatment strategies and identify women with the disease earlier. Symptoms of dysmenorrhea, chronic pelvic pain, dyschezia, and dysuria are regularly reported among women undergoing laparoscopy, even among women with no identified endometriosis pathology. Our findings suggest that while women with endometriosis report more site-specific pain particularly involving dysmenorrhea ($p=0.002$; $p<0.001$), chronic pelvic pain ($p=0.049$; $p<0.001$), dysuria ($p=0.001$; $p<0.001$), and dyschezia ($p<0.001$; $p<0.001$), other comorbid pain conditions, such as leg pain (OR: 1.59 (95% CI: 1.22, 2.08), $p=0.001$; OR: 1.75 (95% CI: 1.39, 2.19), $p<0.001$) and migraine (OR: 1.47 (95% CI: 1.10, 1.96) $p=0.008$; OR: 1.94 (95% CI: 1.51, 2.49), $p<0.001$) were also associated with endometriosis, when compared to symptomatic controls with surgical confirmation and no surgical confirmation. Back pain ($p=0.088$) and ovulation pain ($p=0.258$) were not associated with endometriosis when compared to symptomatic controls. Mechanisms responsible for severity of painful symptoms associated with endometriosis may include the interaction among ectopic endometriotic implant, nociceptors and nerve fibers[17,387,388]. Intermittent or ongoing pain resulting from a disease can produce a sensitized peripheral and central nervous system (peripheral and central sensitization) that becomes maladaptive (centralization of pain). Central sensitization has been reported in women with endometriosis, and can occur with other types of visceral pain[83,86,389]. Most pelvic organs, as well as somatic pelvic tissues to which the pain is referred, share at least part of their central sensory projection. Migraine pain, for example, is initiated and sustained by trigeminal activation involving peripheral and central structures[253,390]. This may trigger the phenomena of cross-sensitization and central sensitization, as well as the presence and coexistence of multiple pain phenotypes that are cross-linked with one another.

There were no clear differences in results when stratifying symptomatic controls into those with surgical investigation vs. no surgical investigation, suggesting that results were not dependent on definition of symptomatic control group. Given that the frequency of pain phenotypes in symptomatic controls, regardless of surgical confirmation, travelled in the same direction of effect, this demonstrates that the requirement of surgical visualization for the control group to confirm 'true' endometriosis diagnosis may not be necessary for future epidemiological studies. The inclusion of the possible undiagnosed cases may have only diluted the observed effects of risk factors to a marginal extent. Therefore, it is more beneficial to focus research efforts on defining a control population that is representative of the source population of cases, than to be overly concerned on obtaining a disease-free control group.

Consistent with previous research[3,17,105], we found no association between pain frequency or severity and rASRM disease stage or location, suggesting the need for further development of classification systems that can better predict outcomes for endometriosis patients with pelvic pain. Women with endometriosis reported significantly greater pain severity as measured by NRS ($p<0.001$; $p<0.001$) and VAS ($p=0.038$; $p<0.001$), and earlier age of symptom onset ($p<0.001$; $p<0.001$), in comparison to both surgically confirmed and non-surgery symptomatic controls. Given that approximately 90% of the women were taking over-the-counter painkillers for the pelvic pain, and were possibly receiving additional treatments, were inadequate to control the pain, perpetuating the significant delay in diagnosing endometriosis[391]. This result likely reflects the lowered responsiveness of endometriosis-associated pain to over-the-counter painkillers and hormonal therapies. These details should be considered markers of potential endometriosis and prompt clinicians to consider further evaluation.

Ever married parous women had a lower likelihood of reporting dysmenorrhea (women with endometriosis: OR 0.52 (95% CI: 0.28, 0.93), $p=0.010$; symptomatic control: OR 0.71 (95% CI: 0.52, 0.96), $p=0.027$) and dysuria (women with endometriosis: 0.64 (95% CI: 0.42, 0.97), $p=0.010$; symptomatic control: OR 0.82 (95% CI: 0.65, 0.99), $p=0.047$), regardless of the presence of an endometriosis condition. There are several potential reasons for this observation. Reduced exposure to retrograde menstruation may prevent lesions

from occurring. Also, pregnancy may be associated with decidualization and subsequent necrosis of the regression of endometriotic lesions during pregnancy, hence suppressing the symptoms of endometriosis. Other possible reasons include hormonal and immunological changes during pregnancy that may impact on the inflammatory intra-peritoneal milieu[121,392].

Also consistent with previous studies[10,52,161,162,189], endometriosis was significantly associated with earlier age (≤12) at menarche, with shorter (≤24) menstrual cycle length, heavy menstrual flow, and long (≥7) duration of menstrual phase, in comparison to all four control groups. Menstrual cycle irregularity was not associated with endometriosis in comparison to symptomatic controls (p=0.411) and hospital controls (p=0.363), however a significant association was present when comparing it to asymptomatic controls (p<0.001) and population controls (p=0.001). This suggests that menstrual irregularity may be more associated with symptoms such as pelvic pain or infertility, than endometriosis *per se*. These menstrual characteristics reflect increased exposure to menstruation and provide strong support to Sampson's theory of retrograde menstruation, where women who have menstrual characteristics that offer greater opportunities for reflux to the peritoneal cavity by menstrual debris are at increased risk of endometriosis[24].

Endometriosis has been linked to infertility and adverse pregnancy outcomes, with potential reasons the increased inflammatory milieu in the peritoneal cavity with high concentrations of cytokines; growth factors and angiogenic factors leading to poorer oocyte quality; progestogen resistance in the endometrium impacting conditions for embryo implantation; molecular and functional abnormalities in eutopic endometrium; and anatomical distortion of Fallopian tubes and ovaries in women with endometriosis[192,392–395]. When investigating the frequency of infertility on the study, 64.9% (281/433) of endometriosis cases and 55.2% (624/1130) of controls were infertile (<0.001). After adjustment to sociodemographic variables, age at menarche and OCP use, women with endometriosis were at a greater risk of being infertile than symptomatic controls (OR: 1.33 (95% CI: 1.05, 1.69); p=0.017). When investigating the impact of parity in women with endometriosis, they were more likely to be nulliparous with fewer number of children, compared to controls. The above demonstrates, consistent with many other studies[182,378,392,396–398], that

women with endometriosis have a higher risk of suffering from fertility-related issues. After decades of observing the association between infertility and endometriosis, underlying causality is still not clear, requiring a longitudinal cohort study to assess the temporal relationship.

An important point that should be brought to attention is that performing laparoscopic surgery for endometriosis seems to be a primary therapeutic option for patients with infertility, rather than pain, in the Middle East. Although surgery remains an important management strategy for endometriosis, the benefits of surgery for infertility is uncertain and has multiple limitations. For example, surgery enables excision of endometriotic lesions, however it does not treat the underlying cause of the disease, associated to a high rate of recurrence[399]. In addition, surgery can have major complications, such as postoperative infection, rectovaginal fistula, neurogenic bladder and bowel dysfunction[400]. In relation to fertility, insufficient data exists to recommend systematic surgery before ART to increase the chances of pregnancy. Therefore, healthcare professionals in the UAE should be made aware that the indications for surgery are highly controversial, and due to the inconsistent data, immediate surgery should no longer be the first-line therapeutic option. It is important to reduce the number of unnecessary and inappropriate surgeries for endometriosis, as they entail a risk of recurrence and may negatively affect the ovarian reserve[401]. The only indication for immediate surgery are rare situations, such as suspicion of malignant lesions in the nature of the ovarian endometriomas, occlusion in bowel deep infiltrating endometriosis, and utereohydronephrosis in ureteral deep infiltrating endometriosis[402]. Government organizations, such as the Ministry of Health, and insurance companies should implement stringent regulations to avoid performing laparoscopic surgery as a primary therapeutic option for patients with infertility, and instead proceed with pharmaceutical treatments and/or ART.

The results for increased risk of miscarriage, ectopic pregnancy, preterm birth and emergency caesarean section among women with endometriosis, across all four control groups, all align with published literature[191,392,394,403–405]. Gestational diabetes, pregnancy related high blood pressure, and pre-eclampsia were not associated with endometriosis, which corroborates with previously published findings[191,394]. The

reason for increased risk of miscarriage and ectopic pregnancy among women with endometriosis is unknown, but may be associated to chronic inflammatory changes in the peritoneal fluid causing the proliferation of macrophages and phagocytic dysfunction, release of proinflammatory and angiogenic factors, or mechanical defects distortion of normal anatomy of the Fallopian tubes hindering tube-ovarian contact or ovaries embedded in adhesions hindering tube-ovarian contact[191,192,392,403,406]. Late pregnancy outcomes, such as pre-term birth and c-section may be due to altered endometrial receptivity resulting from chronic pro-inflammatory mediators, autocrine production of oestrogens and progesterone resistance, and alterations of the myometrium causing altered utero-tubal transport[187,191,395,407,408].

Endometriosis was significantly associated with asthma, eczema, and type 1 diabetes mellites, across all four control groups, which are consistent with published literature[6,179,199,200,374,408–410]. The reasons for the increased frequency of immunological comorbidities in endometriosis are unclear. Contributory factors that have been postulated include the involvement of female hormones interacting with immunological responses, local inflammation, and disruption of immunological processes in endometriosis and comorbid (auto)immune diseases, where endometriosis patients tend to be more susceptible to allergic manifestations and to allergy-related conditions such as asthma or atopic diseases than women without endometriosis[179,199,240,409,411]. Type 1 diabetes mellitus and endometriosis are associated with chronic inflammation triggered by overactivation of the immune response[6,373,375,412].

Our study demonstrated no association between endometriosis and metabolic disorders, such as diabetes mellitus type 2 and hypertension. However, in comparison to asymptomatic controls and population controls, women with endometriosis had a higher rate of cardiovascular disorder ($p=0.015$; $p<0.001$). This association was not significant when comparing it to symptomatic controls ($p=0.111$) and hospital controls ($p=0.122$), demonstrating that this may be associated to the symptoms and not endometriosis *per se*. However, it should be noted that the study sample is young, hence a longitudinal cohort study or a national registry, like the United Kingdom Biobank, would better be suited to measure disorders that are more prevalent in older populations, especially cardiovascular disorders[413–418].

Women with endometriosis had a greater risk of also having been diagnosed with uterine fibroids (symptomatic controls (p=0.003), asymptomatic controls (p=0.014), hospital controls (p=0.002) and population controls (p=0.051), possibly due to the shared common genetic variants associated to the pathogenesis of the condition with endometriosis, including the development of women's reproductive organs during the foetal period (WNT4), cell communication between oestrogenic and progesterone hormones (ESR1, GREB1) and stimulation of ovarian follicles (FSHB)[68,256]. Women with endometriosis had a greater risk of also having been diagnosed with Mullerian abnormalities ((symptomatic controls (p=0.012), asymptomatic controls (p<0.001), hospital controls (p=0.003) and population controls (p<0.001)). Mullerian abnormalities included obstructive Mullerian tube abnormalities or inadequate corpus luteal functions, both of which increase the risk of endometriosis in this study. This could be due to three basic mechanisms: 1) Mullerian anomalies may cause an increase in retrograde menstruation, 2) coelomic metaplasia may occur, and 3) developmental defect of differentiation or migration of the Mullerian duct system during embryogenesis[3,223,419–421]. While adenomyosis is an important gynaecological condition that is commonly concurrent with endometriosis due to similarities in clinical, genetic, biological, and molecular features, the diagnosis of this condition was not collected in the questionnaire and may be a limitation due to the coexistence of the conditions[32,422,423]. However, it was only recent that a diagnostic criterion was provided for adenomyosis (June 2020)[424], followed by an implementation of a new diagnosis code by the International Classification of Diseases 10th Edition (ICD-10) in January 1, 2022. Therefore, future studies should investigate the association of the coexistence between endometriosis and adenomyosis, and their heterogeneous phenotypes and symptomatology.

Strengths of our study include its large sample size, surgically confirmed incident cases, and the selection of multiple control groups facilitating analyses comparing the contribution of control group selection to the results. Restricting our endometriosis cases definition to incidental cases diagnosed by surgery or laparoscopy substantially decreased misclassification. The newly diagnosed incident cases that were recruited from the recruitment sites allowed for unbiased exposure information and accurate approximation

of relative risk by the odds ratio. If prevalent cases were studied, any association found between endometriosis and the exposure would not refer to the exposure itself but to its interaction with an observed effect of a risk factor[145,319]. However, the need for laparoscopy to diagnose or exclude endometriosis implies that all population-based observational studies carry a risk of including women with undiagnosed or asymptomatic endometriosis in population-based control group, resulting in indication biases. Additionally, women with infertility, or moderate/severe pain symptoms were over-represented in our patient sample because cases were enrolled in hospitals (which are typically more complex and severe cases of endometriosis), when compared to those with asymptomatic or mild symptoms that avoid seeking care from a gynaecologist. Therefore, the case group selected is liable to differ from the general population. Until a sample test that may be safely applied at a population level becomes available, care with study design is needed to reduce ascertainment bias, with critical care on the selection of the control group.

The control group was recruited from population and hospitals/clinic sites from which the cases were enrolled. Although controls did not report a prior endometriosis diagnosis, some were likely to have undiagnosed endometriosis, meaning our estimates may be affected by misclassification of endometriosis among the controls. This would have driven the associations observed to the null hypothesis of no difference, rather than creating spurious associations. Choosing an appropriate control group for endometriosis cases is complex, and multiple groups sampled from population and hospital based settings as we used here allow the testing of sensitivity of results to control group choice[11]. Nevertheless, the prevalence of undiagnosed moderate-severe endometriosis in the general population group is likely to be low (<2%), resulting in a very small number of cases being misclassified as controls, especially if they were screened for moderate to severe pelvic symptoms[11]. Partly to address this issue, we limited our case group to women with definite endometriotic disease, and it is unlikely that participants with this extent of disease were included in the control group. In addition, the inclusion of multiple control groups, including surgically screened controls, allowed the examination of effect size modulation based on control group definition. To further address the issue, we stratified the controls to asymptomatic controls and symptomatic

controls. The asymptomatic control group allowed investigation of factors associated with symptoms with or without endometriosis. The separate symptomatic control group allowed us to investigate whether observed associations relate to endometriosis *per se*, and not the presence of symptoms. We conducted an additional sensitivity analysis to quantify hidden bias (such as the possibility of endometriosis cases in the whole control group) between distributions of key exposures (age, state of residence, education, work status, smoking status) from the symptomatic controls with laparoscopic confirmation vs. symptomatic controls with no surgical confirmation. We found no change in our effect estimates, suggesting that the potential presence of undiagnosed cases in our control group had little impact on the results of the analyses we present and demonstrates that the use of a population and hospital-based case-control study improves the generalizability of multiple outcomes related to a specific exposure that are representative of the general population. Additionally, the large sample size may provide more power to detect the effect sizes reduced by misclassification.

Although we tried to limit recall bias using a highly structured questionnaire, there is potential for exposures to have been differentially recalled, leading to an inflation of effect sizes for these factors. Differential recall may also be present based on symptom presentation; however, the selection of incidental cases limited the bias. For example, women diagnosed because of infertility may recall and report the onset of symptoms differently that women experiencing severe pelvic pain (Recall bias). Covariate status was reported retrospectively and thus subject to recall bias and reverse causation. However, every effort was made to measure and adjust for all factors thought to be related to risk of endometriosis diagnosis and exposures of interest. The available data did not allow exploration of results by endometriosis location (peritoneal, ovarian, rectovaginal). Misclassification bias may also be associated with comorbid disease reporting, although again the recruitment of incident cases who completed the questionnaire prior to their surgery would have reduced the likelihood of women with endometriosis to differentially over-report other conditions.

The findings presented in this chapter provide an informed understanding of the factors associated with endometriosis in Arab women, whilst considering the heterogenous array of religious beliefs, cultural norms, and traditional expectations in the community. While there were no major differences in endometriosis clinical presentation between Arab women and women of other ethnic groups, the primary presenting symptoms (pain and infertility) of this condition is heavily influenced by psychosocial factors and sociodemographic factors[425–427]. Psychosocial predictors of symptoms of endometriosis may impact menstrual cycle characteristics, anthropometry, severity and frequency of multiple pain symptoms, and mental health disorders. Culturally there are also differences in health care services, such as differences in health insurance systems, availability to specific medications or surgical procedures, expertise of surgeons available, referral trends for sub-specialists, diet, and other environmental factors. Together, all these factors influence clinical care and further research is required. Large, geographically diverse, multidisciplinary collaborative efforts to study endometriosis will aid to disentangle the complex associations and risk factors and will have important implications in the management and care of endometriosis patients that are culturally specific. Further research should identify symptom control strategies that target those pathways to improve the outlook for affected women. Our study will enable the establishment of communities for ongoing support and intends to build on the strength of women-centred networks for Arab women.

Chapter 4. Health-related quality of life, diagnostic delay, and work productivity impairment

4.1 Introduction

Health-Related Quality of Life (HRQoL), a patient related outcome measure, is a multi-dimensional dynamic concept that estimates the psychosocial impact of a condition. Chronic disorders, like endometriosis, have a negative effect upon HRQoL due to its significant impact on major life activities, such as work, school, daily activities and self-care[14,128–131]. A HRQoL instrument aims to measure the biological, physical, psychological, emotional and social functioning in a single metric[347]. The instrument employed in this study to assess the impact of endometriosis on HRQoL is the Short Form 36 version 2 (SF36v2)[347]. The SF36v2, originally developed from the Medical Outcome Study, is a validated and reliable discriminative tool that represents the operational indicators of health, providing scores on eight areas of functioning and well-being, and two broad areas of subjective well-being, namely physical and mental health[346,354]. Quality of life is affected in a complex way by the person's physical health, psychological state, social relationships, personal beliefs, and sociocultural factors[428]. HRQoL and its association with endometriosis in Arab women needs to be understood in the context of personal and culturally centred beliefs within the realms of their lives as young adolescents and adults.

Due to the chronicity of endometriosis, the complexity of the disease aetiology, and the interference in women's reproductive capacity, endometriosis has been reported to be associated with considerable physical and mental morbidity[14,15,131,429–431]. The reduction of HRQoL among women with endometriosis leads to a significant impact in their daily activities, economic impact due to reduction or loss of work productivity and increase cost of treatment and hospitalization, relationships with partners, fertility planning, and education and work[429,430,432,433]. The Global Study of Women's Health (GSWH), a cross-sectional study conducted in 10 countries among women undergoing their first laparoscopy for symptoms suggestive of endometriosis, demonstrated a negative impact of endometriosis on HRQoL and overall work productivity loss[14]. Although the negative impact of endometriosis on HRQoL has been established, in mostly Western populations, no studies have been conducted in women of Arab ancestry of the association

of HRQoL with endometriosis-related symptom presence, severity and disease stage. Collecting comprehensive data from all patient populations is critical to understanding if there are intrinsic differences in the pathophysiology of endometriosis, in terms of cultural factors, race, genetics, environmental and socioeconomic factors.

Women who experienced longer diagnostic delays for endometriosis report greater impairment in terms of HRQoL[14]. The current clinical requirement of surgical visualization means diagnostic delays of endometriosis from symptom onset average 7 years[6,14]. Adolescent girls who suffer from the symptoms of endometriosis delay seeking medical attention by an average of 4.6 years, and by the time they seek medical attention it takes on average another 4.7 years until they are diagnosed[434]. Early diagnosis is crucial for the effective treatment and prevention of disease progression. Given the unique socio-cultural factors that may influence a delay of diagnosis among Arab women, the diagnostic delay, and its impact on HRQoL will be investigated.

Although the impact of endometriosis on mental health and psychological well-being has been investigated in several studies, there are no studies that have investigated the impact of endometriosis on psychological disorders among women of Arab ancestry. Mental health is one of the most neglected public health issues in the Middle East[270,271]. Poor mental health outcomes among Arab women have been associated with strong patriarchal cultures, limiting the autonomy for women and contributing to overall disease burden[259–261]. Hence, in the context of this thesis it is important to investigate how mental health is impacted in Arab women with and without endometriosis pathology.

Work productivity loss and activity impairment have been reported in women with endometriosis. The GSWH study investigated the annual cost of endometriosis per women, amounting to €9579 (95% CI: €8559–€10599), with the inclusion of direct health care costs, direct non-healthcare costs, and indirect costs. The total annual societal burden of endometriosis associated symptoms has been estimated from €0.8 billion in Denmark to €49.6 billion in the USA[429]. Most previous reports of the economic cost of endometriosis-associated work productivity impairment related to geographically limited populations

focusing on the western region, where healthcare accessibility and cost of treatment differs from the Middle East. A reduction in productivity and job loss, along with the high cost of treatment and care, results in an economic burden on the patient and family's life, as well as on government spending, as work productivity can also adversely affect the gross domestic product (GDP) of countries and threaten sustainable development. Loss of work productivity and activity impairment due to endometriosis associated symptoms leads to a lower HRQoL[14].

Physical activity has been hypothesized to be a protective risk factor to endometriosis, mainly due to the reduction of bioavailable oestrogen, insulin resistance, and inflammatory cytokine markers[180,435]. While studies have demonstrated that regular exercise has been associated with 30-80% reduction in risk for endometriosis, in comparison with women who did not regularly exercise, there are no studies that investigated the impact of physical activity among Arab women. The prevalence of physical inactivity measures between 30-80% in the Middle East and fails to reach the guidelines for sufficient physical activity (an equivalent combination achieving 500 METs-minutes per week)[436]. Hence, investigating the impact of physical activity in this study will allow us to examine the social determinants of physical activity, with special attention to those related to gender and cultural factors.

Algorithms for the calculation of the summary scores have been created by the SF36v2 developers[347,354], which involve the factor analysis of normative datasets from the USA general population. It has been suggested that the US algorithms may be utilized for comparability and simplicity when normative data in different populations are not available[437]. At present, no normative data are available for the Middle Eastern population, specifically the United Arab Emirates, the country where this study has been conducted. As the designers of the SF36v2 have themselves stated, the problem with scale scores is that they do not lend themselves to easy interpretation. This is especially true where items, or domain scores, are weighted, as is the case with the physical and mental component scores. There is an increased interest in incorporating these assessments in research and clinical applications and policymaking, hence, for many countries of different cultures it is necessary to adapt and translate these measures into different languages, and

subsequently investigate their equivalence and measurement properties. Arab countries are lagging considerably behind in this domain, not only in the development of tools, but also in terms of translation of existing measurement tools. We generated normative values from this study to investigate the impact of endometriosis and endometriosis-associated symptoms on HRQoL, work productivity, activity impairment and physical activity in Arab ancestry women. Furthermore, we estimated diagnostic delay of endometriosis from onset of symptoms to laparoscopic diagnosis, as well as the prevalence of psychological co-morbidities.

4.2 Objective

The impact of endometriosis on HRQoL, principally through its symptoms, has been documented in mainly Western population health data. The influence of factors, such as clinical factors, endometriosis phenotype and symptom severity, the diagnostic delay, psychological disorders and work productivity and daily activity impairment on HRQoL in women of Arab ancestry in the Middle East remains unexplored. This chapter investigates the impact of endometriosis on HRQoL in Women of Arab ancestry, by focusing on the following key research questions:

1. Normative data of the SF36v2 questionnaire
    - What are the population normative values for women of Arab ancestry within the reproductive age span (18-50 years)?
    - Are the population norms valid to use in this study, as measured by the instrument's internal consistency, reliability, and validity?
    - What is the difference between the PCS and MCS scores derived from Middle Eastern and USA normative values?
2. Health-Related Quality of Life
    - To what extent is HRQoL affected by endometriosis?

- Is the impact of endometriosis on HRQoL explained by the symptoms of endometriosis?
- Does the severity of endometriosis-related symptoms impact HRQoL?
- Does the stage of endometriosis impact HRQoL?

3. Diagnostic delay
    - What is the diagnostic delay of endometriosis?
    - Is the diagnostic delay of endometriosis explained by marital status or other endometriosis-related factors?
    - Does the diagnostic delay of endometriosis differ based on endometriosis stage?
    - Is the impact of endometriosis on HRQoL explained by diagnostic delay?
4. Psychological disorders
    - What is the association of depression and anxiety with endometriosis, in comparison to symptomatic and asymptomatic controls?
5. Work productivity and daily activity impairment
    - Is work productivity affected by endometriosis? What is the nature and size of the impact?
    - What are the key drivers of endometriosis-related symptoms on work productivity and daily activity impairment?
    - What is the relationship between HRQoL and work productivity and daily activity impairment?
6. Physical activity
    - What is the prevalence of physical activity in the study?
    - Is there an association between physical activity and endometriosis?

4.3 Methodology

4.3.1 Study participants

4.3.1.1 Normative data - sample population

The normative data were collected from women attending public health seminars in the UAE, between August 2018 and August 2019. All participants from the population-based control set were included as part of the normative study sample. As discussed in Chapter 2.2-2.3 (Methods), sampling was performed randomly at six different locations, that consisted of individuals from the city (urban areas) and village (rural areas) across different districts in the UAE. This sample would allow us to detect a 10-point difference in SF36v2 scores between groups with a fixed norm (a general population), assuming two-sided type I error of 5%, with 80% power (sample size required is 800 people).

Admixture analysis has shown consistent patterns of the ethnicities and populations of different parts of the Middle East, demonstrating that the contemporary population of the UAE is a suitable sampling frame from which to conduct representative epidemiological and genetic studies of the Arab population[238,324]. Participants were random women attending public health seminars with an aim to reach a representative population sample that was compared to the most recent census published in the country in 2018[376,438]. In addition, the population-based sites recruited participants in the same catchment area as the case/control recruitment sites of this study.

All women who attended the seminars were recruited, using the following criteria: 1) premenopausal women, 2) aged 18-50 years, 3) self-reported ethnically Arab, 4) willing to give an informed consent form for participation. Women who were illiterate and were unable to comprehend and provide informed consent were excluded from the study. Ten percent (10%) of the respondents had a repeatable accuracy check by filling in the questionnaires, a week later. No missing data was imputed for normative data. Completed questionnaires were obtained from 841 of 884 women originally contacted, giving a response rate of 95.2%.

4.3.1.2 Study population

The study population is explained in detail in Chapter 2.3. Briefly, 2,610 participants were recruited, using the following inclusion criteria: 1) premenopausal women, 2) aged 18-50 years, 3) self-reported ethnically Arab, and 4) no previous diagnosis of endometriosis. Exclusion criteria were: 1) pregnant women, 2) women with special needs, and 3) women who were illiterate, and were unable to comprehend and provide informed consent.

Endometriosis was diagnosed in women scheduled to undergo a diagnostic and/or therapeutic laparoscopy or laparotomy for any indication (pelvic pain, subfertility, pelvic mass, adnexal torsion, infection or to be sterilized) by visual confirmation as is the current golden standard[19,377], and classified into four grades, based on the revised American Society for Reproductive Medicine (rASRM)[16]. The control group comprised three distinct groups: (1) hospital controls who had undergone laparoscopic surgery showing that they were endometriosis-free, (2) clinic controls who were screened using therapeutic/diagnostic tests (such as monitoring for other gynaecological conditions or pre-marital screening, ovulation monitoring, cosmetic gynaecology, reproductive cancer screening and/or gynaecological health check-up), (3) population controls recruited during organized public seminars on women health issues. The control groups were sub-divided into symptomatic and asymptomatic controls, to explore sensitivity of results to control definition.

4.3.2 Questionnaire and data collection tool

Participants completed the following standardized, validated questionnaires and instruments: Short Form-36 version 2 (SF36v2)[348,356] questionnaire, the World Endometriosis Research Foundation EPHect (WERF-EPHect) minimum clinical questionnaire (EPQ-M) version[338], and Work Productivity and Activity Impairment (WPAI)[349,439] questionnaire. The SF36v2 was used to measure HRQoL and is constructed to measure concepts relating to functional health, well-being, relative burden of the disease, objective and subjective ratings, and self-evaluation of general health status[348,356]. WERF-EPHect questionnaire (EPQ-M) were used to collect demographic information, measure the presence and severity of symptoms, risk

factors, phenotypic profile and physical activity assessment[338,351]. WPAI was used to measure absenteeism and presenteeism in employed women, and the impact of symptoms on activities[349,439]. The WERF-EPHect questionnaire included four pain measurement tools: Short Form McGill pain questionnaire[342,350], a visual analogue scale for pain measurement[343,351], a numerical rating scale for pain score[332,351], and a pain catastrophizing scale[344,352]. For all the questionnaires and tools, we have used the Arabic translated versions that have been validated and are publicly available. However, for the EPHECT EPQ-M questionnaire, translations to the Arabic language, validated using the forward-backward translation method, of the questionnaires were utilized.

Data were collected and managed in a web-based research electronic data capture (REDCap)[361] database, with 10% of the questionnaires entered by two independent data processers to find discrepancies. In addition, the following basic anthropometric measurements were taken: 1) weight and height using calibrated digital scaling instruments, and 2) waist and hip circumference using the WHO guidelines[358].

4.3.3 Analyses

4.3.3.1 Health related quality of life

The SF36v2 questionnaire was incorporated into the study questionnaire to measure HRQoL. The SF36v2 questionnaire includes 36 items clustered to measure eight domains: physical functioning (10 items), physical role limitation (4 items), body pain (2 items), general health perception (5 items), energy/vitality (4 items), social functioning (2 items), emotional role limitation (3 items), mental health (5 items). Two summary scores (physical health score and mental health score) were also calculated.

Quality control assessment of the SF36v2 *in this study sample*

The study used the recommended standard scoring algorithms based on the developers' guidelines and the International Quality of Life Assessment (IQOLA) Project[440–446]. The mean and standard deviation (SD) for responses to each item and scale were calculated. General population norms provide a better basis for comparisons across scales. Detailed normative data was collected after undergoing quality control

assessments. The measurement properties of the Arabic versions of these instruments were evaluated based on quality criteria suggested by the developer, which includes: (1) reliability (2) internal consistency, (3) item discriminant validity, (4) floor and ceiling effects, (5) reproducibility and responsiveness, and (6) interpretability.

Reliability measures the extent to which the scales give consistent or accurate results and was assessed by Cronbach's alpha. Internal consistency is an inter-item correlation statistic to measure reliability correlation between items on a scale. Values greater than 0.70 indicate that items on a dimension are correlated, and the scale is tapping an underlying single dimension on the questionnaire with reliability and internal consistency. Item discriminant validity was assessed to measure the extent to which the questionnaire supports pre-defined hypotheses by determining the extent to which scores on different dimensions reflected the expected distribution of the condition for and between groups of the factor-analytic studies. The validity (r=0.40 or greater) was obtained to measure comparisons to other measures per dimension. The percentage of people with scores at the ceiling (percentage of subjects with a score of 100) and floor (lowest level) were calculated for each scale. On the scale level, ceiling and floor effects should be less than 20% to assume that the scale is capturing the full range of potential responses in the population. Reproducibility and responsiveness were measured based on the responsiveness score (>80%). Interpretability was measured based on the rotated principal components using varimax (orthogonal) rotation.

Scale level validity would be supported if the scales measuring mental health (MH, RE, and SF) are substantially more correlated with each other than with other SF36v2 scales. Similarly, scales measuring physical health (PF, RP, and BP) should have higher correlation with each other than with other SF36v2 scales. Principal component analysis with varimax rotation was carried out on correlation among scales to compare the factorial structure of data with that obtained from the USA instrument. The hypothesized physical and mental domains of health underlying the SF36v2 were identified on factor analysis. The validity of the SF36v2 would be further supported if the PF, RP, and BP scales and MH, RE, and SF scales

loaded on both domains of health respectively, and if the GH and VT scales loaded on both domains. The average score from a scale is substantially correlated if the factor loading is greater than 0.7, moderately correlated if the factor loading is between 0.3 and 0.7, and slightly correlated if the factor loading is less than 0.3.

Analysis and interpretation of the SF-36 questionnaire

The SF36v2 questionnaire was analysed as per the developers guidelines[347,355,447–450]. The raw scores of each of the eight SF36v2 dimensions were constructed using the Likert method of summated ratings by subtracting it to the lowest possible raw score, dividing the total amount by the raw score range and multiplying it by 100 to achieve the transformed scale. Each of the eight domains transformed scale was standardized using a z-score transformation. Z-scores were calculated by subtracting each individual's sub-scale score by the total normative populations' means and dividing the difference by the standard deviation of the normative sample. The subscale factor score coefficient for physical component summary (PCS) and mental component summary (MCS) were aggregated using factor analysis through principal component analysis and orthogonal rotation of subscale scores that were standardized. The PCS correlates with physical functioning, role-physical and bodily pain, and the MCS correlates with mental health, role-emotional, and social function. Vitality, general health, and social functioning correlate with both components. T-scores linear transformation was conducted by cantering the obtained PCS and MCS sums to get a mean of 50 and a standard deviation equal to 10[347,354].

In summary, for each dimension, item scores were coded, summed, and transformed on a scale from 0 (worst possible health state measured by the questionnaire) to 100 (best possible health state). Means and standard deviations for each of the eight-dimension scales were presented. Two standardized summary scores were calculated: physical component summary (PCS) and mental component summary (MCS).

4.3.3.2 Diagnostic delay

Diagnostic delay of endometriosis was quantified by averaging the self-reported earliest age of onset of symptoms (dysmenorrhea, chronic pelvic pain, dyschezia, dysuria and infertility) and age of first contact seeking gynaecological consultation, and then subtracting from this the age at surgically confirmed diagnosis of endometriosis. Age at symptom onset was defined as the age at which the participant first noted any of the symptoms for which she underwent laparoscopic surgery. Diagnostic delay was stratified based on civil status (single vs. married women). The association between diagnostic delay and HRQoL, and endometriosis staging (classified according to the rASRM four-stage system), was also investigated.

4.3.3.3 Endometriosis symptoms, risk factors and phenotype

The WERF EPHect minimum clinical questionnaire (EPQ-M) version[338] was used to collect the following information: demographic data, pelvic pain severity, presence of endometriosis-associated symptoms, endometriosis disease stage, presence of psychological comorbidities, diagnostic delay and physical activity. Endometriosis associated symptoms were defined as: 1) women who experienced chronic pelvic pain, dysmenorrhea, dyspareunia, dyschezia, dysuria for at least six months, and a numerical rating scale (NRS)[331,332] score greater than 4[333]; and/or 2) women who were infertile defined as having had unprotected intercourse in the fertile phase of the menstrual cycles for at least 12 months[334]. Pelvic pain severity was recorded using the numerical rating scale[332] (score from 1-10), and was reported for dysmenorrhea and chronic pelvic pain.

Disease stage was classified according to the rASRM four-stage system using the minimal WERF EPHect surgical form (EPS-M) and abstracted from the operative notes within the medical records. Participants were asked to report demographic information (age, marital status, education level and employment status), past medical history and lifestyle factors (physical activity). Psychological disorders included receiving a clinical diagnosis for anxiety and/or depression. Physical activity was assessed by assigning a metabolic equivalent (MET) score to each of the participants' reported recent physical activity: walking, jogging, running, bicycling, racquet sports, lap swimming, calisthenics, and other aerobic activity.

4.3.3.4 Work productivity and activity impairment

The Work Productivity and Activity Impairment Questionnaire (WPAI)[349] is a validated instrument that measures the effect of symptoms and disease on absenteeism, presenteeism, work productivity loss and activity impairment. Work productivity is measured on a 0 ("symptoms had no effect on work") to 10 ("symptoms completely prevented working") scale; a similar rating scale is used for other daily activities. The proportions of employed women in the study population and the reasons for not being in paid work at the time of the study are described. The study population is also described in terms of the number of weekly hours women were contracted to work and number of weekly hours they worked. Absenteeism was calculated as [hours missed due to symptoms/(hours missed due to symptoms + hours worked)] expressed as a percentage. Presenteeism was calculated as [reduced productivity while working] expressed as a percentage. Overall productivity loss was calculated as [((hours missed due to symptoms + (percent reduced productivity while working x hours worked))/(hours missed due to symptoms + hours worked)] x 100. Mean percentage values for these dimensions were compared for working women (employed/self-employed) across endometriosis cases and symptomatic controls.

4.3.4 Statistical analysis

Comparisons were made between the following two groups: 1) women with endometriosis vs. symptomatic control women; and 2) women with endometriosis vs. asymptomatic control women. This allowed us to investigate whether the quality-of-life score is driven by the endometriosis-related symptoms or endometriosis *per se*.

4.3.4.1 Missing values

Missing values were dealt with by listwise deletion where any observation missing a value for a specific variable was dropped completely in the analysis of that variable. The missing data were not substituted for the normative data.

However, when analysing the complete dataset, the missing values in the SF36v2 dimensions were imputed as recommended by the developer[347,354]: if 50% or more items in one dimension were completed, the mean value of the total completed items were imputed in each missing value; if more than 50% of the items were missing, the dimension score was excluded. In our survey, the item response rate of the 36 items in the SF36v2 was 99.77%.

4.3.4.2 Statistical methods

The data were analysed using Statistical Package for Social Science (SPSS) version 20 (SPSS Inc., Chicago, IL) and R (Version 3.4.1). The descriptive variables were verified using frequency analysis. Chi-square and Fisher's exact test were used to study categorical variables. Independent sample t test or nonparametric Mann-Whitney U test were used to study continuous variables. Kruskal-Wallis or ANOVA tests were used to verify the association between the HRQoL domains and the clinical aspects of endometriosis. The chi-squared test was also used to associate the profile of the participants with the staging of endometriosis. Spearman correlations were calculated to establish bivariate relationships between pain severity and HRQoL scores. Multivariate linear regression models tested multivariate relationships between endometriosis-associated symptoms (dysmenorrhea, chronic pelvic pain, dyschezia, dysuria and infertility) and HRQoL scores. Multiple logistic regression analysis was used to study associations between depression and anxiety within the endometriosis and control groups. All regression models accounted for age (continuous), current BMI (underweight, normal weight, overweight, obese), civil status (married, not married), educational status (up to high school level, up to postgraduate level), and work status (working, not working). The significance level adopted for all analyses was $p \leq 0.05$.

4.4 Results

4.4.1 Normative data

Completed questionnaires were obtained from 841 of 884 women originally contacted from the public health seminars that composed the population control group, giving a response rate of 95.1% with a high

degree of acceptability. Table 4.1 summarizes the socio-demographic factors of the normative study population with the 2018 UAE census data.

Most of the women were married (81.4%, n=685), with a post-secondary education (57.3%, n=482) and were employed (63.0%, n=530). To ensure the sample was representative, its composition was compared with the 2018 annual census data in the UAE, which were shown to mirror closely to the characteristics of the general population (married women, 77.1%; post-secondary education, 56.2%; employed, 68.9%)) [376].

Table 4.1. Sociodemographic characteristics of the normative study population in comparison to the 2018 UAE census health data.

	Population-Based Control Sample (n=841)	UAE Census Data	*p*-value*
Age			
18-27	229 (27.2%)	835 (21.3%)	0.322
28-36	242 (28.8%)	1479 (37.9%)	
37-50	370 (44.0%)	1588 (40.7%)	
BMI			
≤18.5	9 (1.1%)	90 (1.1%)	
>18.5 to ≤ 24.9	347 (41.3%)	2784 (34.0%)	0.524
>24.9 to ≤ 29.9	292 (34.7%)	2808 (34.3%)	
>29.9	193 (22.9%)	2505 (30.6%)	
Education Level			
Primary**	11 (1.3%)	238 (5.9%)	
Pre-Secondary	30 (3.6%)	187 (4.6%)	
Secondary	197 (23.4%)	885 (21.8%)	0.119
Post-Secondary	121 (14.4%)	475 (11.7%)	
Bachelors	437 (52.0%)	2214 (54.7%)	
Doctorate	45 (5.4%)	45 (1.1%)	
Employment			
Employed	402 (47.8%)	1774 (43.8%)	NA
Self-Employed	128 (15.2%)	NR	
Not Employed	311 (37.0%)	NR	
Marital Status			
Single	113 (13.4%)	399 (9.9%)	
Married	685 (81.5%)	3460 (85.5%)	0.557
Divorced	14 (1.7%)	63 (1.6%)	
Widowed	29 (3.4%)	123 (3.0%)	
Residential Status			
Abu Dhabi	222 (26.4%)	4999 (34.0%)	
Dubai	234 (27.8%)	5472 (37.3%)	
Sharjah	174 (20.7%)	2319 (15.8%)	
Ajman	57 (6.8%)	797 (5.4%)	0.227
Umm Al-Quwain	22 (2.6%)	161 (1.1%)	
Ras Al Khaimah	110 (13.1%)	578 (3.9%)	
Fujairah	22 (2.6%)	358 (2.4%)	

NR: Not Reported; NA: Not Applicable

*Sample weighting was carried out to investigate differences between population-based normative sample and UAE census data.

**While the participants did not have schooling, there were literate to provide consent and complete the questionnaire. These participants are often older women from the Bedouin populations. However, they were well versed in the Arabic language, as it is the language of their religion.

4.4.1.1 Data quality evaluation

The eight dimensions were calculated using algorithms recommended by the developers[440–446]. Several measures and procedures were implemented to evaluate the quality of data obtained from the surveys, including completeness of data, outlier data, descriptive statistics, component scores, scale reliability, internal consistency, discriminant validity, and convergent validity, presented in Table 4.2. Data quality evaluation, such as reliability, item internal consistency and item discriminant validity, was conducted to determine whether the normative data could be utilized as a normative sample for this study population.

To test reliability, summary scores was estimated using Cronbach alpha coefficient, and alpha values exceeding the 0.70 level were considered satisfactory, where all dimensions in this study exceeded the recommended value (0.75-0.83). Internal consistency, an inter-item correlation statistic to measure correlation between items on a scale was conducted. Values greater than 0.70 indicate that items on a dimension are correlated with internal consistency. As demonstrated in Table 4.2, an internal consistency coefficient was calculated for each subscale and were found to be very acceptable, ranging from 0.72-0.83. Item discriminant validity (r=0.40 or greater) was assessed to measure the extent to which the questionnaire supports pre-defined hypotheses by determining the extent to which scores on different dimensions reflected the expected distribution of the condition for and between groups of the factor-analytic studies. In this study, the validity score ranged from 0.51 to 0.88, demonstrating that all the scores passed the score deemed acceptable. Ceiling effect and Floor effect was also noted to measure consistency and align with the developers' guidelines.

Factor analysis of the eight SF36v2 scales yielded two-factor rotated principal components corresponding to the hypothesized physical and mental domains of health underlying the SF36v2. Table 4.2 shows the Physical Functioning scale (PF, RP, and BP) loading most on the "physical" component and least on the "mental component", and vice versa with the mental functioning (MH, RE, SF). The dimensions VT and GH had similar correlations to the physical and mental health components.

Table 4.2. Normative values, reliability coefficients, validity values and factor analysis of the SF-36-dimension scores.

	Normative Values					Reliability		Validity			Rotated Principal Component	
Dimension	**Item**	**Level**	**Mean**	**SD**	**95% CI**	**Cronbach's alpha Coefficient**	**Item Internal Consistency**	**Item Discriminant Validity**	**Floor Effect**	**Ceiling Effect**	**Physical**	**Mental**
PF	10	21	76.03	20.95	1.58	0.83	0.81	0.83	1.9	10.1	0.77	0.41
RP	4	5	70.94	22.92	1.85	0.82	0.83	0.88	3.7	14.7	0.76	0.46
BP	2	4	67.39	22.24	1.53	0.83	0.77	0.53	1.8	6.9	0.68	0.54
GH	5	11	60.29	22.87	1.37	0.79	0.80	0.64	1.0	1.7	0.59	0.55
VT	4	21	51.93	17.27	1.05	0.76	0.74	0.82	1.4	2.1	0.54	0.58
SF	2	21	73.11	23.03	1.62	0.82	0.83	0.79	0.88	13.3	0.51	0.71
RE	3	9	65.52	24.23	1.53	0.75	0.72	0.75	1.8	9.8	0.43	0.69
MH	5	26	63.31	20.41	1.05	0.82	0.74	0.51	0.5	1.9	0.41	0.77

PF: Physical Function; RP: Role Physical; BP: Bodily Pain; GH: General Health; VT: Vitality; SF: Social Functioning; RE: Role Emotional; MH: Mental Health; PCS: Physical Component Score; MCS: Mental Component Score

Since all the participants were female, it was not necessary to stratify by sex, and information on social class was not provided. Table 4.3 shows the normative data in the form of means and standard deviation, broken down by age. For the totality of SF36v2 scales, dimension and domain mean score were all in the expected directions and worsened as the age group increased. Hence, age had a significant impact on the perceived health status, and the probability of having good health decreased with age.

Table 4.3. Mean (SD) scores for the eight dimensions and two summary scores of SF36v2 by age group.

	Age Group (Years)				
Dimension	**18-28 (n=214)**	**29-35 (n=220)**	**36-40 (n=204)**	**41-50 (n=203)**	***p*-value**
PF	85.74 (16.07)	77.35 (21.64)	68.72 (25.82)	65.82 (23.60)	**<0.001**
RP	84.52 (17.28)	73.68 (24.49)	65.77 (28.57)	56.97 (30.81)	**<0.001**
BP	78.92 (14.93)	70.25 (20.58)	65.54 (22.62)	58.82 (27.04)	**<0.001**
GH	70.83 (14.47)	63.62 (18.08)	57.37 (21.65)	52.16 (21.72)	**<0.001**
VT	60.96 (13.07)	54.85 (12.66)	48.61 (16.13)	46.92 (16.89)	**<0.001**
SF	86.57 (14.72)	79.53 (18.12)	65.86 (25.44)	60.78 (27.71)	**<0.001**
RE	76.58 (16.36)	72.14 (15.78)	58.59 (24.75)	57.33 (26.73)	**<0.001**
MH	74.65 (10.83)	69.53 (11.77)	60.19 (15.06)	57.27 (18.34)	**<0.001**
PCS	53.86 (6.39)	50.06 (9.64)	49.23 (11.64)	46.55 (10.44)	**<0.001**
MCS	55.31 (6.24)	52.89 (6.09)	46.19 (11.62)	45.25 (11.77)	**<0.001**

PF: Physical Function; RP: Role Physical; BP: Bodily Pain; GH: General Health; VT: Vitality; SF: Social Functioning; RE: Role Emotional; MH: Mental Health; PCS: Physical Component Score; MCS: Mental Component Score

4.4.1.2 Comparison of the summary scales

The methods used to construct the PCS and MCS for use in the Middle East, were identical to those used by the developers[354], and the comparison of the results, in the form of a frequency distribution, from the eight dimensions and two scoring (PCS and MCS) are reported in Table 4.4. As demonstrated, the normative mean values (Z-scores) for all eight dimensions were lower than the USA sample. The mean value summary scores (Z-scores) were used to convert the subscales to summary scores, then multiplying

them by the coefficient for each subscale. When a large Z-score is multiplied by a lower coefficient it deflates the scale. Hence, by utilizing the USA normative population scores (a higher Z-score than the normative values representative of the population), this will lead to a lower estimate of the HRQoL scores.

Principal components analysis was used to test the generalizability of the two-dimensional SF36v2 model using identical methods across this study and the USA normative study. Principal components analysis gauges the congruence between the hypothesized physical and mental health constructs and the SF36v2 scales used to measure demonstrated in Table 4.4 (PCS and MCS). While the factor scores analysis of the PCS and MCS scores differed slightly between both populations, they followed the same direction of effect, which is expected with the varimax method or principal component analysis. It should be noted that the USA sample included the values from participants from 18 years to 70 years of age[354], however the Middle East sample included values from 18 years to 50 years of age. However, while age inversely correlates to mean dimension scores, the USA sample still demonstrated healthier mean dimension scores across all dimensions.

Table 4.4. Mean (SD) and factor score coefficients used to derive the weighted PCS and MCS summary scale scores in the USA and the Middle East population.

	Middle East Sample				USA Sample			
Dimension	**Mean**	**SD**	**PCS**	**MCS**	**Mean**	**SD**	**PCS**	**MCS**
PF	74.03	20.95	0.52	-0.25	81.47	24.60	0.42	-0.23
RP	70.94	22.92	0.55	-0.26	77.77	36.20	0.35	-0.13
BP	67.39	22.24	0.10	0.10	73.59	24.25	0.32	-0.10
GH	60.29	22.87	0.10	0.05	70.61	21.50	0.25	-0.02
VT	51.93	17.27	-0.05	0.16	58.43	21.47	0.03	0.24
SF	73.11	23.03	-0.06	0.27	81.54	23.74	-0.01	0.27
RE	65.52	24.23	-0.18	0.11	79.47	34.43	-0.19	0.43
MH	63.31	20.41	-0.38	0.66	73.25	18.68	-0.22	0.49

PF: Physical Function; RP: Role Physical; BP: Bodily Pain; GH: General Health; VT: Vitality; SF: Social Functioning; RE: Role Emotional; MH: Mental Health; PCS: Physical Component Score; MCS: Mental Component Score
Extraction Method: Principal Component Analysis.
Rotation Method: Varimax with Kaiser Normalization.

Country-specific algorithms transform scores to have the same mean and standard deviation in each country (50 and 10), hence there are differences when using summary scores from the USA population in the Middle Eastern dataset (Table 4.5). For both the Middle East and the USA weighted PCS and MCS the mean is set to 50 (SD 10) in their respective populations. It can be seen from the percentile points that the PCS and MCS scores are not normally distributed but skewed for a lower-than-average health status when using the

US statistic for the Middle Eastern population results. Due to the higher Z-value (mean and SD of the eight-dimension scores) and different T-scores in both populations, utilizing the USA standardized scores gives a lower PCS and MCS score for the normative population (PCS: 48.29, MCS: 45.05), in comparison to the Middle East standardized scores (PCS: 49.52, MCS: 49.63), where the latter is closer to the weighted norm scores set to 50. Additionally, paired t-tests indicated significant difference between the two methods of weight and calculating the summary scores ($p<0.001$ for PCS; $p<0.001$ for MCS), demonstrating that the two groups greatly differ. Evidence presented here suggests that different results are obtained between the PCS and MCS derives score from the Middle Eastern and USA population to weight the summary scores, and there are advantages of adopting country specific weights from a higher-order factor analysis of the SF36v2. For this study, the population normative values of the Middle Eastern region, detailed in this section, were utilized for disease specific comparisons.

Table 4.5. Frequency statistic and component measure scores as quartile levels in the Middle East and USA sample.

	Middle East Sample		USA Sample	
	PCS	**MCS**	**PCS**	**MCS**
Mean	49.52	49.63	48.29	45.05
Median	51.69	51.28	50.72	47.39
Standard Deviation	11.83	13.56	13.62	10.56
Minimum	21.83	23.56	23.62	20.56
Maximum	67.06	65.85	62.84	60.17
Percentiles				
25	46.03	45.78	44.25	41.35
50	51.69	51.28	49.27	47.39
70	55.35	55.32	53.74	50.78

4.4.2 Health-related quality of life

Compared with symptomatic and asymptomatic women, mean HRQoL scores were significantly lower in the endometriosis case group in all eight dimensions and for the two composite scores (Table 4.6); the breakdown of proportion from the clinic and population controls; asymptomatic and symptomatic controls were detailed in Chapter 3.4.3. The SF36v2 dimension scores for endometriosis women ranged from 62.38 to 45.15, for symptomatic controls from 66.96 to 50.01, and for asymptomatic controls from 73.75 to 58.88, as shown in Table 4.6. Statistical testing using a two-sample t-test against a mean of 50 and SD 10 for the normative population showed that after adjustment for demographic factors, HRQoL was significantly impaired in women with endometriosis, as demonstrated when compared to the PCS and MCS scores in

symptomatic control group (p=0.001; p=0.002, respectively) and asymptomatic control group (p<0.001; p<0.001, respectively). Asymptomatic controls were not different to the normative population with respect to physical and mental HRQoL. As per the SF36v2 guidelines, a 10-point change in the dimension scores between two groups is clinically significant. This was demonstrated in all eight dimensions between endometriosis cases vs. asymptomatic controls, where for some scores the difference was more than 10-points.

Table 4.6. HRQoL endometriosis vs. control group in women of Middle Eastern population.

	Endometriosis Cases (n=518) Mean (±SD)	**Symptomatic Controls (n=1131) Mean (±SD)**	**Adjusted* *p*-value**	**Adjusted** *p*-value**	**Asymptomatic Controls (n=762) Mean (±SD)**	**Adjusted* *p*-value**
Physical Function	62.38 (22.59)	66.95 (25.07)	**0.001**	**0.040**	73.75 (23.40)	**<0.001**
Role-Physical	58.03 (27.06)	64.62 (27.66)	**0.001**	**0.004**	71.48 (27.65)	**<0.001**
Body Pain	53.77 (29.09)	63.00 (24.35)	**<0.001**	**<0.001**	71.36 (22.15)	**<0.001**
General Health	51.46 (19.41)	55.08 (20.90)	**0.003**	0.099	61.75 (20.63)	**<0.001**
Vitality	45.15 (17.08)	50.01 (19.07)	**0.001**	**0.015**	58.88 (20.43)	**<0.001**
Social Functioning	61.12 (23.39)	66.46 (25.11)	**0.001**	**0.004**	72.66 (24.37)	**<0.001**
Role Emotional	56.39 (22.15)	59.16 (25.49)	**0.009**	**0.047**	66.55 (25.79)	**<0.001**
Mental Function	52.64 (16.77)	56.58 (17.68)	**0.002**	**0.009**	64.84 (16.44)	**<0.001**
PCS	46.83 (7.77)	49.01 (7.88)	**0.001**	**0.001**	50.80 (7.70)	**<0.001**
MCS	42.41 (7.87)	44.43 (8.79)	**0.002**	**0.011**	48.06 (8.54)	**<0.001**

MCS: Mental Component Score; PCS: Physical Component Score; SD: Standard Deviation
*Adjusted for age, current BMI, civil status, educational status, and work status
**Adjusted for age, current BMI, civil status, educational status, work status, and severity (NRS) of dysmenorrhea, chronic pelvic pain, dysuria and dyschezia

4.4.2.1 HRQoL and endometriosis-related symptoms

An inverse relationship was present between severity of pelvic pain and PCS/MCS scores. A greater severity of dysmenorrhea and chronic pelvic pain (measured using the NRS scale from 0-10)[342] were associated with lower PCS and MCS scores (Table 4.7), and this was evident among both endometriosis cases and symptomatic controls.

Table 4.7. Multivariate linear regression between endometriosis symptomatology and SF36v2 domain scores based on severity.

		Physical Component Score		**Mental Component Score**	
		Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**
Dysmenorrhea	**Endometriosis**	-0.244; 0.003	-0.236; 0.001	-0.113; 0.003	-0.120; 0.004
	Symptomatic Control	-0.158; 0.001	-0.143; 0.001	-0.109; 0.001	-0.091; 0.001
Chronic Pelvic Pain	**Endometriosis**	-0.206; 0.007	-0.196; 0.001	-0.118; 0.007	-0.101; 0.016
	Symptomatic Control	-0.221; 0.001	-0.201; p.001	-0.174; 0.001	-0.150; 0.001

Adjusted for age, current BMI, civil status, educational status, and work status

Table 4.8 demonstrates how the presence and chronicity of endometriosis-associated symptoms, such as dysmenorrhea, chronic pelvic pain, dyschezia, dysuria and infertility, had an impact on the PCS and MCS scores. After stratifying by pain symptoms and infertility, and adjusting for demographic factors, women with endometriosis had significantly impaired PCS, but not MCS scores, in comparison to symptomatic controls. This is consistent with other studies that showed that women with and without pathology, showed no difference in their MCS scores[451]. However, PCS scores were significantly lower when comparing endometriosis cases to symptomatic controls, for all symptom groups except for dysuria (p=0.078). The significant difference between endometriosis cases and symptomatic controls on PCS scores may be because women with endometriosis experience multiple pain symptoms with a greater pain severity. As demonstrated in Chapter 3.4.5, women with endometriosis had a higher frequency of multiple pain symptoms with a greater pain severity that hinders their physical and daily activities. In fact, after adjustment for demographic variables and severity (NRS) of each pain phenotype, the effect size travelled in the same direction of effect for MCS scores (A vs. C; *p*-value) and PCS scores (B vs. D; *p*-value): dysmenorrhea (p=0.025; p=0.304), chronic pelvic pain (p=0.008; p=0.309), dysuria (p=0177; 0.651) and dyschezia (p=0.039; p=0.982).

Table 4.8. Association of endometriosis symptomatology and SF36v2 domain scores.

	Endometriosis		**Symptomatic Control**		**Endometriosis vs. Symptomatic Control**	
	PCS (A) Mean (±SD)	**MCS (B) Mean (±SD)**	**PCS (C) Mean (±SD)**	**MCS (D) Mean (±SD)**	**A vs. C *p*-value**	**B vs. D *p*-value**
Dysmenorrhea	46.48 (7.67)	42.66 (7.90)	48.04 (7.95)	42.92 (8.93)	**<0.001**	0.074
Chronic Pelvic Pain	45.40 (7.72)	41.69 (8.04)	47.58 (7.89)	42.68 (9.01)	**<0.001**	0.079
Dyschezia	44.65 (6.55)	40.85 (7.37)	46.30 (7.21)	40.68 (8.27)	**0.007**	0.828
Dysuria	44.99 (6.55)	40.22 (7.71)	46.30 (6.99)	40.89 (8.05)	0.078	0.441
Infertility	46.82 (7.92)	42.71 (7.85)	47.94 (7.86)	43.29 (8.73)	**0.035**	0.440

MCS: Mental Component Score; PCS: Physical Component Score; SD: Standard Deviation
Adjusted mean and p-values for age, current BMI, civil status, educational status, and work status

4.4.2.2 HRQoL and endometriosis stage

Next, the association between endometriosis stage, as measured by the rASRM classification, with HRQoL was tested. Stage 1 (minimal) and stage 2 (mild) disease were grouped together vs. stage 3 (moderate) and stage 4 (severe) subtypes as in previous reports, on the basis of shared genetic and biological origins, and to maximise sample size[6,68]. As shown in Table 4.9, endometriosis stage was not associated with any of the SF36v2 domain scores, or the physical (p=0.994) or mental (p=0.157) component scores[168]. This is consistent with previous studies, as well as this study (Chapter 3.4.5), where rASRM surgical staging was not associated with susceptibility or severity of pain or infertility of endometriosis[17].

Table 4.9. Association of endometriosis stage and SF36v2 domain scores.

	Stage 1 and Stage 2 (n=320) Mean (±SD)	Stage 3 and Stage 4 (n=198) Mean (±SD)	Unadjusted *p*-value	Adjusted *p*-value
Physical Function	66.28 (24.64)	63.16 (22.33)	0.340	0.494
Role-Physical	65.48 (27.44)	58.37 (26.32)	0.796	0.982
Body Pain	63.15 (24.31)	54.67 (29.40)	0.554	0.657
General Health	55.08 (20.90)	51.95 (19.42)	0.487	0.560
Vitality	50.01 (19.07)	46.16 (16.91)	0.102	0.158
Social Functioning	66.67 (24.98)	61.93 (23.68)	0.534	0.774
Role Emotional	59.97 (25.48)	57.38 (21.74)	0.214	0.294
Mental Function	56.94 (17.16)	53.58 (15.74)	0.117	0.202
PCS	46.83 (7.94)	46.75 (7.53)	0.853	0.994
MCS	42.89 (7.62)	41.69 (8.20)	0.087	0.157

MCS: Mental Component Score; PCS: Physical Component Score; SD: Standard Deviation
Adjusted p-values for age, current BMI, civil status, educational status, and work status

4.4.3 Diagnostic delay of endometriosis

Dysmenorrhea had the earliest symptom onset in the study population, and infertility the latest onset. The delay intervals from the onset of symptoms to first gynaecological consultation, and intervals from first gynaecological consultation to confirmed diagnosis are depicted in Table 4.10. Considering the average age at diagnosis was 34.04 (SD: 4.81) years for women with endometriosis, the interval between symptom onset and laparoscopic diagnosis of disease was on average 11.61 (SD: 5.59) years. Within this, the interval from the first onset of symptoms to first gynaecological consultation was 6.01 (SD: 4.19) years, and the interval between first gynaecological consultation to diagnosis was 6.96 (SD: 4.33) years.

Table 4.10. Symptom onset and diagnostic delay of endometriosis.

			Delay intervals		
	Age at Symptom Onset (Years) Mean (±SD)	**Age at First Gynaecological Consultation (Years) Mean (±SD)**	**Onset of Symptoms to First Gynaecological Consultation (Years) Mean (±SD)**	**First Gynaecological Consultation to Diagnosis (Years) Mean (±SD)**	**Total Diagnostic Delay (Years) Mean (±SD)**
Dysmenorrhea	17.10 (3.85)	24.02 (5.87)	6.92 (4.86)	9.92 (4.81)	16.83 (5.65)
Chronic Pelvic Pain	20.14 (3.20)	26.57 (5.20)	6.43 (4.20)	7.37 (4.65)	13.80 (5.36)
Dyschezia	23.76 (2.76)	28.92 (4.69)	5.52 (3.98)	5.16 (3.77)	10.33 (5.24)
Dysuria	23.39 (2.80)	28.91 (5.17)	5.16 (3.73)	5.40 (4.10)	10.94 (4.87)
Infertility	NA	26.06 (2.77)	NA	7.32 (4.53)	7.32 (4.53)
Total	21.10 (3.15)	26.90 (5.78)	6.01 (4.19)	6.96 (4.33)	11.61 (5.59)

NA: Infertility is often diagnosed by a physician, and women are unaware of their age at infertility onset, thus we have included the age at first diagnosis of infertility.

The delay from symptom onset to diagnosis varied from 7.32 years among women with infertility to 12.44 among those with pelvic pain. Arab women were more likely to seek surgical confirmation of endometriosis when they suffered from infertility, as opposed to pain, hence the shorter diagnostic delay when including infertility confirmation. This is also demonstrated when participants were asked for their chief clinical complaint and primary reason for surgical investigation (infertility, 61.8%; pain, 36.8%). When investigating the diagnostic delay of pain symptoms, married women experience 10.78 years of delay and single women experience 15.81 years of delay. In addition to marital status ($p<0.001$), increased diagnostic delay was associated with higher BMI ($p=0.011$), and work status (employed, $p=0.028$). Diagnostic delay was not associated with level of education ($p=0.160$).

4.4.3.1 Diagnostic delay and endometriosis stage

Increased endometriosis staging was associated with increased diagnostic delay (Spearman's rho correlation coefficient: 0.117, $p=0.009$). Women with stage IV endometriosis were older at age of diagnosis (35.34), and the delay before diagnosis for stage IV remained significantly greater than for stage I after adjustment for confounding factors (Table 4.11, $p=0.036$). As the study only included incident diagnostic cases, this represented a case group who had not previously been surgically diagnosed with endometriosis. One reason for the delay could be the ability of diagnosing stage 4 endometriosis, associated with deep

pelvic endometriosis, via imaging techniques (ultrasound and MRI), hence a delay in operative treatment of the endometriomas.

Table 4.11. endometriosis staging and diagnostic delay of endometriosis.

	Unadjusted		Adjusted	
rASRM Staging	**Odds Ratio**	***p*-value**	**Odds Ratio**	***p*-value**
Stage I	1.00		1.00	
Stage II	1.02 (0.98, 1.07)	0.221	1.05 (0.99, 1.13)	0.083
Stage III	1.03 (0.98, 1.07)	0.286	1.04 (0.96, 1.11)	0.326
Stage IV	1.08 (1.03, 1.14)	**0.001**	1.08 (1.00, 1.17)	**0.036**

Adjusted p-values for age, current BMI, civil status, educational status, and work status

4.4.3.2 Diagnostic delay and HRQoL

There was a significant correlation between longer diagnostic delay of endometriosis and reduced HRQoL (PCS: correlation coefficient: -0.366, p<0.001; MCS: correlation coefficient: -0.419, p<0.001). When stratifying the endometriosis cases based on endometriosis-associated symptoms (pelvic pain - dysmenorrhea, chronic pelvic pain, dyschezia, dysuria - or infertility), diagnostic delay was also significantly correlated with a lower PCS and MCS score (Table 4.12). More than 20% of the participants suffered for more than 14 years of pelvic pain and 11 years of infertility.

Table 4.12. Diagnostic delay of endometriosis and quality of life.

	n (%)	PCS	Adjusted *p*-value	MCS	Adjusted *p*-value
Pelvic Pain					
<8	119 (23.3%)	49.35 (7.34)		47.60 (5.44)	
9-13	270 (52.8%)	46.67 (7.71)	**<0.001**	42.07 (7.84)	**<0.001**
>14	122 (23.9%)	43.40 (6.64)		37.94 (7.03)	
Infertility					
<4	88 (34.6%)	49.21 (7.02)		47.87 (5.30)	
5-10	102 (40.2%)	47.17 (8.12)	**0.02**	40.93 (8.01)	**<0.001**
>11	64 (25.2%)	46.11 (7.02)		39.16 (7.32)	

Adjusted p-values for age, current BMI, civil status, educational status, and work status

4.4.4 Psychological disorders and endometriosis

Endometriosis can have a negative impact upon women's psychological wellbeing, with an increased risk of developing anxiety and depression[136,452]. Participants were asked to report if they have been clinically diagnosed with anxiety and/or depression disorders. Of endometriosis cases, 28.0% (n=145) reported anxiety, 21.9% (n=292) of symptomatic controls and 6.0% (n=46) of asymptomatic controls. For depression disorder the numbers were 26.3% (n=136), 20.0% (n=266) and 6.6% (n=50), respectively. After adjustment for demographic factors, there was a significant association between endometriosis status both when comparing with symptomatic and asymptomatic controls (Table 4.13). Additional adjustment was conducted for demographic factors and presence and severity of dysmenorrhea, chronic pelvic pain, dyschezia, and dysuria, demonstrating that anxiety (OR: 1.31 (1.03, 1.66); p=0.026) and depression (OR: 1.44 (1.12, 1.84), p=0.004) are significantly associated with endometriosis.

Table 4.13. Anxiety and depression in women with endometriosis.

	Endometriosis Cases vs. Symptomatic Controls				**Endometriosis Cases vs. Asymptomatic Controls**			
	Odds Ratio (95% CI)	***p*-value**	**Adjusted Odds Ratio (95% CI)**	**Adjusted *p*-value**	**Odds Ratio (95% CI)**	***p*-value**	**Adjusted Odds Ratio (95% CI)**	**Adjusted *p*-value**
Anxiety								
No	1.00		1.00		1.00		1.00	
Yes	1.40 (1.11, 1.78)	**0.006**	1.38 (1.09, 1.74)	**0.007**	6.04 (4.24, 8.61)	**<0.001**	6.46 (4.47, 9.35)	**<0.001**
Depression								
No	1.00		1.00		1.00		1.00	
Yes	1.44 (1.15, 1.82)	**0.003**	1.41 (1.11, 1.78)	**0.005**	5.06 (3.57, 7.16)	**<0.001**	5.43 (3.77, 7.83)	**<0.001**

Adjusted odds ratio and p-values for age, current BMI, civil status, educational status, and work status

4.4.5 Work productivity and activity impairment

Participants were asked to rate the impact of their symptoms on work productivity and daily life using a 10-point scale in the WPAI questionnaire (Table 4.14). Most women in the study population were employed (63.6%, n=1,660), and those who did not work were mostly housewives or carers (75.3%; n=716). Of the symptomatic women who were not in employment, approximately one in six (18.0%; n=204) reported that they did not work because of the symptoms for which they underwent surgery.

The average number of hours/week that the symptomatic women in the study population were contracted to work was 48. However, they reported working an average of 34.2 hours/week (SD: 5.11), leading to approximately 13.8 hours/week being absent from work. Approximately 16.68% of endometriosis cases and 13.61% of symptomatic controls reported absence (absenteeism) from work because of symptoms (p=0.001).

Women in the study population also reported a reduction of effectiveness at work due to symptoms (presenteeism) in 22.68% of endometriosis cases vs. 18.67% of symptomatic controls (p=0.006). With respect to overall work productivity loss, women with endometriosis had significantly less (p=0.002) overall work productivity impairment due to their symptoms, compared to symptomatic controls. However, no significant difference was observed on the impact of symptoms on activity impairment (p=0.059). The results show that pain presence and severity was a major driver of absenteeism (p=0.001), presenteeism (p=0.008) and overall work productivity loss (p=0.003). Activity impairment showed no significance between endometriosis and symptomatic controls (p=0.142), demonstrating that impairment in non-work-related activities may be due to symptoms, and not endometriosis *per se*.

Table 4.14. Work productivity and activity impairment in women with endometriosis.

	Endometriosis Cases n=518 %, mean (±SD)	**Symptomatic Controls n=1331 %, mean (±SD)**	**Unadjusted *p*-value**	**Adjusted* *p*-value**	**Adjusted** *p*-value**
Absenteeism	16.74 (12.69)	14.76 (12.61)	**0.002**	**0.001**	**0.001**
Presenteeism	22.68 (23.06)	18.67 (22.58)	**<0.001**	**0.006**	**0.008**
Overall Work Productivity Loss	34.32 (25.11)	29.67 (24.14)	**<0.001**	**0.002**	**0.003**
Activity Impairment	36.87 (21.56)	33.98 (23.77)	**0.008**	**0.059**	**0.142**

Absenteeism: Time absent from work due to symptoms
Presenteeism: Reduced Effectiveness while on the job due to symptoms
Overall Work Productivity Loss: Combination of Absenteeism and Presenteeism
Activity Impairment: Reduced effectiveness while doing non-work-related activities
*Adjusted p-values for age, current BMI, civil status, educational status, and work status
** Adjusted p-values for age, current BMI, civil status, educational status, work status, pain presence and pain severity

4.4.6 Physical activity

The protective effects of regular exercise have been widely described in the treatment of diseases involving inflammatory processes, such as endometriosis, hypothesised to be due to change in metabolism and resulting cytokine production in tissues and organs[363,453]. In our study, intensity of physical activity was assessed based on a metabolic equivalent (MET), that is defined as the amount of energy the body uses per minute, using the Compendium of Physical Activities. A greater proportion of controls than cases reported doing recreational physical activity. As demonstrated by Table 4.15, we did not observe any significant association between exercise activity and endometriosis. However, all groups (endometriosis cases, symptomatic controls and asymptomatic controls) performed less exercise than the recommended guidelines of at 500 MET-minutes per week[436]. The prevalence of physical inactivity was 67.2% (n=1,754) in the study.

Table 4.15. Physical activity in women with endometriosis measured by MET-minutes/week.

	Endometriosis Cases n=518 Mean (±SD)	**Symptomatic Controls n=1331 Mean (±SD)**	***p*-value**	**Asymptomatic Controls n=761 Mean (±SD)**	***p*-value**
Light MET	46.68 (44.16)	46.22 (44.16)	0.839	48.49 (45.57)	0.481
Moderate MET	102.85 (183.62)	118.86 (186.07)	0.101	121.46 (201.73)	0.109
Vigorous MET	182.61 (285.08)	186.14 (243.06)	0.790	203.33 (282.97)	0.200
Total MET	332.15 (486.99)	351.22 (423.63)	0.405	373.28 (498.45)	0.144

MET: metabolic equivalent
Light-intensity MET: Activities that are those with less than 3.0 METs
Moderate-intensity MET: Activities are those between 3.0 and 6.0 METs
Vigorous-intensity MET: Activities that score more than 6 METs

4.5 Discussion

HRQoL assessment as an indicator of public health is of great importance to health service and policy research, enabling comparison of results across different cultural groups and countries. There are many studies assessing the impact of endometriosis on HRQoL, mainly in Western countries[14,15,131,429,432]. These have demonstrated that the chronicity and severity of pain and infertility associated with endometriosis

have a negative impact upon quality of life, psychological wellbeing, and daily functioning. However, many of these studies that have attempted to elucidate the impact of the disease on HRQoL have lacked methodological rigor and geographical reach. For the first time, we provide evidence from a combined hospital and population-based study that Arab women with endometriosis, as well as symptomatic women without endometriosis, experience significant impacts on their HRQoL.

Similar to other studies, women with endometriosis also experience a substantial diagnostic delay after the onset of symptoms[12–14]. The findings of this study have an international significance within the Arab diaspora in the Middle East. Further work is needed to dissect the reasons for women to seek care, but it is likely that cultural sensitivities, tradition, and religious heterogeneity are important factors that can act as barriers. Understanding those barriers, along with the considerable impact of symptoms demonstrated in this study, is the first step in helping to solve disparities in the health of women in the Middle East, as well as in the representation of Arabs in endometriosis research.

As there was a lack of normative values available for the SF36v2 scores for the Middle Eastern region, the population-based controls were utilized to establish normative data for the SF36v2 for women of Arab ancestry. There was good evidence for the internal consistency of the domains, construct validity of the measure and factor loading of the weight dimensions, with the demographic data representative of the general population, suggesting the normative data are a valid new comparator for women in the region. Country-specific scores have the advantage of better representing the structure of health in each country. In order to compare the quality of life of women with endometriosis with the general population, the official norm-based scores derived from the 1998 USA general population by Quality metric Incorporated were used[354]. The reason for choosing this normative population was to allow cross-cultural comparisons, however, the US general population may not be representative of the general Middle Eastern population, for which normative scores have not been published. Higher US scores would lead to a conservative estimation of the decreased quality of life in women with endometriosis. A SF-36 norm-based score must be developed from the Middle Eastern population to utilize for future HRQoL studies. Factor loadings and

factor coefficients produced in the analyses of our study population in the Middle East varied significantly from the USA, suggesting a substantial systematic difference between the groups. The sensitivity to change of the summary scores when weighted with USA or Middle East factor score coefficients demonstrated the need for country-specific algorithms for summary measures in our study. Interestingly, all the SF-36 dimensions were moderately (>0.4) or severely (>0.7) correlated to either PCS or MCS score, in comparison to the USA score where the correlation of three dimensions were low (<0.3)[443]. This could be due to a stronger correlation of physical and mental health in Arab women, since they are not used to talking about their feelings and emotions in public leading to a potential stronger impact on their daily and physical activities. The results reaffirm that it is possible to apply a global health status instrument across cultures and standardise HRQoL measurement across countries across regions, but that careful evaluation of the utility of normative data is important. Further research with a larger sample size, specifically to investigate the applicability of the SF36v2 in this important and growing part of the Middle Eastern population is required so that it can be used confidently in this group.

Endometriosis women and symptomatic controls both had significantly poorer physical and mental HRQoL than the normative population. HRQoL scores were significantly impaired in women with endometriosis, as demonstrated by the PCS and MCS scores when compared to both symptomatic controls ($p=0.001$; $p=0.003$, respectively) and asymptomatic controls ($p<0.001$; $p<0.001$, respectively). The effect of endometriosis on physical and mental HRQoL of women was substantial, with SF36v2 scores similar to those reported in Arab women with breast cancer, although it should be noted that the USA population normative scores was utilized in that particular study[454]. The fact that the extent of impairment in physical and mental HRQoL observed in women in this study population is similar to that reported in women with cancer indicates the significant burden of endometriosis and its symptoms on women. Arab women find it difficult to cope with society, friends, and family's negative reactions to their illness, where they may be blamed for the pain as a sign of punishment or uncontrolled anger, leading to social humiliation and ridicule[260,275,277–279].

There was no association of physical (p=0.655) or mental (p=0.875) component scores with surgical staging of endometriosis in the present study. This is consistent with previous studies where rASRM surgical staging was not associated with severity of pain or infertility in endometriosis[17]. This suggests, perhaps not surprisingly, that the reduction of the HRQoL in women with endometriosis is related to symptomatology rather than rASRM surgical stage. Susceptibility of pain types and infertility in women with endometriosis was the main indicator of a lower HRQoL with impaired PCS and MCS scores, regardless of presence of endometriosis. While pain was one of the major concerns of patients with endometriosis, the MCS score was not significantly different when comparing endometriosis cases vs. symptomatic controls. This is again consistent with other studies in which women with and without pathology, matched for pain type, showed no difference on their MCS score[451]. When investigating the association of pelvic pain severity, with or without surgically confirmed endometriosis pathology, on the PCS and MCS, both were similarly associated (p<0.001). Reduced HRQoL is associated with pelvic pain symptoms and is unrelated to the presence of endometriosis. Hence, the management of pelvic pain of patients with chronic pain symptoms, independent of the causal factor, is the best approach to improve quality of life of these patients.

The diagnostic delay from first onset of symptoms to diagnosis was 11.61 years among Arab women. Within this, the interval from the first onset of symptoms to first gynaecological consultation was 6.01 years, and between first gynaecological consultation to diagnosis was 6.96 years. The diagnostic delay of 11.61 years among Arab women is approximately 5 years greater than what was reported in the GSWH study (6.7 years), and the highest when comparing it to other country specific scores Norway (6.7 years)[13], USA (8 years)[408], and UK (9 years)[455]. The delay was mainly driven by the delay in seeking the first gynaecological consultation from symptom onset (6 years among Arab women vs. 1 year in the GSWH study)[14]. Several reasons for diagnostic delays in endometriosis have been proposed, involving both patient and physician related factors, lack of awareness of endometriosis, inability to distinguish normal from abnormal menstrual features, sociological stigma in relation to menstruation and cultural factors of visiting a gynaecologist before marriage. In the Middle East, women with endometriosis experience heterogeneous

care that is hampered with numerous deficiencies. Due to cultural stigma, single women do not visit a gynaecologist when experiencing chronic pain or menstrual irregularities, hence prolong suffering.

Due to cultural stigma, it is not common for single women to visit a gynaecologist when experiencing chronic pain or menstrual irregularities, hence prolong suffering, as demonstrated in our study where only <20% of the women were single. This is also reflected in the delay of diagnosis by 15.81 years among single women, with approximately 18% (n=15) of the single women experiencing more than a 20-year delay in diagnosis due to chronic pain. Single Arab women were found to have fewer affirming attitudes toward seeking medical care, as they may endanger future marital prospects[272]. Additionally, women are often told that their debilitating menstrual pain is normal or unexplained. Hence, the greater delay of diagnosis when suffering from pelvic pain (12.44 years) versus infertility (7.32 years). Chronic peripheral pain stimulation followed by sensitization of the central nervous system can result in irreversible damage[389,456]. The diagnostic delay that is evident in this study suggests a critical window for attention and early intervention among women with symptoms suggestive of endometriosis. An increased diagnostic delay was associated with poorer HRQoL, due to a longer duration of painful symptoms without an accurate diagnosis and adequate treatment, worsening of the prognosis for fertility and pain, and increasing the risk for repeated operative procedures. The consequence of persistent pain emphasizes that women with endometriosis and symptomatic women with no endometriosis pathology need to consult immediately after symptom onset and be treated actively when they first seek medical care[93,389,456–458]. This may minimize the development of a state that can cause long-term suffering and reduced HRQoL. Early diagnosis is likely crucial for the effective treatment and prevention of disease progression, as symptoms related to endometriosis can present immediately upon onset of menarche. The low HRQoL demonstrates that the persistent pain *per se*, rather than the endometriosis pathology, contributes to the development of central sensitization. Arab women may feel reluctant to seek help for their symptoms and sacrifice their own needs and welfare for the sake of the family unit[274,275]. Therefore, in additional to diagnostic delay among the physicians and referral patterns, cultural issues may contribute to the delay in seeking gynaecological help.

Along with the presence, duration and severity of the pain state, this study showed for the first time that women in the Middle East experience among the highest diagnostic delays of endometriosis, which might be a driving force in the development of sensitisation[389,456]. Central sensitisation suggests that endometriotic tissue, as disease advances, generates persistent pain stimuli in the central nervous system, resulting over time in heightened pain awareness even from regions with no implanted tissue[93,389,456,459]. If true, such heightened awareness could explain the persistent impact of worsening endometriosis on HRQoL and would highlight the need to reduce the impact of the disease by early symptom control approaches that target central sensitisation. Prolonged noxious physical or pathological stimuli have been demonstrated to lead to central sensitisation, in which the central nervous system amplifies the perception of pain leading to a lower HRQoL[459]. The lack of adequate management and treatment of the disease results in emotional distress, powerlessness, and limited ability of pharmacological treatment regiments to produce lasting relief of the symptoms. This study contributes to the knowledge and understanding of the symptomatic burden of endometriosis and its impact on HRQoL.

Anxiety ($p=0.007$) and depression ($p=0.005$) were significantly associated with endometriosis, when compared to symptomatic controls, consistent with the results for the SF36-MCS. The overlapping impacts of endometriosis on different aspects of life (physical, psychological, reproductivity, economical, and quality of life), as well as the early onset of symptoms and later diagnosis of the disease, collectively, have a considerable impact on mental health[15,130,280]. The prolonged period of the unknown cause of the exacerbating symptoms can have critical impact on a woman's illness trajectory[12,430]. Endometriosis is a condition that is misdiagnosed, mismanaged, and ignored[460]; in addition to the need for increased health literacy among the population, there is also a lack of proper recognition by health professionals of the symptoms, psychological and interpersonal impact associated with endometriosis, requiring care from a multi-disciplinary team – and this is an issue that is recognised globally[128,131,133].

Women with symptoms are negatively affected in a variety of ways relating to work productivity. When comparing the impact of endometriosis-associated symptoms on work productivity and activity impairment,

women with endometriosis reported a greater impairment in terms of absenteeism (p=0.001), presenteeism (p=0.006) and overall work productivity loss (p=0.002). However, no significant difference was observed in activity impairment between symptomatic women with and without endometriosis. Greater usage of empirical, over-the-counter medication by affected women often leads to unsuccessful attempts to mitigate the pain[391]. Presence and severity of multiple pelvic pain symptoms have been reported as the major drivers of work productivity loss in endometriosis[14,129,432]. Women work through their pains and a focus on reducing understanding the mechanisms of pain in endometriosis and treatment to mitigate symptom severity would benefit individual women with endometriosis specifically and society in general.

Inconsistent associations have been reported between various types of physical activity and endometriosis in published literature[10,156,164,432,461]. These studies also draw attention to the possibility of an inverse relationship between the practice of physical exercise and the risk of endometriosis[180,435]. In this study, the intensity of physical activity was not associated with endometriosis, when compared to symptomatic (p=0.405) or asymptomatic controls (p=0.144). The WHO recommends a weekly minimum of 500 MET minutes of physical activity[436], which exceeds the level observed even among the healthy, asymptomatic control group. The prevalence of physical inactivity in the study was very high, at 67.2%. There are various personal and environmental factors that act as barriers for Arab women to participate in physical activity: cultural norms and practices of public modesty, lack of accessible environments and fitness facilities for women to feel comfortable to exercise, lack of supportive social milieu for women, conservative dress that is not suitable for physical activity, and lack of information on the importance of physical activity in schools[253,254]. Thus, both general and gender norms are a barrier to physical activity among Arab women, and as such programmes aimed at increasing physical activity are difficult to implement.

The key strength of this study is that, for the first time, it describes the comprehensive personal impact of endometriosis on HRQoL among women of Arab ancestry, in the context of diagnostic delay, endometriosis-associated symptoms, surgical rASRM stage, psychological disorders, work productivity and activity impairment, and physical activity. To limit information bias, the study was restricted to

endometriosis cases undergoing a laparoscopy for the first time for symptoms suggestive of endometriosis or sterilization, and relevant data were therefore collected prior to diagnosis. While the objective of this study was to recruit incident endometriosis cases to avoid recall bias, future studies should also aim to represent women living with endometriosis at varying stages. For instance, this should include women seeking and undergoing treatment after imaging diagnosis or post-surgical interventions for symptom recurrence and reoperations. The control group was recruited from community sites and hospitals, and clinics from which the cases were enrolled. However, although controls did not report a prior endometriosis diagnosis, some were likely to have undiagnosed endometriosis, meaning our estimates may have been affected by misclassification of endometriosis among the controls. This would have driven the associations observed to the null hypothesis of no difference, rather than creating spurious associations. Choosing an appropriate control group for endometriosis cases is complex, and multiple groups sampled from population and hospital based settings, as we used here, allow the testing of sensitivity of results to control group choice[11]. Additionally, a longitudinal cohort study would be required to understand the temporal relationship between HRQoL and endometriosis. Women with infertility, or moderate/severe pain symptoms were over-represented in our patient sample because cases were enrolled in hospitals (which typically see more complex and severe cases of endometriosis), when compared to asymptomatic women or those with mild symptoms who avoid seeking care from a gynaecologist. Another potential limitation inherent in the design of the study relates to the fact that the data on HRQoL collected in the days or weeks leading up to scheduled surgery might be affected both by the impending surgery and symptoms themselves.

In summary, this study highlights the significant impact of endometriosis, principally via its symptoms, on HRQoL. Along with the presence, duration and severity of the pain state, women in the Middle East experience a diagnostic delay of endometriosis that is among the highest reported globally, which could be associated with a high prevalence of psychological disorders and impact on their daily activity and work impairment. Women with endometriosis-associated symptoms should be referred to centres of expertise,

led by those with training in complex benign gynaecology and referred to a multi-disciplinary team including experts in pain management, with support from patient organisations. The significantly lower HRQoL in women with endometriosis and symptomatic controls demonstrate that medical care should also address the emotional and social problems that come with endometriosis. Our study will enable the establishment of communities for ongoing support and intends to build on the strength of women-centred networks in the Middle East, to provide early diagnosis and treatment and increase the likelihood of a positive HRQoL trajectory.

Chapter 5. The role of gene polymorphisms in endometriosis: candidate gene association study

5.1 Introduction

The role of genetic variation in the origin of endometriosis has been firmly established in twin and family studies, estimating heritability to be around 50%[55–57]. Genetic association and linkage studies have led to the identification of genetic loci that alter women's risk of developing endometriosis and provide new insights into potential underlying pathways, albeit mostly in women of European ancestry. As the potential clinical utility of risk alleles in endometriosis are considered, the need to understand how these genetic variants affect diverse ethnic groups is important[462]. Different ethnic populations can have varying morphological, anatomical, and physiological characteristics of endometriosis presentation, which may be encoded within the genome of the population[463,464].

To investigate the association of common causal genetic variants of endometriosis, population-based gene association studies, -both genome wide association studies (GWAS) and hypothesis driven candidate gene association studies (CGAS) - use single nucleotide polymorphisms (SNPs) as common genetic markers. The marker allele may directly result in increased susceptibility for the disease as a causative genetic variant, but more likely, the marker allele will be in linkage disequilibrium with a disease-causing allele. However, allele frequency will differ according to a population's history, and may even be specific to a population. Hence, to identify alleles that may be specific to, or display differential frequency in, populations, it is helpful to conduct studies in different ethnic populations.

Hundreds of candidate gene association studies have been performed for endometriosis, by examining putative genes of interest, with the majority of them not producing replicable results[59,73,75,76,465]. However, all robust endometriosis-associated loci to date have been identified through GWAS. Most of these have been performed in women of European ancestry, with loci implicated in the regulation of cell cycle and transcription, inflammation, cell adhesion and signalling, oxidative stress, and metabolism. Interestingly, most of the conducted GWAS have highlighted that the signals for most loci are clearer and distinct at

rASRM stage III/IV disease, thus suggesting that these loci affect mainly the advanced stage of endometriosis.

GWAS have demonstrated to be a powerful method to uncover common disease-risk loci that alter a women's risk of developing the disorder and provide new insights into potential causal pathways of complex diseases, including gynaecological diseases. For endometriosis, the latest published GWAS and replication meta-analysis of 15 studies, involving 58,115 endometriosis cases and 733,480 controls primarily of European ancestry identified 27 genome-wide significant variants associated with the condition and illustrated genetically-associated comorbidity with other chronic pain conditions, infertility, as well as genetic sharing with main obesity-related genetic risk-variants[59,76]. It is known that there are population differences for endometriosis in terms of locus-specific risk and disease manifestations[59]. For instance, the genetic locus with lead SNP rs10965235, at *CDKN2BAS1*/9p21.3, shows heterogeneity in the recent endometriosis GWAS results, where the intronic risk variant on chromosome 9p21 was identified in the Japanese population, but due to the different ancestral background of the populations, difference in allele frequencies and LD structure, the variant was found to be monomorphic in the European population[69,466]. With further studies, an independent signal was later observed near the same locus (SNP rs1537377) in European populations, demonstrating that there are independent variants associated with endometriosis in the same region, associated with endometriosis in populations of different ancestries[75].

Genomic diversity, which is defined as variation in alleles and allele frequency, is inherent within and across human populations. Published GWAS studies of all common complex conditions have mainly studied individuals of European ancestry, with only 19% of studies conducted in non-European ancestry populations, even though 75% of the world population live in Africa and Asia[467]. Of this, the Middle Eastern region is represented in less than 1% of the GWAS studies, however, it is a region that constitutes 6.5% of the world population. Genetic association studies need to be conducted in diverse populations, to counter under-representation, characterise genetic heterogeneity, and allow trans-ethnic fine mapping of genetic signals.

The Middle East is characterised by a very interesting genetic architecture, that is challenging to study. Due to high rates of consanguineous marriages, endogamous unions, and large family sizes within the Bedouin Arab population, it is believed that this population is a homogenous group with a highly conserved gene pool[237,240,247,468]. In fact, the Middle East has a roughly 100-fold higher rate of consanguinity than the United States and Europe, and this leads to greater homozygosity rates[469]. On the other hand, the Arab population has arisen from intercontinental migration between Africa (Tanzania), Persia (Iran), Asia (Baluchistan, Pakistan, Afghanistan) and Europe, providing it with a rich, distinctive genetic history[229,470]. Unfortunately, despite the significant efforts put into compiling fine-scale genomic sequencing data from ethnic groups from around the globe, populations from the nations of the Middle East remain underrepresented in these efforts. While there are several GWAS studies that has been conducted in Arab ancestry, such as for type 2 diabetes and rheumatoid arthritis, there has been a lack of genome-wide statistically significant results due to insufficient availability of reference panels for genotype imputation, which is crucial to increase statistical power to detect association, enables complete meta-analysis of results from multiple studies, and facilitates the identification of causal variants through genetic fine-mapping[471,472]. The 1000 Arab Genome Project is an ongoing project that is led by Principal Investigator Dr. Habiba Al Safar, one of my supervisors, and is intended to create reference sequences to establish databases for developing customized molecular diagnostic assays and personalized medicine strategies, for individuals of Arabian descent[244].

As a pilot project, I led the investigation of replication of two genes that have been robustly associated with endometriosis: *WNT4* and *VEZT*. Several large gene mapping studies have demonstrated an association between endometriosis and markers located in or near to the wingless-type MMTV integration site family member 4 (*WNT4*) gene (rs12037376 SNP located 21 kb downstream of *WNT4*, 1p36 cytogenic region), and the Vezatin (*VEZT*) gene (rs10859871 SNP located 17 kb upstream of *VEZT*, 12q22 cytogenic region)[71,75,168,308]. *WNT4* is expressed in human endometrium during the proliferative and secretory phases, and has been associated with development of the female reproductive tract, suggesting that endometriosis may arise through metaplasia using developmental pathways[308,473]. Variants at 1p36 involving the *WNT4*

gene might contribute to endometriosis susceptibility through abnormal cell growth by affecting the degree of expression of the gene, and the levels of the protein[308]. *VEZT* is a sex steroid hormone that is involved in the pathway and synthesis of oestrogen, as well as implantation, and has been found to be more active in endometrial lesions, and to be down-regulated in gastric cancer[71]. Comprehensive analysis of the *WNT4* and *VEZT* regions showed a number of SNPs in linkage disequilibrium with lead GWAS SNPs rs12037376 and rs10859871[466].

The effect sizes of the risk variants for *WNT4* and *VEZT* tend to be greater for more severe disease stages (revised American Society for Reproductive Medicine, rASRM, Stage III and IV endometriosis[16]), consistent with the observation that this case subtype has a greater genetic burden relative to stage I/II disease (Figure 2 in Rahmioglu et al., 2014).[168] Thus, *WNT4* and *VEZT* genes are strong targets for further studies aimed at understanding the molecular pathogenesis of endometriosis. To begin to better understand the potential roles for these risk variant associations in endometriosis pathology, I have undertaken a focused investigation of these two genome-wide significant endometriosis-associated loci with associated SNPs in proxy, in women diagnosed with endometriosis of Arab ancestry and controls. The CGAS findings will pave the way for GWAS studies, once the 1000 Arab reference panel is setup.

5.2 Objective

Given the important implications that genetic variant knowledge may have in future on a patient's treatment and outcome, the goal of this study was to better understand and characterize genetic variants previously associated with endometriosis in the Arab population. Specifically, the objective was to test known endometriosis-associated genetic markers from the European ancestry populations, for replication in women of Arab ancestry. Ethnic-specific association studies provide novel evidence that can confirm previously reported genetic associations in different populations or question their direct associative role.[474] To date, there are no published articles that investigate the role of genetic variants in endometriosis in women of Arab Ancestry.

Candidate association of ten SNPs were conducted in this chapter that are selected from two genome-wide significant endometriosis-associated loci in European ancestry for replication in women of Arab ancestry:

- rs12037376 SNP located 21 kb downstream of wingless-type MMTV integration site family member 4 (*WNT4*) with 4 SNPs in proxy
- rs10859871 SNP located 17 kb upstream of the Vezatin (*VEZT*) gene with 4 SNPs in proxy

5.3 Methodology

5.3.1 Study populations

5.3.1.1 Case selection

From a subset of consenting women who completed the questionnaire and underwent laparoscopic surgery, a saliva sample was collected post-procedure for DNA extraction. The case group (n=100) included pre-menopausal women aged 18 to 50 years, scheduled to undergo a diagnostic and/or therapeutic laparoscopy or laparotomy, regardless of clinical indication, at one of the participating surgical centres in the UAE. The saliva samples were only collected for more severe disease stages (rASRM Stage III, IV endometriosis)[16], as the effect sizes and genetic burden of these loci tend to be larger for more severe disease stages[168]. Women with a history of uterine fibroids, adenomyosis or presence of a malignancy found at laparoscopy were excluded due to the potential association of selected candidate genes and non-endometriosis pathology.

5.3.1.2 Control selection

The control group (n=100) included pre-menopausal women aged 18 to 50 years, scheduled to undergo a diagnostic and/or therapeutic laparoscopy or laparotomy, regardless of clinical indication, at one of the participating surgical centres in the UAE. Women were selected who had been screened for endometriosis via laparoscopy, with no diagnosis of endometriosis, and asked to donate a saliva sample. Clinic-based controls undergoing laparoscopy were more powerful for my genetic study, as they will not include women with endometriosis and therefore enable me to obtain more accurate effect sizes. Women with a history of

uterine fibroids, adenomyosis or presence of a malignancy found at laparoscopy were excluded due to the potential association of selected candidate genes and non-endometriosis pathology.

In a genetic association study, bias due to environmental factors is not generally a problem; the primary potential confounding bias is related to differential ethnic origin of cases and controls due to population stratification. However, population stratification is minimized when controls are matched to cases on ethnicity, which of a candidate-gene association study without availability of genome-wide genotyping data, needs to be ascertained through self-descriptive data[336].

5.3.2 Collection tools

5.3.2.1 Questionnaire and forms

The WERF EPHect EPQ-M and SSF-M, for which detailed information is provided in Chapter 2.4, capture nonsurgical and surgical clinical information from endometriosis cases and controls. Briefly, the demographic and personal information was collected from the EPHect EPQ-M, and the clinical information was collected from the EPHect EPQ-S.

5.3.2.2. Saliva sample collection

Saliva samples specimens were obtained from women who have met the eligibility criteria outlined in 5.3.1 for DNA extraction and genotyping. Saliva samples were collected using the ORAGENE-DNA Saliva Self-Collection kits (OG-600, DNA Self-Collection Kit, DNA Genotek, Ottawa, Ontario, Canada), which is the gold standard to collecting high quality DNA via a non-invasive method[360]. The saliva collection kit preserves the DNA stable at room temperature up to 8 years, the provision of high-quality DNA, median yield of DNA of 110 µg from 2 mL of Oragene DNA/saliva solution. The manufacturer concedes that the yield may range from 15 µg to more than 300 µg and recommends that final concentration of DNA should be less than 200 µg/mL (200 ng/µL). A total of 2 mL of saliva sample is collected from each participant[359,360], up to the mark of a collection vial.

The SOP that comes with the saliva collection kit was followed by each participant and overseen by the research assistant. The sample was collected at least 1 hour after eating a meal and brushing of teeth. Participants were asked to rinse their mouth 30 minutes before collection. After sample was collected, the vial was sealed, and gently inverted for 10 times to mix the saliva samples with the Oragene solution. The sample collection tube was labelled with the unique identifier of the participant and the date/time of sample collection. Samples were transported in a sealed biohazard bag using a cool transport container to Khalifa University Centre for Biotechnology in Abu Dhabi for genotyping and analysis. Samples were collected during the data collection stage (August 1, 2018, to August 1, 2019), and processing of the samples initiated from 1 November 2019 to 31 January 2020.

5.3.3 SNP selection

5.3.3.1 Rationale for the SNP selection process

Single nucleotide polymorphisms (SNP) are genetic markers used to measure associations with phenotypes. SNPs are highly suited for association studies due to their genomic abundance and biallelic presence. The approach for selecting SNPs in candidate gene studies are typically based on: (1) a biological assumption or hypothesis underlying evidence for direct protein-coding alterations ('coding SNPs'), and/or (2) evidence of association of that SNP, or SNPs in proxy of the genotyped variant, in GWAS. Candidate gene approach employs a targeted evaluation of selected variants, implying a search for putatively functional SNPs. Often, as in the present study, a composite approach is used to identify a panel of SNPs that explore the allelic diversity of the gene and include variants that may be potentially functional. The ideal panel would include a subset of SNPs that capture most of the information regarding variability in the region with the minimum expenditure of genotyping resources.

The International Haplotype Mapping Project (HapMap) and 1000 Genome Project were a major first step in characterizing the distribution and extent of linkage disequilibrium (LD) throughout the human genome in diverse population samples. Given that LD varies with ancestral origin, the optimal panel of SNPs for a certain population is expected to differ by racial and ethnic origin. However, the HapMap project and 1000

Genome Project did not include any samples from the Middle Eastern population. Hence, for this study of an Arab population, the distribution of LD across different ethnic populations (European, African, South Asian, and East Asian ancestry) was studied to understand if these alleles appeared to be consistently present in haplotype blocks with high LD. In doing so, the sampling density is critical to maximize the probability that at least one of the sampled SNPs is in high LD with an undiscovered SNP which could potentially be the causal variant. Patterns of LD observed in a small reference sample may not be representative of a study population.

Several factors such as population stratification, admixture, the number of founders and the demographic history of a population play a significant role in defining the fine patterns of LD. Hence, several tools were utilized to select SNPs based on LD pattern, including Tagger analysis (a pairwise tagging method) from Haploview software (Broad Institute of MIT and Harvard, Cambridge, MA, http://www.broadinstitute.org/).

5.3.3.2 SNP characterization

To arrive at selection of SNPs for my candidate gene analysis, I utilized the largest GWAS meta-analyses results published, including 14 European studies and 1 Japanese study[59]. I selected SNPs that were:

- All common (minor allele frequencies, MAF, >0.10)
- Large effect sizes (OR > 1.15)
- Functional regulation annotation of the SNPs in candidate gene and each SNP in proxy

I used several resources for targeted selection of SNPs and to corroborate the data across programs. I used databases including the National Centre for Biotechnology Information (NCBI), a US government-funded national resource for molecular biology information, Entrez Gene (http://www.ncbi.nlm.nih.gov/Entrez) and Ensembl (http://www.ensembl.org) that host a collective resource linking various tools to provide knowledge of the genes functional and structural elements, putative function of the gene variants and encoded proteins, phenotypic traits associated with each SNP, and LD patterns measured by r^2 and D'.

As detailed previously, LD is an important measure in the study of population genetics and disease-gene association. Analysing extended long haplotypes carrying specific alleles and examining LD block structure between population can provide evidence for genetic heterogeneity and even positive selection[475]. I investigated the LD structure of European, African, East Asian, and South Asian populations for the previously reported sites of positive selection by comparing LD block construction results based on 1000 Genomes Project data and NIH Entrez Gene, as shown in Figure 5.1.

I studied the common polymorphisms identified in the GWAS and found a high similarity of allele frequencies and measures of LD (genotyping with an r^2 threshold of 0.90 to completely represent allelic variation in a genomic segment) for two of the genetic loci, which I chose for genotyping: rs12037376 SNP near *WNT4* (Cytoband: 1p36) with 4 SNPs in proxy (Table 5.1), and rs10859871 in *VEZT* (Cytoband: 12q22) with 4 SNPs in proxy (Table 5.2). The LD measures demonstrated low evidence of recombination, with the SNPs lying in the same haplotype block between populations (Red blocks, Figure 5.1).

Ten SNPs were selected for testing for further association with endometriosis in an Arab population. For each SNP in proxy, the following factors were considered to include polymorphisms with biological impact: type of variant, location of variant, functional effect, frequency in genome, predicted relative risk of phenotype.

Table 5.1. rs12037376 SNP near WNT4 (cytoband: 1p36) in with 4 SNPs in proxy.

RS number	Position	R^2
rs12037376	1:22462111	1.00
rs3820282	1:22468215	0.962
rs56318008	1:22470407	0.933
rs55938609	1:22470451	0.932
rs10917151	1:22422721	0.903

Table 5.2. rs10859871 in VEZT (cytoband: 12q22) with 4 SNPs in proxy.

RS number	Position	R^2
rs12320196	12:95712695	1.00
rs6538621	12:95627237	0.991
rs10777678	12:95658282	0.990
rs10859863	12:95661809	0.989
rs4762326	12:95668951	0.988



Figure 5.1. Linkage disequilibrium plots (r^2) demonstrating the non-random association of alleles at different loci in the region of rs12037376 SNP, WNT4 gene 1p36.12 at the 22462111 positions and the region of rs10859871 in VEZT 12q22 at the 12:95712695 positions in four different populations.

5.3.3.3 Functional regulation annotation of the SNPs in candidate gene

The SNPs located in *WNT4* and *VEZT* gene are in intronic regions; however, they are both strong candidates for functional changes that may increase risk of endometriosis (Table 5.3). To investigate the functional assays of the SNPs, I used HaploReg version 1[476] to search for SNPs with functional annotations and RegulomeDB[477] program to rank potential functional roles for SNPs based on their location across the entire 150 Kb region. The scoring system for RegulomeDB ranges from 1-7 with the strongest evidence for functional roles as scores 1 (a-f). The RegulomeDB probability score ranges from 0 to 1, with 1 being most likely to be a regulatory variant. Both databases use the international ENCODE project to identify functional regions of the genome outside of gene coding regions, which includes areas of open chromatin identified using DNaseI hypersensitivity, Formaldehyde-Assisted Isolation of Regulatory Elements, and Chromatin immunoprecipitation experiments and the locations of functional regulatory elements including promoters, enhancers, silencers, insulators, locus control regions and novel elements[478–480].

Table 5.3. Functional regulation annotation for the SNPs using HaploReg and RegulomeDB

Gene	SNP	SNP Rank	Probability Score	Genomic Position	Motifs Changed
VEZT	**rs12320196**	7	0.18412	Intronic	CEBPA, CEBPB
	rs10859863	7	0.18412	Intronic	CEBPA, CEBPB
	rs4762326	7	0.51392	Intronic	CEBPA, CEBPB
	rs6538621	5	0.58955	Intronic	BCL
	rs10777678	6	0.34125	Intronic	Foxa, CDP, Ncx, Sox
WNT4	**rs12037376**	5	0.0	Intronic	SEF-1, YY1
	rs3820282	2b	0.60537	Intronic	ERalpha-a, Esr2, Zic
	rs55938609	4	0.60906	Intronic	ZID
	rs56318008	4	0.60906	Intronic	Gfi1b, Gfi1, NRSF, BCL
	rs10917151	2b	0.46415	Intronic	Crx, Maf, Pitx2

Dynamic shifts in transcription factor binding are central to the regulation of biological processes by allowing rapid changes in gene transcription. While the SNPs located in the *VEZT* gene are all intronic, with a low probability score (least likely to be a regulatory variant), the CEBPA/CEBPB transcription factors that are likely to be affected are involved in changes to follicular cell differentiation and increasing steroidogenic capacity, which may be associated to endometriosis, an oestrogen-dependent condition[481].

The SNPs located in *WNT4* gene are all located in the intronic region, however SNPs rs3820282, rs55938609 and rs56318008 have a high probability score of functional effect, which indicates potential of being a regulatory variant, with a low rank score regarding involvement in transcription factor binding,

DNase peaks and any motif change. SNP rs12037376 is linked to the SEF-1 motif, which regulates iron uptake, and YY1, which is known to regulate transcriptional activation and repression of many genes associated with multiple cellular processes including cellular differentiation, DNA repair, autophagy, cell survival vs. apoptosis, and cell division[482,483]. This transcription factor might determine its function as an activator or repressor of transcription as well as its role as a suppressor or promoter in association to endometriosis. SNP rs3820282 is predicted to lie in a conserved region within regulatory motifs bound by the transcription factors oestrogen receptor 1 (*ESR1*) and oestrogen receptor 2 (*ESR2*), an important transcription factor associated with endometrial changes and in the secretory endometrium in endometriosis[484–488].

5.3.4 DNA extraction

Prior to genomic DNA extraction, the Oragene DNA Saliva vial was mixed by inversion and gently shaken for 10 seconds, then incubated in a heated water bath, set at 50ºC for 1 hour. The heat-treatment step was essential to ensure that DNA was released, and the nucleases are permanently inactivated. Genomic DNA was extracted using the prepIT1L2P (catalogue: PT-L2P) system (DNA Genotek, Ottawa, Canada) according to manufacturer's instructions. After incubation, 500 µL of saliva sample in the Oragene DNA vial and 20 µL of PT-L2P was transferred into a 1.5 mL microcentrifuge tube (Oxygen #MCT-150-C). This allowed the sample to become turbid as impurities and inhibitors are precipitated. The sample was then vortexed for 10 seconds, then incubated on ice for 10 minutes to remove impurities. Following this, the sample was centrifuged at room temperature for 5 minutes at 15,000 x g that reduced the turbidity of the DNA solution.

The clear supernatant was transferred to a fresh 1.5 mL microcentrifuge tube, and the pellet that contained the impurities discarded. To clot the DNA fibres as a fine precipitate, 600 µL of 95% ethanol was added to the tube. Incubation at room temperature for 10 minutes allowed the DNA to fully precipitate. The tube was then centrifuged at room temperature for 2 minutes at 15,000 x g to reduce the turbidity of the final DNA solution. The supernatant was removed as the pellet contains the DNA. Ethanol wash was conducted

by adding 250 µL of 70% ethanol, and the tube was incubated at room temperature for 1 minute. To dissolve the DNA pellet, 50 µL of TE (10 mM Tris-HCl, 1mM EDTA, pH 8.0) solution was added to the tube for 1 hour.

DNA quantity and quality was evaluated by ultraviolet (UV) spectrophotometry (Nano drop 2000C spectrophotometer) using an Eppendorf biophotometer (Eppendorf, Hamburg) at a dilution of 5:95 (10µL of sample in 190µL of Milli-Q); readings at 260 nm, 280 nm and 320 nm were performed. The ratio between absorbance readings was calculated using the following formula, as suggested by the kit: RAT=(A260 - A320)/(A280 – A320). The yield of extraction was calculated by multiplying the concentration by the total volume of DNA solution after extraction and divided by the volume of Oragene DNA/saliva solution processed in each extraction. A total of 20% of samples were extracted twice for quality control, and two-tailed p value difference was conducted.

5.3.5 SNP genotyping

The TaqMan SNP Genotyping Assay (Applied Biosystems, Foster City, CA) was used in this study because it includes two locus-specific PCR primers that flank the SNP of interest, and two allele-specific oligonucleotide TaqMan for amplifying and detecting specific polymorphisms in purified genomic DNA samples. Two TaqMan minor groove binder (MGB) probes with nonfluorescent quenchers (NFQ) were used: a VIC-labelled probe to detect Allele 1 sequence and a FAM-labelled probe to detect Allele 2 sequence. When activated, an intact probe emits a fluorescent signal, because of the close physical proximity of the 5’ fluorophore to the 3’ quencher. A fluorescent signal was generated when the intact probe, which was hybridized to the target allele, are cleaved by the 5’ exonuclease activity during each cycle of the PCR reaction.

The PCR primers amplified a specific locus on the genomic DNA template, and each fluorescent dye-labelled hybridization probe reported the presence of its associated allele in the DNA sample. In each PCR cycle, cleavage of one or both allele-specific probes produced an exponentially increasing fluorescent signal by freeing the 5’ fluorophore from the 3’ quencher. The use of two probes allowed detection of both alleles

in a single tube. Fluorogenic probes with an MGB produced an enhanced allelic discrimination, because the MGB stabilized the double-stranded probe template structure, thereby increasing the probe Tm (melting temperature) without increasing probe length. This provides enhanced mismatch discrimination between these shorter probes, resulting in improved allele specificity. The TaqMan SNP genotyping assay primers are provided in Table 5.4 and 5.5.

Table 5.4. TaqMan SNP genotyping assay primers: WNT4 /1p36.12

RS number	Position	Polymorphism	Context Sequence [VIC/FAM]
rs12037376	1:22462111	G/A, Transition Substitution	GGGTGGTTACGGGACTGCCTGGACA**[G/A]**TATGGAAGCCTGTGGTCTCTGTAGC
rs3820282	1:22468215	C/T, Transition Substitution	TTCCAGCCTGGAGGGCTCTGGCTGG**[C/T]**CACAATGACCTCATAGCAACAGCCA
rs56318008	1:22470407	C/T, Transition Substitution	TCTCATCCGGGAAGTGGGCTTAAGA**[C/T]**GCTGTGATTGGGAGGACAGGAGGAG
rs55938609	1:22470451	G/C, Transversion Substitution	GGAGGAGTTTAGGGAAGCTCTCTTG**[G/C]**CTCACTCACCAAGTCTTACTTTGCA
rs10917151	1:22422721	G/C, Transversion Substitution	CCCTCCTCAGCCTCCCAAAGTGCTG**[G/C]**GATTATAGGCATGAGTCACTGCGC

Table 5.5. TaqMan SNP genotyping assay primers: VEZT /12q22

RS number	Position	Polymorphism	Context Sequence [VIC/FAM]
rs12320196	12:95712695	A/G, Transition Substitution	CTATAACATTGGCTATTTTGAAGCA**[A/G]**TCTAAGACTATAAAATTTGGGACAG
rs6538621	12:95627237	C/T, Transition Substitution	ATATTATGTTGAAATGTGTAAGCTC**[C/T]**GAAAAGCATTTCCTATTATTTTATA
rs10777678	12:95658282	A/T, Transversion Substitution	TTATTTATTTATTTATTTATTTTTT**[A/T]**ATTGATCATTCTTGGGTGTGATTTG
rs10859863	12:95661809	C/T, Transition Substitution	CTGGAGACAACAGATTCTGTCTAGG**[C/T]**TGGGCAACAGACTTGGTCTCAAAAA
rs4762326	12:95668951	C/T, Transition Substitution	TGAATTTACTTTAATTGGAGGCCAA**[C/T]**GTGAGTGATTTTATAACTAGCCATT

Allelic discrimination was carried out using pre-made TaqMan SNP Genotyping assays from Applied Biosystems. All TaqMan Real-Time PCR reaction were performed in 96 well plates (Applied Biosystems, Foster City, CA) with a final reaction volume of 10 µL in each well that contained: 10 ng of genomic DNA, 2X TaqMan Master Mix (5.00 µl), 20X Assay Working Stock (0.50 µl) and Nuclease free water (4.50µl). Negative controls were included in each plate. These TaqMan probe and primer sets (assays) uniquely aligned with the genome to provide unmatched specificity for the allele of interest. Reactions were carried out in thermocycler Step One Real-Time PCR System. The Real-Time PCR thermal conditions were as follows: initial polymerase activation at 95ºC for 10 minutes, denaturing at 95ºC for 15 seconds, 40 cycles of 95ºC for 3s (denaturing) and 60ºC for 60s (annealing/extension). Amplification was performed in

ViiATM 7 Real-Time PCR system (Applied Biosystems, Foster City, CA) and results were assessed using the ViiATM 7 software (Applied Biosystems, Foster City, CA). Allelic discrimination plots were reviewed individually for quality.

5.3.6 Quality control

Plates included both cases and controls to avoid the interference of plate batch effects with genotyping results, with one negative control (water) on each plate to identify contamination. Genotyping errors were identified for repeat assays where there were: (1) discordant results in duplicate samples (<0.5%), (2) indeterminate genotype calls (<1%), (3) deviation from Hardy-Weinberg Equilibrium (HWE; $p<0.05$), and (4) very low MAF (<5%). Genotyping was repeated for the above questionable results as well as randomly for additional samples that included concordant duplicates in the first run to provide an extra instance of validation. Replicate samples were collected from 20% of the participants for quality control analysis from DNA extraction through DNA genotyping. Each assay was run with negative controls.

5.3.7 Statistical analysis

The genetic variants under investigation were evaluated for deviation from the HWE by comparing observed and expected genotype frequencies by means of Chi-squared ($\chi 2$) test. Haploview was used to evaluate LD between SNPs and identify haplotype blocks. Haplotype frequencies were obtained, and case-control association testing was carried out using PLINK (v1.05), comparing frequencies of variants between cases and control including haplotype specific tests, allelic and genotypic tests. All the cases and controls used in the analysis were self-reported unrelated. Because this was a pilot study with limited funding, our study was insufficiently powered (*P:* 0.38-0.48 for an additive model with an average effect size of 1.15 with a power of 0.8, at a significance level of 0.05) for detecting single-site association of endometriosis, hence we did not apply a multiple testing correction for interpreting the individual effect of the variants. The Chi-squared ($\chi 2$) test, with one or two degrees of freedom, was used to examine differences of genotype and allele frequencies between patients and controls, where all SNPs had a call rate of >99%. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Association of SNPs or haplotypes with

endometriosis was evaluated using logistic regression, adjusting for BMI and age due to the association of potential overlap in genetic variants underlying the aetiology of endometriosis and BMI using GWAS data[76]. A two-tailed p-value <0.05 was defined as statistically significant.

5.4 Results

5.4.1 Dataset

A total of 100 rASRM stage III/IV cases and 100 controls (who have undergone a tubal ligation, or were diagnosed with appendicitis, pelvic inflammatory disease, irritable bowel syndrome, adhesions, Crohn's disease, inflammatory bowel disease, incisional hernia, interstitial cystitis, and ruptured corpus luteal cyst) were included in the genetic analyses. The mean age of the case group was 36.24 (SD: 5.08) and of the control group 36.19 (SD: 5.88; p=0.95); the BMI of the case group was 25.63 (SD: 4.21) vs. the control group 26.78 (SD: 5.04; p=0.083).

5.4.2 Quality control

Replicate samples were collected from 20% of the participants (n=40; equally divided between the case and control groups) to permit quality control analysis of study procedures from DNA extraction through DNA genotyping. No significant difference in DNA yield, purity or contamination was observed between the replicate samples (Table 5.6).

Table 5.6. Quality control on repeated samples.

	First Run (N=40) Mean (SD)	**Second Run (N=40) Mean (SD)**	***p*-value**
Nanodrop Concentration of the total DNA yield per specimen (µg)	91.08 (93.72)	88.61 (90.95)	0.108
A260/A280	2.46 (0.94)	2.75 (0.94)	0.182
A260/A230	0.19 (0.17)	0.17 0.25)	0.118

p-value was calculated using a paired sample t-test
A260/A280: provides insight regarding the type of nucleic acid present (dsDNA or RNA) as well as providing a rough indication of purity
A260/A230: is a sensitive indicator of contamination that absorbance at 230 nm.

Out of the 10 SNPs genotyped, three (rs6538622, rs56318008 and rs10777679) reported an error regarding failure of auto-calling the SNPs. The genotyping was replicated in another plate; however, no reliable genotyping signal for these 3 SNPs was obtained the second round either. The supplier of the primers was contacted for this error, and I was advised to adjust the threshold quality level manually. After ruling out genotyping, machine and human error, failure of auto-calling the SNPs may be due to: 1) an error with the genotyping assay where the SNPs fail to produce any results at all, or 2) appear monomorphic in this population due to presence of single cluster of genotype[489]. An error may be introduced for the assay if there are neighbouring SNPs that alter allele-specific binding of probes, or if local genomic sequence is enriched for guanine-cytosine content. Commercially available SNP arrays were primarily designed using haplotype and sequence information from outbred populations, such as the European ancestry. Consequently, the SNPs included in these arrays may be less informative for isolated populations because of the difference in linkage disequilibrium and failure to capture variants that are either novel to a population or that occur at a much higher frequency than in outbred populations.

Hence, based on the amplification of local sequence surrounding the SNP of interest, redundant sequences are amplified, which may lead to bias in allele calling and fidelity of the polymorphisms between the different segments. Mapping the SNP probe sequence to a reference genome and incorporating contextual information into SNP filtering pipelines has the potential to substantially improve the calling rate of assays. The SNPs that were categorized as being monomorphic may be caused by a rare haplotype presented in this population or possibly by genotyping errors. Even though population-specific monomorphic sites could be explained by either low mutation rate or positive natural selection, before making such a conclusion, it is imperative to thoroughly consider the study population, reliability of genotyping methods applied and publicly available SNP databases used for comparison[490]. Due to the lack of a large-scale Arab reference genome available on a public database, it is difficult to distinguish between allele calling errors, mutations, and monomorphic SNPs in candidate gene studies. Further studies must be conducted in the Arab ancestry to understand population differentiation in allele frequencies for these variants.

After excluding the above three SNPs, seven SNPs were included in association analysis, for which the quality controls measure are shown in Table 5.7. All SNPs passed quality control, apart from rs10917151 which deviated from HWE (p=0.01), possibly due to the high consanguinity in this population, hence this SNP was excluded from further analyses.

Table 5.7. Quality control per SNP.

			Allele Frequency			Hardy Weinberg Equilibrium		
	Missingness per Individual	**Missingness per marker**	**Minor Allele**	**1000G Population**	**MAR'A Study Sample**	**Observed Heterozygosity**	**Expected Heterozygosity**	***p*-value**
rs12320196	0%	0%	G	0.48	0.43	0.49	0.52	0.47
rs10859863	0%	0%	C	0.47	0.43	0.49	0.51	0.66
rs4762326	0%	0%	T	0.47	0.42	0.48	0.53	0.38
rs12037376	0%	0%	A	0.15	0.15	0.25	0.26	1.00
rs3820282	0%	0%	T	0.13	0.14	0.24	0.26	0.77
rs55938609	0%	0%	C	0.14	0.12	0.21	0.24	0.08
rs10917151	0%	0%	A	0.14	0.15	0.24	0.28	0.01

5.4.3 Candidate gene association analysis

5.4.3.1 *VEZT* on 12q22

All three SNPs included in this locus showed nominal associations with endometriosis and showed the same direction of effect between each other, with significantly different genotype frequencies in endometriosis cases compared to the controls (Table 5.8). Endometriosis cases showed a significant increase in allelic frequency compared to the controls only for the lead European GWAS variant rs12320196 ($OR_{A\ vs.\ G}$=1.57 (95% CI: 1.05, 2.34), p=0.033). Adjusting for age and BMI, did not materially change the results (allelic OR for rs12320196=1.60 (95% CI: 1.05, 2.45), p=0.027)(Table 5.9).

5.4.3.2 *WNT4* on 1p36.12

Two out of three SNPs located in the *WNT4* gene showed an increase in genotypic frequencies in participants in cases vs. controls. However, none of the SNPs showed significant association in terms of allelic frequencies between endometriosis cases vs. controls (Table 5.8). There were no instances of CC homozygotes for SNP rs55938609, even though this was a common SNP (MAF=0.14) in other populations. After adjustment of age and BMI, SNP rs12037376 ($OR_{A\ vs.\ G}$=1.89 (95% CI: 1.06, 3.37), p=0.029) and

rs3820282 ($OR_{T\ vs.\ C}$ =1.90 (95% CI: 1.05, 3.46), p=0.033) were positively associated with endometriosis (Table 5.9).

Table 5.8. Genotype and allele frequency comparisons of endometriosis cases vs. controls.

Gene	SNP	Genotype/Alleles		Frequency n (%)		Odds Ratio (95% CI)	*p*-value
				Case	Control		
VEZT	rs12320196	Genotype	GG	26	36	1.00	**0.021**
			GA	51	53	1.33 (0.71, 2.51)	
			AA	23	11	2.90 (1.20	
		Alleles	G	103	125	1.00	**0.033**
			A	97	75	1.57 (1.05, 2.34)	
	rs10859863	Genotype	TT	26	36	1.00	**0.039**
			TC	51	51	1.38 (0.73, 2.62)	
			CC	23	13	2.45 (1.05, 5.71)	
		Alleles	T	103	123	1.00	0.055
			C	97	77	1.50 (1.00, 2.24)	
	rs4762326	Genotype	GG	26	36	1.00	**0.046**
			GC	53	52	1.41 (0.75, 2.66)	
			CC	21	12	2.42 (1.01, 5.79)	
		Alleles	G	105	124	1.00	0.068
			C	95	76	1.48 (0.99, 2.20)	
WNT4	rs12037376	Genotype	GG	65	78	1.00	**0.034**
			GA	32	21	1.83 (0.96, 3.47)	
			AA	3	1	3.60 (0.37, 35.4)	
		Alleles	G	162	177	1.00	0.051
			A	38	23	1.81 (1.00, 3.16)	
	rs3820282	Genotype	CC	66	79	1.00	**0.042**
			CT	32	20	1.92 (1.00, 3.66)	
			TT	2	1	2.39 (0.21, 26.99)	
		Alleles	C	164	178	1.00	0.064
			T	36	22	1.78 (1.00, 3.14)	
	rs55938609	Genotype	GG	72	79	1.00	0.249
			GC	28	21	1.54 (0.80, 2.96)	
			CC	0	0	N/A	
		Alleles	G	172	179	1.00	0.360
			C	28	21	1.39 (0.76, 2.54)	

Table 5.9. Association analyses of the SNP with endometriosis using the additive model.

		Unadjusted		Adjusted	
Gene	SNP	Odds Ratio (95% CI)	*p*-value	Odds Ratio (95% CI)	*p*-value
VEZT	rs12320196	1.57 (1.05, 2.33)	0.026	1.60 (1.05, 2.45)	**0.027**
	rs10859863	1.50 (1.01, 2.23)	0.043	1.51 (0.99, 2.28)	0.051
	rs4762326	1.47 (0.99, 2.19)	0.054	1.51 (0.99, 2.31)	0.053
WNT4	rs12037376	1.80 (1.03, 3.16)	0.037	1.89 (1.06, 3.37)	**0.029**
	rs3820282	1.77 (1.00, 3.14)	0.046	1.90 (1.05, 3.46)	**0.033**
	rs55938609	1.38 (0.76, 2.53)	0.285	1.51 (0.78, 2.92)	0.213

Adjusted for Age and BMI

5.4.4 Haplotype association analysis

Haplotype analyses was performed to estimate the genetic contribution of haplotypes to endometriosis which can be more informative and powerful than association of individual variants[491]. Three haplotypes were identified for the *WNT4* gene (Block 1, "GCG", p=0.0370), and two haplotype blocks for the *VEZT* gene (Block 2, "GTG", p=0.0343; "ACC", p=0.0431). Two haplotype blocks for *VEZT* gene and 1 haplotype block for *WNT4* gene were significantly associated with endometriosis (Table 5.10).

Table 5.10. Association analyses of the haplotype block with endometriosis.

Block	Haplotype	Case, Control Frequencies	*p*-value
***WNT4*/1p36.12: Block 1**			
GCG	0.847	0.810, 0.885	**0.0370**
ATC	0.120	0.139, 0.100	0.2243
ATG	0.025	0.041, 0.010	0.0516
***VEZT*/12q22: Block 2**			
GTG	0.562	0.510, 0.615	**0.0343**
ACC	0.425	0.475, 0.375	**0.0431**

5.5 Discussion

Endometriosis is a complex polygenic and multifactorial disease, caused by multiple genetic and environmental factors (inter)acting in parallel[6,492]. Recently, several genome-wide association studies have demonstrated an association between endometriosis and markers located in or near to *VEZT* gene and *WNT4*[59,70,71,74,75]. Here, I have conducted a pilot candidate gene association study to examine the association of 6 SNPs within the *VEZT* and *WNT4* genes to stage III/IV endometriosis in Arab ancestry women.

We observed a significant association for rs12320196 (OR=1.60 (95% CI: 1.05, 2.45), p=0.027) intronic to the *VEZT* gene. Even though the p-value was not significant in the other SNPs, the effect size of the disease locus, the frequency of the disease allele and the extent of LD between marker and disease locus were consistent with expectation. Interestingly, while only the lead SNP in the *VEZT* gene was significantly associated with endometriosis, when haplotype association was conducted based on the three SNPs, both blocks with risk haplotype GTG (p=0.0343) and risk haplotype ACC (p=0.0425) were associated to endometriosis. This demonstrates the added value of capturing the haplotype structure in a candidate region.

It should be noted that there is no evidence that any of the SNPs are causal, and that they could be in LD with a non-genotyped SNP or, indeed, other type of variant. *VEZT* has been demonstrated to have increased expression levels in endometrial tissue samples, suggesting a potential treatment target for endometriosis[493]. *VEZT* is also essential for implantation; embryos from *VEZT*-null mice fail to develop past the blastocyst stage due to a loss of cell–cell adhesion[71]. Given the known physiological roles of VEZT, the potential for a functional role in endometriosis is plausible.

For *WNT4*, an association was identified for SNPs rs12037376 (OR=1.89 (95% CI: 1.06, 3.37), p=0.029) and rs3820282 (OR=1.90 (95% CI: 1.05, 3.46), p=0.033). One haplotype in *WNT4* gene was significantly associated with increased risk of endometriosis (haplotype GCG, p=0.0370). Because of its biological functions, including promoting Müllerian-duct differentiation during embryonic development, as well as cell proliferation, migration, and invasion in the endometrium, *WNT4* is a plausible gene in endometriosis pathogenesis. The *WNT4* gene family is composed by structurally related genes that encode secreted signalling proteins that influences oncogenesis and different embryo developmental processes[66,494]. The *WNT4* gene at 1p36.12 encodes a secreted signalling factor that promotes female sex development, and regulates both postnatal uterine development and progesterone signalling during decidualization[473,495].

VEZT and *WNT4* gene have been repeatedly associated with an increased susceptibility for endometriosis in women of European and Japanese ancestry. Comparison of results for women of Arab ancestry, in this study, and the results for other ethnicities demonstrate the risks have the same directions of effect (Table 5.11). However, the odds ratios in this study of Arab women were consistently higher. There are several possible reasons for the discrepancies in addition to true population-based differences. Fluctuations in sample size along with difference in case selection based on stage, will lead to variation in allele frequency and risk estimation. The inflation observed in Arab women may also be due to consanguinity, where due to high relatedness, genetic drift reduces the number of variable genetic loci and causes the remaining variants to have higher frequencies and effect size. The frequencies of the disease-associated variants are higher, which increases the chances to identify them even with a small sample size[496,497].

Table 5.11. Gene polymorphism among different populations.

SNP	Study	Type	Ethnicity	Number of Cases	Number of Controls	Sample Size	rASRM Stage	Odds Ratio (95% CI)	*p*-value
rs12037376	Luong et al. 2013	Fine Mapping	Caucasian	930	959	1889	Stage I-IV	1.37 (1.15-1.61)	2.73×10^{-4}
	Powell et al. 2016	GWAS	Caucasian	2213	2044	4257	Stage I-IV	1.23 (1.13–1.36)	4.24×10^{-5}
	Sapkota et al. 2017	GWAS	Caucasian + Japanese	17045	191596	208641	Stage III-IV	1.28 (1.18–1.36)	2.69×10^{-9}
	Rahmioglu et al. 2018	GWAS	Caucasian + Japanese	58115	733480	791595	Stage III-IV	1.23 (1.15-1.32)	1.33×10^{-9}
	Galarneau et al.	GWAS	Caucasian	2969	3770	6739	Stage I-IV	1.07 [1.05-1.09]	5.2×10^{-13}
rs3820282	Mafra et al.	CGAS	Caucasian	400	400	800	Stage I-IV	1.32 (1.00–1.75)	0.048
	Powell et al. 2016	GWAS	Caucasian	2213	2044	4257	Stage I-IV	1.24 (1.12–1.35)	1.84×10^{-5}
	Sapkota et al. 2017	GWAS	Caucasian + Japanese	17045	191596	208641	Stage III-IV	1.27 (1.17-1.35)	1.31×10^{-8}
	Rahmioglu et al. 2014	GWAS	Caucasian + Japanese	77167	113636	190803	Stage III-IV	1.35 (1.20-1.52)	5.21×10^{-7}
rs55938609	Powell et al. 2016	GWAS	Caucasian	2213	2044	4257	Stage I-IV	1.24 (1.12–1.37)	2.88×10^{-5}
	Sapkota et al. 2017	GWAS	Caucasian + Japanese	17045	191596	208641	Stage III-IV	1.27 (1.17-1.35)	1.53×10^{-8}
	Uimari et al.	GWAS	Caucasian	3194	7060	10254	Stage III-IV	1.33 (1.20–1.48)	8.33×10^{-7}
rs4762326	Sapkota et al.	GWAS	Caucasian + Japanese	17045	191596	208641	Stage III-IV	1.15 (1.08–1.21)	1.08×10^{-5}
	Galarneau et al.	GWAS	Caucasian	2969	3770	6739	Stage I-IV	1.04 [1.02- 1.06]	5.2×10^{-8}
rs12320196	Sapkota et al. 2017	GWAS	Caucasian	17045	191596	208641	Stage III-IV	1.15 (1.08–1.21)	9.12×10^{-6}
	Rahmioglu et al. 2018	GWAS	Caucasian + Japanese	58115	733480	791595	Stage III-IV	1.14 (1.08-1.20)	2.66×10^{-6}
rs10859863	Sapkota et al. 2017	GWAS	Caucasian	17045	191596	208641	Stage III-IV	1.15 (1.08–1.21)	1.08×10^{-5}
	Galarneau et al.	GWAS	Caucasian	2969	3770	6739	Stage I-IV	1.05 (1.03, 1.06)	1.6×10^{-6}
	Nyholt et al.	GWAS	Caucasian + Japanese	4604	9393	13997	Stage III-IV	1.20 (1.14-1.26)	5.5×10^{-9}
	Rahmioglu et al. 2001	GWAS	Caucasian + Japanese	9039	27343	36382	Stage III-IV	1.20 (1.15–1.27)	3.0×10^{-13}

An advantage of our study was our selection of stage III/IV cases[16], which will likely have increased effect sizes of these loci, and therefore power of detection, consistent with the observation that this case subtype has a greater genetic burden[168]. Because this was a pilot study with limited funding, our study was a-priori insufficiently powered to detect single-site association of endometriosis, hence we did not apply multiple testing correction for interpreting an individual effect of these endometriosis-related variants. Effect size estimation should therefore also be interpreted with caution. The small sample size of this study also explains the large confidence intervals present in single site, genotypic and allelic association analysis. Another limitation is the potential impact of the hidden case-control ancestral admixture and undetected family relationships (consanguinity) on the results of our study. Due to the small sample size, sub-analysis on phenotypic profiles, symptoms or comorbidities was not conducted. Hence, the results must be further explored in an independent, larger study.

Due to the lack of a large-scale Arab reference genome available on a public database, it is difficult to distinguish whether the 3 SNPs that failed quality control analyses were due to allele calling errors, allele frequency differences in populations, or if they were monomorphic SNPs in candidate gene studies. Further studies must be conducted in the Arab ancestry to understand population differentiation and genetic architecture of the allele frequencies in these variants. In addition, comparison of allele frequencies in other available populations, issues with the primers, genotyping problems, and consanguinity may also impact the failed quality control SNPs. How large a contribution the high level of consanguinity plays is unclear. However, it has been reported that longer runs of homozygosity are found in the Arab population, reflecting substantial consanguinity and leading to an increased rate of deleterious variants[498,499], this is demonstrated in our study where one SNP (rs10917151) deviated from HWE ($p=0.01$), possibly due to the high consanguinity in this population[311,500]. In addition, there were no instances of CC homozygotes for SNP rs55938609, even though this was a common SNP (MAF=0.14) in other populations, demonstrating the importance of assessing genetic variants in different populations to define the genetic architecture of endometriosis and the magnitude of the effects of specific risk alleles present in different ethnicities.

The expansion of GWAS to ethnically diverse populations is important to bring medical advances resulting from genome science to the worldwide populations, as well as the fact that the use of diverse populations provides considerable scientific benefits in characterizing risk variants beyond what is achieved in individuals of European descent alone. As more research better elucidates the genetic underpinnings of this disease, and genetic testing continues to enter the clinical arena, it will be imperative to get to a stage in research where we have a sufficiently large panel of SNPs to screen symptomatic women with endometriosis. The panel of genetic variants may be dominantly present in one ancestry, but could be ineffective for other ethnicities, which may lead to misinterpretation and propagate undiagnosed causes. There is a widely different prevalence of variant alleles across different ethnic groups, with some variants being confined primarily to one or the other ethnic group. When extrapolating data from one ethnic group to another, it is also self-evident that inter-ethnic differences (in drug pharmacokinetics) will be most apparent that are functionally relevant and prevalent with widely different ethnic frequencies.

GWAS specific to Arab women may enable us to possibly identify new genes associated with endometriosis. A few limitations with GWAS studies in Arab population is confounding bias due to relatedness and consanguinity. Currently available technology has been customized from outbred populations. For example, commercially available SNP arrays were primarily designed using haplotype and sequence information from outbred populations. Consequently, the SNPs included in these arrays may be less informative for isolated populations because of the difference in linkage disequilibrium and failure to capture variants that are either novel to a population or that occur at a much higher frequency than in outbred populations. Therefore, in addition to performing GWASs, many studies in isolated populations have directly assessed risk alleles identified in outbred populations to determine their effect in isolated populations. In some limited cases, where there is a very strong family history of endometriosis, family-based linkage studies could additionally be used to identify rare, highly penetrant variants associated with endometriosis, although stigma around endometriosis and its symptoms - in particular infertility – may limit the identification of such families, while consanguinity complicates analyses. In addition, family-based

approaches have not been very successful identifying rare variants for endometriosis in women of European ancestry to date.

In conclusion, the results from this study demonstrate the necessity of GWAS in larger sample sizes to reveal and/or confirm genetic variants associated with endometriosis in the Arab population. Such data will also be important for 'trans-ethnic fine mapping' and functional studies an important method to narrow down the signal towards a causal variant. Our data emphasize the importance of assessing genetic variants in different populations to define the genetic architecture of endometriosis and the magnitude of the effects of specific risk alleles in different populations.

Chapter 6. Conclusion

6.1 Discussion

Endometriosis is a chronic and complex gynaecological disease, which provides a substantial challenge for investigators and the health care system[6]. One of the challenges of managing endometriosis is the delayed diagnosis due to the requirement for a surgical investigation[12]. Characterising risk and protective factors could help identify women at risk of endometriosis to improve their diagnostic and care pathway. Available data on this subject are scarce and lack methodological rigour, especially among Arab women. For the first time, this study provides novel data on patient symptomatology and disease experience among Arab women, and investigated differences related to comparison group selection.

Arab ancestry women with endometriosis are underrepresented in research publications and databases, and further research is required to better understand potential variability in the endometriosis phenome and pathophysiology due to environmental and genetics differences. I conducted a systematic review including a meta-analysis of articles to identify the number of peer-reviewed articles that reported the prevalence of multiple gynaecological conditions, including endometriosis, in the Middle Eastern populations. The meta-analysis identified only 12 articles that estimated the prevalence of endometriosis in women of Arab ancestry (12.9% among women undergoing laparoscopy for any indication; 24.9% among infertile women; 12.2% among women hospitalized for pelvic pain; 1.28% in a population-based setting). However, the reliance on surgical confirmation of endometriosis, access to clinics that is mostly limited to married women, and consequent selection biases affect these estimates, as is demonstrated by the heterogeneity estimates in our meta-analyses (Chapter 1.3 and Appendix I for the systematic review and meta-analysis). As the main presenting symptomatology of endometriosis and mode of diagnosis are both influenced by psychosocial factors, women of different cultural backgrounds may present with different clinical phenotypes. Therefore, further epidemiological studies must be conducted to investigate symptomatology and risk factors in women of this region to deliver culturally sensitive healthcare and provide the best practice for diverse patient populations.

With 200 million women in the region, the importance of conducting more research in women's health is clear and is needed to serve as a benchmark for evaluation of future research activities and comparative purposes with Middle Eastern immigrants and other populations. In this thesis, I used the MAR'A study sample to explore the symptomatology, phenotypic profiles, comorbidities, and risk factors among women of Arab ancestry. Key to this endeavour is advancing our understanding of how environmental and genetic factors interplay to disease predispositions and mechanisms in different populations. To investigate whether clinical variables and risk factors were driven by the endometriosis-related symptoms or endometriosis *per se*, comparisons were made between: (1) ascertainment criteria (endometriosis cases vs. hospital controls; and endometriosis cases vs. population controls); and (2) symptomatic criteria (endometriosis cases vs. symptomatic controls; and endometriosis cases vs. asymptomatic controls). The association of risk factors and clinical variables for the development of endometriosis were investigated in Chapter 3. The effect of endometriosis on quality of life, work productivity and estimation of diagnostic delay in this population were demonstrated in Chapter 4. Candidate gene association studies of SNPs within *VEZT* and *WNT4* genes with endometriosis were presented in Chapter 5.

6.1.1 Key findings and clinical significance

Sociodemographic risk factors

Women with endometriosis had a lower BMI, lower WHRadjBMI, and more frequent family history of endometriosis, in comparison to all four control groups. Smoking and parental consanguinity was not associated to endometriosis. While women with endometriosis had a greater risk of obtaining a higher educational level in comparison to asymptomatic and population control group, endometriosis women had a significantly higher unemployment rate. The association with higher educational level may reflect socioeconomic biases, such as access to medical care and importance placed on seeking such care, or it may be associated to delay in childbearing resulting in a higher rate of endometriosis diagnosis[383]. However, in comparison to symptomatic controls and hospital controls, endometriosis women had no significant difference in educational level or employment rate. This indicated that these variables are associated with

symptoms (pain and infertility), or correlated factors such as health care seeking behaviour, and not endometriosis *per se*. These health care seeking factors include the ability to recognize symptoms and signs, perception of severity, social characteristics, availability of treatment resources, and competing needs[384]. Divorce rate was higher in women with symptoms, regardless of gynaecological pathology. There may be a cultural link where childlessness strongly influences marital life, and may lead to divorce from their husband, or becoming a second wife in a polygamous marriage[281,282]. In fact, 88.2% of the divorced women in this study sample were from a childless marriage. It was observed that war exposure is associated with symptoms, and not endometriosis *per se*, possibly due to the exposure of these chemicals on the immunological response, stress, malnourishment and lack of access to medical facilities[284,386].

Physical activity

In this study, the intensity of physical activity was not associated with endometriosis, when compared to symptomatic (p=0.405) or asymptomatic controls (p=0.144). All groups (endometriosis cases, symptomatic controls and asymptomatic controls) performed less exercise than the recommended guidelines of at least 500 MET-minutes per week of moderate-to-vigorous physical activities[436]. The prevalence of physical inactivity was 67.2%, which could partly contribute to the high proportion of overweight and obese women in this study (65.2%). There are various personal and environmental factors that act as barriers for Arab women to participate in physical activity, including: cultural norms and practices of public modesty, lack of accessible environments and fitness facilities for women to feel comfortable to exercise, lack of supportive social milieu for women, conservative dress that is not suitable for physical activity, and lack of information on the importance of physical activity in schools[253,254]. Thus, both general and gender norms are a barrier to physical activity among Arab women, and as such programmes aimed at increasing physical activity are difficult to implement. Therefore, culturally tailored physical activity intervention need to be implemented, such as a women-only setting with female facilitators, social support, improve physical environment interventions, and deliver physical health education to increase physical activity and decrease the prevalence of obesity in the region[501,502].

Pain phenotype

Characterising the frequency of multiple types of pain associated with endometriosis in diverse ethnic groups is important to optimise treatment strategies and early diagnosis. Our findings suggest that while women with endometriosis report more site-specific pain particularly involving dysmenorrhea, chronic pelvic pain, dysuria, and dyschezia, other comorbid pain conditions, such as leg pain and migraine were associated with endometriosis, when compared to symptomatic controls with surgical confirmation and no surgical confirmation. Mechanisms responsible for severity of painful symptoms associated with endometriosis may include the interaction among ectopic endometriotic implant, nociceptors and nerve fibers[17,387,388]. Intermittent or ongoing pain resulting from a disease can produce a sensitized peripheral and central nervous system (peripheral and central sensitization) that becomes maladaptive (centralization of pain). Central sensitization has been reported in women with endometriosis, and can occur with other types of visceral pain[83,86,389]. Most pelvic organs, as well as somatic pelvic tissues to which the pain is referred, share at least part of their central sensory projection. Migraine pain, for example, is initiated and sustained by trigeminal activation involving peripheral and central structures[253,390]. This may trigger the phenomena of cross-sensitization and central sensitization, as well as the presence and coexistence of multiple pain phenotypes that are cross-linked with one another. Follow-up studies to assess the impact of race, ethnicity, and socioeconomic factors on the pain catastrophizing scores in this patient population are warranted.

For dysmenorrhea and chronic pelvic pain, women with endometriosis have a higher NRS severity, more severe VAS stage, earlier age of symptom onset and pain catastrophizing score, in comparison to symptomatic controls that are endometriosis-free (laparoscopy-confirmed) and symptomatic controls with no surgical confirmation. Given that approximately 90% of the women were taking over-the-counter painkillers for the pelvic pain, which were inadequate to control the pain, women might be perpetuating the significant delay in diagnosing endometriosis[391]. In addition, even while hormonal treatments are predominantly used for pain management, only less than half of the women (42%) agreed to use hormonal medications to relief the endometriosis-related pain. Women in the Middle East are often discouraged to

use contraceptive methods due to the pro-natal attitudes and prevailing fears that contraception may reduce a woman's fertility[503].

Ever married parous women had a lower likelihood of developing dysmenorrhea (women with endometriosis, p=0.010; symptomatic control, p=0.027) and dysuria (women with endometriosis, p=0.010; symptomatic control, p=0.047), regardless of the presence of endometriosis. There are several potential reasons for this observation, including reduced exposure to retrograde menstruation that may prevent lesions from occurring, and that pregnancy may be associated with decidualization and subsequent necrosis of the regression of endometriotic lesions during pregnancy, hence suppressing the symptoms of endometriosis[121,392].

Rigid cultural norms and expectations oblige Arab women to accept and conceal physical pain, and the consequence of persistent pain emphasizes that women with endometriosis need to consult immediately after symptom onset and be treated actively when they first seek medical care[93,389,456–458272]. The prolonged period of the unknown cause of the exacerbating symptoms has a critical impact on a woman's illness trajectory.

Menstrual characteristics

As described in other populations, endometriosis was associated with earlier age (≤12) at menarche, with shorter (≤24) menstrual cycle length, heavy menstrual flow, and long (≥7) duration of menstrual phase, compared to symptomatic controls, asymptomatic controls, hospital controls and population controls. Menstrual cycle irregularity was not associated with endometriosis in comparison to symptomatic controls (p=0.411) and hospital controls (p=0.363), however a significant association was present when comparing it to asymptomatic controls (p<0.001) and population controls (p=0.001). This suggests that menstrual irregularity may be more associated with symptoms such as pelvic pain or infertility, than endometriosis *per se*. These menstrual characteristics reflect increased exposure to menstruation and provide strong support to Sampson's theory of retrograde menstruation, where women who have menstrual characteristics

that offer greater opportunities for reflux to the peritoneal cavity by menstrual debris are at increased risk of endometriosis[24].

Fertility and reproductive characteristics

When investigating the frequency of infertility on the study, 64.9% (281/433) of endometriosis cases and 55.2% (624/1130) of controls were infertile (<0.001). After adjustment to sociodemographic variables, age at menarche and OCP use, women with endometriosis were at a greater risk of being infertile than symptomatic controls (OR: 1.33 (95% CI: 1.05, 1.69); p=0.017). Infertility has psychological effects in terms of anxiety, stress, depression and self-esteem, mostly affecting mental health[136]. While this association is common across different populations, it may be intensified in this ethnic group because childlessness strongly influences marital life, and unfortunately may lead to divorce, or becoming a second wife in a polygamous marriage[281,282]. Divorced women in Arab societies suffer emotionally and socially, especially when they are infertile. Infertility has a significant impact on the mental health components in our study because Arab women are often blamed when conception does not occur, and feel pressure from their husband as if they are not fulfilling their reproductive responsibility[371].

Women with endometriosis were also more prone to have adverse pregnancy outcomes, such as risk of miscarriage, ectopic pregnancy, preterm birth, and emergency caesarean section among. Gestational diabetes, pregnancy related high blood pressure, and pre-eclampsia were not associated to endometriosis.

Comorbidities

Endometriosis was significantly associated with asthma, eczema, and type 1 diabetes mellites, across all four control groups. Our study demonstrated no association between endometriosis and metabolic disorders, such as diabetes mellitus type 2 and hypertension. However, in comparison to asymptomatic controls and population controls, women with endometriosis had a higher rate of cardiovascular disorder (p=0.015; p<0.001). This association was not significant when comparing it to symptomatic controls (p=0.111) and hospital controls (p=0.122), demonstrating that this may be associated to the symptoms and not

endometriosis *per se.* Women with endometriosis had a greater risk of uterine fibroids and Mullerian tube abnormalities. Anxiety and depression were significantly associated with endometriosis, in comparison to all four control groups.

Quality of life

Due to the lack of normative values available for the SF36v2 scores on the Middle Eastern countries, the population-based controls were utilized to establish a normative data for the SF36v2 questionnaire for women of Arab ancestry. Country-specific scores have the advantage of better representing the structure of health in each country, where these are likely to differ substantially from published population normative data. Our results indicated credible reliability and validity of the SF36v2 normative values, which were consistent with the outcomes of other countries, and applicable for evaluating the quality of life in the general population.

HRQoL scores were significantly impaired in women with endometriosis, as demonstrated in the PCS and MCS scores in symptomatic control group ($p=0.001$; $p=0.003$, respectively) and asymptomatic control group ($p<0.001$; $p<0.001$, respectively). Susceptibility of multiple pain symptoms and infertility in women with endometriosis was the main indicator of a lower HRQoL. Cultural expectation for Arab women to conceal mental distress, whilst suffering from physical pain and/or infertility, may contribute to poor mental HRQoL and increased risk of developing psychological disorders[262,276].

When investigating the impact of pelvic pain severity, with or without surgically confirmed endometriosis pathology, a similar impact on PCS score ($p<0.001$) and MCS score ($p<0.0001$) was observed. Arab women who suffer from chronic pain are subjected to pressure because of the transition from care-provider to care-receiver when suffering from debilitating, symptomatic episodes[504]. Due to the burden to their commitments of their roles as mothers and housewives, it may be the presence of multiple pain phenotypes and severity that is associated with HRQoL, and not the presence of endometriosis *per se.* The evidence presented in this study supports the existence of multifactorial impacts of endometriosis on quality of life, particularly

the degree and severity of influence of individual symptoms (pain and infertility) and the delay in diagnosis from age at symptom onset.

Diagnostic delay

The diagnostic delay from first onset of symptoms to diagnosis was 11.61 years among Arab women. Within this, the interval from the first onset of symptoms to first gynaecological consultation was 6.01 years, and between first gynaecological consultation to diagnosis was 6.96 years. Due to cultural stigma, single women do not visit a gynaecologist when experiencing chronic pain or menstrual irregularities, hence prolong suffering. This is reflected in the delay of diagnosis by 15.81 years among single women. This is also demonstrated in the greater delay of diagnosis when suffering from pelvic pain (12.44 years) versus infertility (7.32 years). Chronic peripheral pain stimulation followed by sensitization of the central nervous system can result in irreversible damage[389,456]. This may lead to chronic pain, scarring, compromised fecundability and psychological distress, as demonstrated in this study where diagnostic delay led to a significant impairment on HRQoL, with poorer PCS and MCS scores (PCS: $p<0.001$, MCS: $p<0.001$)[505,506].

Time for symptom onset to first consultation with medical physician was significantly longer for Arab women, which may be due to normalization of menstrual pain among patients and their families, particularly if present at menarche. We need to ensure that women from a culturally and linguistically diverse background are provided with adequate knowledge. Several reasons for diagnostic delays in endometriosis have been proposed, involving both patient and physician related factors, lack of awareness of endometriosis, inability to distinguish normal from abnormal menstrual features, sociological stigma in relation to menstruation and cultural factors of visiting a gynaecologist before marriage. Therefore, in addition to diagnostic delay among the physicians and associated referral patterns, cultural issues may contribute to the delay in seeking gynaecological help.

Work productivity and activity impairment

When comparing the impact of symptoms on work productivity and activity impairment, women with endometriosis reported a greater impairment in terms of absenteeism (p=0.011), presenteeism (p=0.002) and overall work productivity loss (p=0.001) in comparison to symptomatic controls. This demonstrates the importance of addressing these symptoms to improve, not only HRQoL, but also on the employment and career components of the life course of women with endometriosis.

Candidate gene association study of VEZT and WNT4 genes

In addition to investigating the epidemiological factors, I have conducted a candidate gene association study to examine the association of six SNPs within the *VEZT* and *WNT4* genes to stage III/IV endometriosis in Arab ancestry women. We observed a significant association for rs12320196 (p=0.027) intronic to the *VEZT* gene. Interestingly, while only the lead SNP in the *VEZT* gene was associated with endometriosis, when haplotype group associations were investigated including the three SNPs, both blocks with haplotype GTG (p=0.0343) and haplotype ACC (p=0.0425) were associated to endometriosis. For the SNP located in the *WNT4* gene, an association was identified for SNP rs12037376 (p=0.029) and rs3820282 (p=0.033). One haplotype window located in *WNT4* gene was significant (haplotype GCG, p=0.0370). Further fine-mapping efforts needed to find the causal SNPs and additional genetic work in the population.

6.1.2 Strengths and limitations of the study

The study recruited 2,610 women from multiple recruitment sites across the UAE that offered sufficient statistical power for testing each study hypothesis. Standardized and comprehensive epidemiological information on endometriosis and its associated symptoms was collected using validated tools and questionnaires. The questionnaire collected detailed information on the lifelong medical history and experiences of women with endometriosis not previously reported in this population. The case-control analyses provided novel insights into the effects of endometriosis on women's lives and tested the

association of the disease with several sociodemographic, reproductive, contraceptive, lifestyle, and personal characteristics.

The advantage of the case-control design is that we were able to investigate a wide range of risk factors and test hypotheses[313]. The design of the study attempted to address methodological limitations of previous epidemiological studies, particularly in relation to the application of consistent case definitions, appropriate selection of controls sampled from the same source population as cases, and collection of comprehensive information on risk-factor exposure to allow control of confounding factors. Another area of strength of the study is that it recruited women across diverse health systems (public and private hospitals), and controls from hospitals and population-based sites, thus enabling comparisons across these settings. The use of surgically confirmed incident endometriosis cases and the selection of multiple control groups facilitated analyses by comparing the contribution of control group selection to the results. In addition, incident rather than prevalent endometriosis cases was recruited to allow for the collection of unbiased exposure information pre-dating disease onset. The interval between risk factor exposure and onset of disease is however unknown and recruiting incident cases may not completely isolate the influence of disease duration on exposure, particularly if symptoms are long-standing.

Potential limitations of a case-control study are selection biases, when cases and controls are not sampled from the same source population and thus are not comparable in terms of exposures; recall bias where the cases are likely to recall their exposure history more reliability than controls; and information bias where exposure status may be ascertained after disease has already occurred[315–318]. I carefully considered precision (Chapter 2.6.2), internal validity (Chapter 2.3.3 and Chapter 3.4.2), and external validity (Chapter 2.3.3 and Chapter 3.4.2) of the results. We selected a representative source population (Chapter 2.2.1, Chapter 2.2.2, and Chapter 3.3.1) and we implemented maximum efforts to reduce various biases (Chapter 2.3.3) in the recruitment process (Chapter 2.2.2). The need for laparoscopy to diagnose endometriosis demonstrates the risk of including women with undiagnosed endometriosis in population-based control groups, resulting in indication biases. Until a non-invasive sample test is available that may be applied at a population level,

critical care is needed on the selection of the control group to reduce ascertainment bias. Choosing an appropriate control group for endometriosis cases is complex, and multiple groups sampled from population and hospital based settings, as we used in this study, allowed the testing of sensitivity of results to control group choice[11]. The control group was recruited from population sites and hospitals/clinics from which the cases were enrolled. Although controls did not report a prior endometriosis diagnosis, some were likely to have undiagnosed endometriosis, meaning our estimates may be affected by misclassification of endometriosis among the controls. This would have driven the associations observed to the null hypothesis of no difference, rather than creating spurious associations. Nevertheless, the prevalence of undiagnosed moderate-severe endometriosis in the general population group is likely to be low (<2%), therefore the control group is unlikely to contain many undiagnosed cases, especially if they were screened for moderate to severe pelvic symptoms[11]. In addition, we found no significant magnitude of effect on the distribution of demographic factors or pain phenotypes among symptomatic controls (endometriosis-free) with laparoscopic confirmation vs. symptomatic controls with no surgical diagnosis or between hospital-based and population-based controls, suggesting that the potential presence of undiagnosed cases in our symptomatic control group had little impact on the results of the analyses we have presented.

Social and cultural factors play a role in diagnostic bias. Women in this region will more likely consult a physician for fertility-related issues, as opposed to pain or menstrual irregularities. Even though nearly all women suffered from pelvic pain in this study sample, only 36.8% of Arab women proceeded with surgical investigation due to pain-related symptoms, whereas 61.8% proceeded for fertility-related reasons. Therefore, women with infertility, or moderate/severe pain symptoms were over-represented in our patient sample because cases were enrolled in hospitals (which are typically more complex and severe cases of endometriosis), when compared to those with asymptomatic or mild symptoms that avoid seeking care from a gynaecologist. This may also make it difficult to assess the temporal relation of the outcomes with endometriosis. Potential under-ascertainment is a possibility if potential cases in the population suffer from pain without infertility, or single women who are less likely to proceed with surgical confirmation. Until a

non-invasive sample test is available that may be applied at a population level, critical care is needed on the selection of the control group to reduce ascertainment bias.

Dyspareunia is an important pain aetiology in women with endometriosis and may be a clinical marker for central sensitization. In this study sample, only 4% of the women answered questions relating to dyspareunia. Arab women with sexual pain may suffer in silence, impacting their quality of life, wellbeing, management, and treatment plan. The lack of data on this topic demonstrates that Arab women with sexual pain may suffer in silence, and the impact of psychosocial expectations to prioritize privacy over their quality of life and wellbeing. Further understanding of the type and severity of dyspareunia phenotype may lead to a more personalized treatment approach. To study this sensitive topic among Arab women, sex education and psychosexual therapy must be easily accessible to be able to tackle cultural taboos and social pressures regarding dyspareunia. Even though the forward/backward translation panel included 5 scientists and medical physicians that assisted in translated the questionnaires, it would be beneficial to include a panel of patients that will provide a new perspective when developing culturally sensitive translated questionnaires.

While this study included a range of pain scales, such as the Visual Analog Scale, Numeric Rating Scale, Pain Catastrophizing scale, and McGill Pain Questionnaire, further pain tools, such as the Central Sensitization scale[507] and the painDETECT scale[508] would be beneficial to measure in Arab women. The Central Sensitization scale[507] is used to measure central sensitization, including neuronal dysregulation, hyperexcitability, noxious and non-noxious stimuli, and the painDETECT scale[508] consists of seven sensory symptom items to measure neuropathic components. These tools were not included initially because they have not been translated and validated in the Arabic language. Therefore, after standardization and validation of both tools in the Arabic language, they would be implemented and measured among Arab women in future studies.

Misclassification of comorbid conditions is possible and may under or overestimate the true prevalence of coexisting disease. It is possible that the symptomatic women and highly educated women would have

sought diagnosis of other conditions. However, the use of the population-based sample limited this bias. In addition, sensitively analyses were done on the comparison between sociodemographic factors of hospital and population-based controls with the UAE census data. This provides support for the validity of the conclusions with respect to these reported diagnoses.

It should be noted that the findings may not be generalisable to women who currently reside in countries that are exposed to war (Iraq, Palestine, Syria, Lebanon, Yemen) due to the lack of access to healthcare, low standard of care, low accessibility to adequate medical supplies, lack of qualified medical staff, mental health impact and the lack of attention for women's health due to high mortality and morbidity directly due to war and conflict. In addition, while the study findings may not be generalisable to Arab women residing in countries outside the Middle Eastern region, these findings could be used to make cross-cultural comparisons. Investigating the quality of life of Arab women residing in Western societies can be compared with those in this study, to elucidate similarities and differences among cultures, as well as the genetic and non-genetic underpinnings of clinical variables. This may enable an exploration of geographical variations in healthcare provisions for women with endometriosis.

There are methodological drawbacks with case-control studies, such as uncertain temporality and causality in the relationships between exposure and outcome in this study. Hence, longitudinal cohort studies would be more suited to investigate protective and risk factors and are the gold standard for the assessment of exposure risk factors as they are less prone to differential measurement error due to poor recall of past exposures, less susceptibility to selection bias, and could study multiple comorbid conditions to endometriosis. Prospective cohort studies are associated with a higher level of evidence for causality, mostly because exposures are recorded prior to outcome data. In addition, cohort studies can examine various outcome variables with a more efficient way to eliminate all possibility of a confounding variables.

6.2 Future suggestions

This study has presented novel findings of the investigation of symptomatology, risk factors and phenotypic information for epidemiological and genetic studies in women of Arab ancestry. The findings need further

validation, and there are various areas of research that remain to be explored in women of Arab ancestry. Advancements in nonsurgical diagnosis and in obtaining epidemiologic data among diverse groups are first steps in addressing ethnic disparities.

Large, longitudinal prospective studies with sufficient statistical power are the best option to investigate temporal associations between endometriosis and clinical variables and outcomes in subgroups based on stage, site, symptoms, and age. Therefore, the objective is to expand the MAR'A project with the potential to provide: (1) valuable leads into poorly understood causes and consequences of endometriosis, (2) robust data to confirm or refute association of endometriosis with various long term health outcomes, (3) exploration of novel associations and modifiable risk factors, (4) identification of a critical window for prevention or targeted interventions, (5) risk stratification for the development of personalised medicine, and (6) estimation of the disease burden to inform health services planning. In addition, we also aim to collect saliva samples from specific patient subgroups, such as adolescents or women with different symptoms (pain or infertility), which in prospective studies may provide further opportunities to explore variations in endometriosis pathogenesis.

To facilitate large-scale internationally collaborative, longitudinal, epidemiological research in endometriosis, we aim to continue to utilize the following four World Endometriosis Research Foundation (WERF) Endometriosis Phenome and Biobanking Harmonisation Project (EPHect) tools for data collection: (1) Surgical phenotype data collection in endometriosis research[339], (2) Clinical and covariate phenotype data collection in endometriosis research[338], (3) fluid biospecimen collection, processing, and storage in endometriosis research[340], and (4) tissue collection, processing, and storage in endometriosis research[341]. This study is envisaged to promote evidence-based reproductive medicine in the region, not only benefitting the local population, but also providing a basis for Middle Eastern women abroad.

A substantial proportion of women in this study delayed seeking gynaecological help when they were suffering from pelvic pain resulting in the observed substantial diagnostic delay. Therefore, studying the adolescent group will allow us to provide detail of diagnostic and referral patterns in the longer term.

Despite the prevalence of endometriosis and its significant burden on women, their families, society and the healthcare system, the disease is under researched and underprioritized. An important challenge in endometriosis research is that diagnosis is dependent on the visualisation of lesions, irrespective of symptoms. This is a major issue due to a higher likelihood of misdiagnosis and a lack of a non-invasive diagnostic tools (biomarker or radiologic imaging). A reliable, non-invasive biomarker serves as a surrogate for the presence of endometriosis would resolve this issue. Future in vitro and in vivo studies are required to identify biomarkers for diagnosing and monitoring the progression of endometriosis, with the consideration of the diverse set of symptoms and heterogeneous lesion types, whilst being culturally sensitive and accessible to a diverse set of population.

Global endometriosis research is dominated by studies in women of European ancestry, with limited studies conducted in the Asian, Arab, and African populations. The need for an assessment of the worldwide endometriosis research architecture becomes even more pressing when the limited number of studies with a global perspective on endometriosis is compared with the fact that this enigmatic disease heavily affects female health in a global context. A closer look into the global endometriosis research architecture exemplifies that a large gap of research activity exists in the Middle East.

In addition, the association of candidate genes to endometriosis demonstrated in this study showed that these specific common variants also affect endometriosis risk in women of Arab ancestry. Previous studies on European and Japanese populations have now identified 46 loci harbouring common risk variants, but the definite genetic variants causally related to endometriosis are yet to be defined. Ethnicity can confound results in pharmacogenomic studies. Allele frequencies of loci that influence drug metabolism can vary substantially between different ethnicities and underlying ancestral genetic differences can lead to spurious findings in pharmacogenomic association studies. To assess gene-gene and gene-environment interactions robustly without a strong prior hypothesis, well-designed studies in even larger samples and more diverse GWAS studies are necessary.

There are analytical challenges to performing GWAS in individuals of Arab ancestry, with care needed in quality control, imputation, and association testing, but the benefits to genetic discovery from recruiting ancestrally heterogenous populations are considerable. To facilitate GWAS studies in the Arab ethnic group, the 1000 Arab Genome project, led by one of my external supervisors (Dr. Habiba Alsafar), aims to provide data to sequence Arab ethnic participants to provide data to improve our understanding of the Arab genome and catalogue variants that are unique to the Arab population of the UAE. The outcomes of this project include establishing a customized DNA-based assay to screen for the genetic polymorphisms and a genome panel that will serve as a reference for future imputation studies. This will be an exciting avenue in the region, with the first GWAS being conducted pertaining to women's reproductive health. It will also encourage trans-ethnic studies to ensure that the benefits of the genetic revolution and of personalized medicine are universal.

While the results of this study have been a step forward to better our understanding on endometriosis among Arab women, further support is required to target younger Arab women in this region to advance their understanding of reproductive health literacy and increase awareness of the severe impact of this condition and associated symptoms. The scientific and medical professional need an informed understanding of the heterogenous array of religious beliefs, cultural norms, and traditional expectations in the community, to ensure they are providing culturally sensitive, comprehensive care. There is a need to distribute an in-depth understanding of the personal and culturally centred beliefs of Arab women within the realms of their lives as young adolescents and adults, and how their psychological measures impact endometriosis phenome and clinical presentations.

6.3 Conclusion

This study provided novel findings and a comprehensive understanding of the true burden of endometriosis among Arab women. Along with the presence, duration and severity of the pain phenotypes, women in the Middle East experience among the highest diagnostic delay of endometriosis, which might be a driving force in the development of pain sensitization[389,456]. In addition, social exacerbation may influence management of endometriosis-associated pain, due to sociocultural factors, stress-related physiological responses and psychological distress[509–511]. Greater prevalence of empirical, over-the-counter medication usage by affected women leads to unsuccessful attempts to mitigate multiple pain phenotypes[391]. In fact, less than half of the participants in this study stated that medical treatment has relieved their pain. Central sensitisation suggests that endometriotic tissue, as disease advances, generates persistent pain stimuli in the central nervous system, resulting over time in heightened pain awareness even from regions with no implanted tissue[93,389,456,459]. If true, such heightened awareness could explain the persistent impact of worsening endometriosis on HRQoL and would highlight the need to reduce the impact of the disease by early symptom control approaches that target central sensitization.

It is important to acknowledge the influence of cultural sensitivities, traditions, and religious heterogeneity in different aspects of reproductive health disparities in healthcare that can act as barriers and directly impact Arab women. This will improve the need to elucidate the role of risk and protective factors in their relationship with endometriosis. Societal normalization of women's pain and the taboo around topics like dyspareunia, pain or menstruation may prevent women from seeking care or discussing symptoms. Given the well-established racial and ethnic disparities in the treatment of individual conceptualization of pain[157,512] and the traditional barriers that women face when trying to receive a diagnosis, validated tools to improve clinical recognition are an important consideration for future work to minimize disparities. Further areas of research should define barriers faced by Middle Eastern women, including access to diagnostic and high-quality surgical treatment, where the cultural and religious features of Arab populations, along with

the patriarchal nature of these societies, greatly influence the beliefs, preference, and health-seeking behaviour of endometriosis.

Due to the lack of information and awareness on reproductive health in the educational system for young adolescent girls, it is important to educate them of the cyclical physiological processes of their bodies to be able to recognize normal and pathological changes. This will also encourage adolescent Arab women to consult with a gynaecologist when suffering from pelvic pain or menstrual irregularity.

Women with endometriosis-associated symptoms should be referred to centers of expertise, led by those with training in complex benign gynaecology and referred to a multi-disciplinary team that includes a psychologist, gynaecology radiologist, pain specialist and with support from patient organizations. Further research should identify symptom control strategies that target those pathways to improve the outlook for affected women.

Our study will enable the establishment of communities for ongoing support and intends to build on the strength of women-centered networks for Arab women. There is a need to conduct an in-depth understanding of the personal and culturally centered beliefs of Arab women within the realms of their lives as young adolescents and adults. Such understanding will allow policymakers, stakeholders, and medical physicians to improve management and develop targeted health education awareness campaigns for Arab women that struggle with endometriosis, which will differ from the current, more western-centric approaches. Additional support is required to target younger Arab women in this region to advance their understanding of reproductive health literacy and increase awareness of the severe impact of this condition and associated symptoms.

Appendices

Appendix 1.

Mousa, Mira, Moamar Al-Jefout, Habiba Alsafar, Christian M. Becker, Krina T. Zondervan, and Nilufer Rahmioglu. "Impact of Endometriosis in Women of Arab Ancestry on: Health-Related Quality of Life, Work Productivity, and Diagnostic Delay." *Frontiers in Global Women's Health* (2021): 66.

Appendix II.

Mousa, Mira, Moamar Al-Jefout, Habiba Alsafar, Shona Kirtley, Cecilia M. Lindgren, Stacey A. Missmer, Christian M. Becker, Krina T. Zondervan, and Nilufer Rahmioglu. "Prevalence of Common Gynecological Conditions in the Middle East: Systematic Review and Meta-analysis." *Frontiers in Reproductive Health* 3 (2021): 7.

Appendix III.

Participant information sheet, informed consent form and questionnaire in the English language.

Appendix IV.

Participant information sheet, informed consent form and questionnaire in the Arabic language.

Appendix I

frontiers in Reproductive Health

SYSTEMATIC REVIEW
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Prevalence of Common Gynecological Conditions in the Middle East: Systematic Review and Meta-Analysis

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Introduction: High prevalence of gynecological conditions in women of Middle Eastern origin is reported, likely due to regional risk factors and mediators. The objective of this systematic review and meta-analysis is to investigate the prevalence of polycystic ovary syndrome (PCOS), endometriosis, uterine fibroids, and adenomyosis in women of Middle Eastern origin.

Methods: MEDLINE, EMBASE, PsycINFO, Global Health, and Google Scholar databases were searched from database inception until 14 February 2021 to identify relevant studies. Peer-reviewed research articles that reported the prevalence of PCOS, endometriosis, uterine fibroids, and adenomyosis in the Middle Eastern population were written in English or Arabic. The primary outcome was the estimated pooled prevalence of PCOS, endometriosis, uterine fibroids, and adenomyosis in the Middle Eastern populations. The secondary outcome was to assess the evidence in the data for the presence of heterogeneity, by conducting subtype-pooled analysis of prevalence estimates of the conditions. Total weighted prevalence was calculated via Freeman–Tukey arcsine transformation and heterogeneity through the I^2 statistic. Quality control was performed using GRADE criteria.

Results: A total of 47 studies, 26 on PCOS, 12 on endometriosis, eight on uterine fibroids, and seven on adenomyosis, were included. The pooled prevalence of PCOS diagnosed according to the NIH criteria was 8.9% (95% CI: 6.5–11.7; prevalence range: 4.0–27.6%), with a higher prevalence from the Gulf Arab states (18.8%, 95%

CI: 9.5–30.3; range: 12.1–27.6%). According to the Rotterdam criteria, the pooled prevalence of PCOS was 11.9% (95% CI: 7.1–17.7; range: 3.4–19.9%) with studies limited to the Persian and Levant regions. Endometriosis was diagnosed in 12.9% (95% CI: 4.2–25.4; range: 4.2–21.0%) of women undergoing laparoscopy, for any indication. Uterine fibroid and adenomyosis prevalence of women was 30.6% (95% CI: 24.9–36.7; range: 18.5–42.6%) and 30.8% (95% CI: 27.1–34.6, range: 25.6–37.7%), respectively. Heterogeneity was present between studies due to statistical and methodological inconsistencies between studies, and quality of evidence was low due to sample size and unrepresentative participant selection.

Conclusion: This is the first review that has reported the prevalence of gynecological diseases in the Middle Eastern population, suggesting that gynecological morbidity is a public health concern. Due to the health disparities in women, further research is required to understand the relative roles of environmental and genetic factors in the region to serve as a benchmark for evaluation and comparative purposes with other populations.

Keywords: gynecological disease, epidemiology, global health, Middle East, polycystic ovary syndrome, endometriosis, uterine fibroids, adenomyosis

INTRODUCTION

Polycystic ovary syndrome (PCOS), endometriosis, uterine fibroids, and adenomyosis are common benign gynecological conditions that affect women of reproductive age. They are often associated with dysfunctional uterine bleeding, pelvic pain, subfertility, psychological morbidity, and comorbid diseases (1–4). Genetic and environmental factors contribute to the risk of gynecological conditions, but none are currently specific enough to be clinically relevant. In addition, little is known regarding the reasons for the heterogeneity in symptomatology and contributing factors attributable to gynecological conditions in different populations of women, especially women of Middle Eastern origin. **Table 1** summarizes the clinical epidemiology of PCOS, uterine fibroids, endometriosis, and adenomyosis, based on global statistics of mainly European ancestry populations.

The Middle East represents 6.8% of the world's population (23 countries), yet it contributes <1% toward scientific research (28–31). Cross-population comparisons and regional differences, influenced by geographic, cultural, socioeconomic, genetic, and environmental factors, may alter health outcome measures associated with prevalence, symptomatology, diagnosis, and management of gynecological phenotypes. A high prevalence of gynecological conditions has been suggested in women of Middle Eastern origin, possibly due to consanguinity, obesity rates, environmental toxins from war exposure, and lack of awareness of reproductive health among adolescence (32–37).

The Middle East is a transcontinental region that consists of the Gulf Cooperative Council (GCC) Region (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates, Yemen), the Levant region (Cyprus, Iraq, Israel, Jordan, Lebanon, Palestine, Syria, Turkey), the North African region (Algeria, Egypt, Libya, Morocco, Somalia, Sudan, Tunisia), and the Persian region (Iran). The Middle Eastern populations have different degrees of genetic admixture, and higher prevalence of globally rare genetic variations with a highly conserved gene pool, due to consanguineous marriages and intercontinental migration (38–41). Consanguineous marriages account for 20–50% of marriages in the Arab ancestry Middle Eastern populations, resulting in higher frequency of recessive Mendelian diseases, large prevalence of deleterious genetic missense variants, and community-specific founder mutations (33, 42, 43). Nevertheless, the Middle East has a very diverse ancestral background, due to intercontinental migration between Africa, Asia, and Europe. Nine Middle Eastern countries have ranked highest in the global obesity statistics, with 70–75% of their populations being obese or overweight, with a 2-fold risk among women vs. men (36, 44–48). Physical inactivity and obesity rates in the region have been associated with gynecological diseases and menstrual disorders (49, 50). Additionally, exposure to war and environmental toxins may alter circulating hormone levels and the immune system of women (51).

This systematic review critically assesses the available evidence and quality of epidemiological studies that focus on the prevalence of common benign gynecological diseases in Middle Eastern populations, to inform public health policy and encourage studies into risk factors and prevention. The primary aim was to conduct a systematic review and meta-analysis of the prevalence of polycystic ovary syndrome, endometriosis, uterine fibroids, and adenomyosis in women of Middle Eastern origin. The secondary aim was to assess the evidence in the data for the presence of heterogeneity by conducting subtype-pooled analysis of prevalence estimates of the conditions.

METHODS

Search Strategy

This systematic review was reported in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (52, 53) and registered for inclusion in PROSPERO: CRD42019119804.

TABLE 1 | Prevalence estimates, symptoms, diagnostic criteria, treatment method, risk factors, and average annual cost estimate of PCOS, endometriosis, adenomyosis, and uterine fibroids.

Condition	Prevalence	Symptoms	Diagnosis	Treatment	Risk factors	Annual patient cost estimate in European populations
Polycystic Ovary Syndrome	- NIH criteria (~5–9%)[a,b] - Rotterdam Criteria (~10–20%)[b,c]	- Hyperandrogenism[d,e,f] - Menstrual irregularity[d,e,f] - Oligo-anovulation[d,e,f] - Hirsutism[d,e,f] - Obesity[d,e,f] - Dyslipidemia[d,e,f] - Infertility[d,e,f]	- Ultrasonography[d,e,f] - Biochemical[d,e,f] - Clinical evidence (NIH criteria and Rotterdam criteria)[d,e,f]	- Medical treatment (suppressive hormonal therapy)[d,e,f] - Ovarian drilling[d,e,f]	- Early age of menarche[d,f,g] - Ovulatory dysfunction[d,f,g] - High body mass index[d,f,g] - Insulin resistance[d,f,g] - Metabolic syndrome features[d,f,g] - Altered glucose homeostasis [d,f,g] - Family history [d,f,g]	€4,413 to €7,293[h,i]
Endometriosis	5–10%[j]	- Dysmenorrhea[j,k,l,m,n,o] - Dyspareunia[j,k,l,m,n,o] - Dyschezia[j,k,l,m,n,o] - Dysuria[j,k,l,m,n,o] - Infertility[j,k,l,m,n,o] - Abnormal uterine bleeding[j,k,l,m,n,o] - Chronic pelvic pain[j,k,l,m,n,o]	- Laparoscopy or laparotomy[j,n] - Magnetic resonance imaging [j,n] - Ultrasonography[j,n]	- Surgical removal of lesions[j,n] - Medical treatment (suppressive hormonal therapy)[j,n]	- Early age of menarche[n,p,q] - Short menstrual cycles[n,p,q] - Increased menstrual flow[n,p,q] - Low body mass index[n,p,q] - Family history[n,p,q] - Late menopause[n,p,q]	€9,579[r]
Adenomyosis	14–57%[s]	- Menorrhagia[t,u] - Dysmenorrhea[t,u] - Endometrial polyps[t,u] - Leiomyomata uteri[t,u] - Chronic pelvic pain[t,u]	- Transvaginal ultrasonography[t,u] - Magnetic resonance imaging[t,u] - Hysterectomy[t,u]	- Surgical extirpation[u] - Medical treatment (Suppressive hormonal therapy)[u]	- Increase in age[t] - Number of births[t] - Smoking[t] - Previous uterine surgery[t]	€6,719.9[w]
Uterine fibroids	5–30%[x]	- Abnormal uterine bleeding[x,y] - Pelvic pain[x,y] - Pelvic mass[x,y] - Dyspareunia[x,y] - Infertility[x,y]	- Magnetic resonance imaging [x,y] - Ultrasonography[x,y]	- Medical treatment (suppressive hormonal therapy)[x,y] - Uterine artery embolization[x,y]	- Ethnicity [x,y] - Early age of menarche [x,y] - High body mass index [x,y] - Parity[x,y] - Smoking[x,y]	€12,654 to €30,075[z]

(5)[a]; (6)[b]; (7)[c]; (2)[d]; (8)[e]; (9)[f]; (10)[g]; (11)[h]; (12)[i]; (4)[j]; (13)[k]; (14)[l]; (15)[m]; (16)[n]; (17)[o]; (18)[p]; (19)[q]; (20)[r]; (21)[s]; (22)[t]; (23)[u]; (24)[v]; (25)[w]; (3)[x]; (26)[y]; (27)[z].

The electronic bibliographic databases, MEDLINE, EMBASE, PsycINFO, and GLOBAL HEALTH (through the OVID platform), and Google Scholar database, were searched from database inception until 14 February 2021. Search terms included a combination of free-text or controlled vocabulary terms (MeSH and EMTREE) for gynecological conditions including "Polycystic Ovary Syndrome," "Endometriosis," "Uterine Fibroids," and "Adenomyosis." We combined these with terms related to "Epidemiology" and "Prevalence" -related terms and terms for the "Middle East" -related countries. No other limits were applied to the search to obtain a comprehensive literature including the maximum possible number of studies. Details of the full search strategy used for the MEDLINE database are provided in **Supplementary Text 1**.

Eligibility Criteria and Selection of Studies

Peer-reviewed research articles that reported the prevalence of PCOS, endometriosis, uterine fibroids, and adenomyosis in women of Middle Eastern origin were included, in English and Arabic languages. The primary aim was to estimate the pooled prevalence estimate of PCOS, endometriosis, uterine fibroids, and adenomyosis in the Middle East, based on the following diagnostic criteria: NIH (54) and Rotterdam criteria (55) for PCOS; laparoscopic diagnosis for endometriosis; ultrasound sonography, MRI, and/or hysterectomy for adenomyosis; and ultrasound sonography, MRI, and/or hysterectomy for uterine fibroids. The secondary aim was to assess the evidence in the prevalence data for the presence of heterogeneity, in association to the following characteristics: ascertainment criteria (hospital-based/population-based), diagnostic criteria, age group of participants (adolescent/adult), country of origin (GCC region/Levant region/North Africa region/Persian region), type of study design (cross-sectional/cohort study), and availability of health insurance coverage.

The study outcomes to assess the pooled prevalence of PCOS were population-based study with the NIH criteria; population-based study with the Rotterdam criteria; hospital-based study with the Rotterdam criteria for any gynecological indication; and hospital-based study with the Rotterdam criteria for infertility investigation. For the pooled prevalence of endometriosis, distinction was made between population-based studies with a laparoscopic confirmation; hospital-based studies with a laparoscopic confirmation for any gynecological indication; and hospital-based studies with a laparoscopic confirmation for infertility investigation. The pooled prevalence of uterine fibroids and adenomyosis was divided into hospital-based studies with a hysterectomy or imaging diagnosis for any gynecological indication and hospital-based studies with a hysterectomy or imaging diagnosis for abnormal uterine bleeding investigation.

To reduce the risk of selection bias, methodological bias, and heterogeneity, studies were included in the meta-analysis when (i) the sample size involved >100 participants; (ii) diagnostic criteria were described; and (iii) prevalence estimates were reported. Reviews, editorials, and organizational guidelines were excluded to avoid bias toward more frequently cited publications. Case reports/series were excluded given that they use no control group to compare outcomes and have little statistical validity. Conference abstracts were excluded as there was no access to the full report and the studies were not peer-reviewed. To avoid over-representation of cases, when several studies on the same series of participants were published, only the report with the largest sample size was included in the meta-analysis.

Data Extraction

Retrieved articles were uploaded to EndNote and duplicates deleted. One reviewer (M.M.) reviewed the full library for relevance. A second reviewer (N.R.) reviewed the retrieved articles; inter-reviewer concordance was checked, and the third reviewer (K.Z.) adjudicated discordant results. A second round of review was conducted, and full texts were assessed for inclusion. Data was extracted into a standard form including study design, participant characteristics, ascertainment method, nationality, diagnostic criteria, confounding factors, prevalence estimates, and outcome measures. Missing data were collected where possible by emailing the corresponding author, or through statistical calculations reported in the Cochrane handbook for systematic reviews (56). All procedures conformed to the guidelines for systematic review and meta-analysis of observational studies in epidemiology: the Meta-analysis Of Observational Studies in Epidemiology Checklist (57).

Assessment of Risk of Bias

The quality control, assurance, and bias of the studies were assessed by two independent reviewers (M.M. and N.R.) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria (58, 59). The quality of evidence was monitored for each study based on risk of bias, imprecision, inconsistency, indirectness, and publication bias and scored on four levels of evidence: very low, low, moderate, and high. The studies and outcomes were rated down for clinical heterogeneity, methodological heterogeneity, unrepresentative control groups, insufficient diagnostic criteria for case definition, lack of adjustment to confounding variables, unclear selection criteria, sample size, confidence interval around effect estimate, and selection bias.

Data Synthesis

Statistical analyses were conducted using the metaprop function in R (R package: meta, Schwarzer 2008, Version 2.7.1). Meta-analysis was used to synthesize the pooling proportion estimates of the gynecological condition. The Freeman–Tukey double arcsine transformation was applied for normalizing and variance stabilizing of the proportion sampling distribution. This transformation also provided confidence limits of proportions between zero and one. Heterogeneity among studies was assessed via I^2 statistic. I^2 of 50% or above was designated significant heterogeneity and 30–49% moderate heterogeneity (60). The random-effect model of DerSimonian and Laird was used to estimate the pooled prevalence and its 95% CI, and I^2 heterogeneity was calculated for sensitivity analysis. Significant heterogeneity was explored by performing *post-hoc* subgroup meta-analyses to allow reliable conclusions to be drawn from analyses that involved subgroups. Forest plots demonstrate the

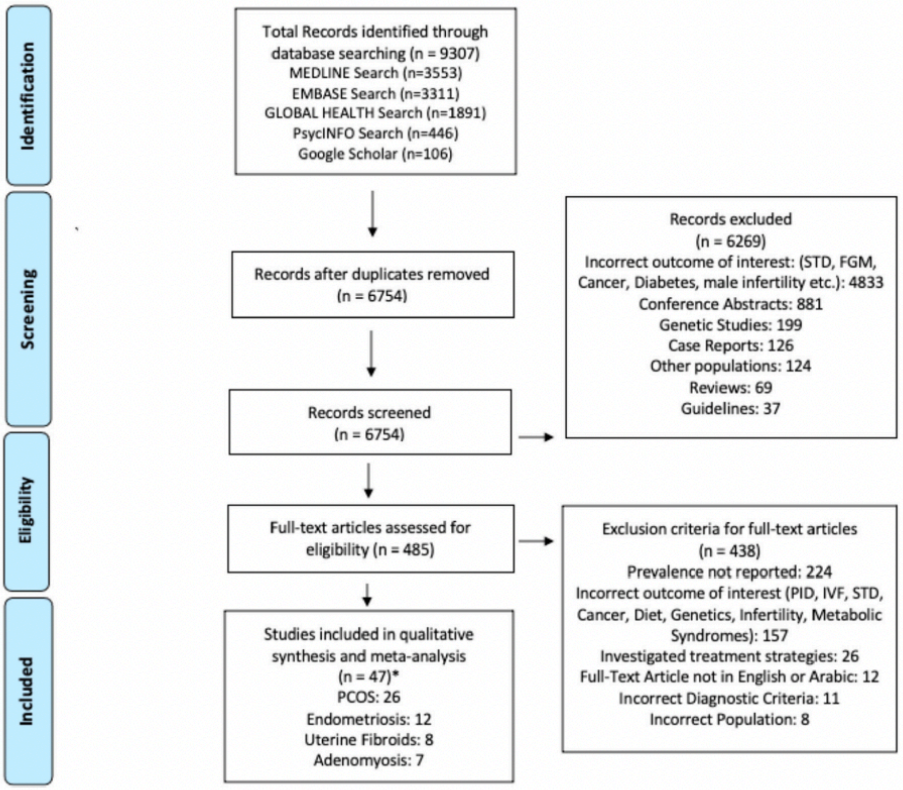


FIGURE 1 | PRISMA Figure. *Six studies reported prevalence estimates for more than one condition.

pooled prevalence estimates of the meta-analysis results. $P < 0.05$ was used as the threshold for statistical significance.

RESULTS

Study Selection and Characteristics

The search strategy across all databases retrieved 9,307 studies, 6,754 studies after duplicates were removed (**Figure 1**); 6,269 failed to meet the inclusion criteria based on abstract review. Following a full-text review of 485 studies, 438 were excluded because they did not meet the inclusion criteria. Of the 47 articles, 26 covered prevalence of PCOS, 12 endometriosis, 8 uterine fibroids, and 7 adenomyosis. There were 25 retrospective studies using electronic medical records and 22 cross-sectional studies; 29 were hospital-based and 18 population-based. There were 14 studies published from the GCC region, 14 studies from the Persian region, 14 studies from the Levant region, and 5 studies from the North African region. Detailed characteristics of the studies included are given in **Table 2**.

Of the 47 included studies, 27 received a GRADE score of "very low" and 20 studies received a GRADE score of "low" (**Supplementary Table 1**). The summary of the quality assessment for the studies included in the meta-analysis for each study outcome ($N = 11$; grouped based on multiple diagnostic criteria, sampling method, and definition of patient group prevalence estimation provided by each study, see Methods) also showed GRADE scores of "very low" and "low" (**Table 3**).

Polycystic Ovary Syndrome

Twenty-six studies reported prevalence estimates of PCOS, with eight reporting NIH criteria-based prevalence, 15 Rotterdam criteria-based prevalence, and three studies utilizing both the NIH and Rotterdam criteria (**Figure 2**). The population-based pooled prevalence of PCOS according to NIH criteria was 8.9% (95% CI: 6.5–11.7; range: 3.0–27.6%) (**Figure 2A**). Due to high heterogeneity ($I^2 = 94.0\%$) observed among the studies, results are presented from a random-effects model. Pooled prevalence of PCOS in the Levant region and Persian region was estimated

TABLE 2 | Characteristics of the 47 studies included in the meta-analysis.

References	Country	Study period	Study design	Participant ascertainment	Sample size	Age Mean ± Sd (Range)	Gynecological condition	Diagnostic method/criteria
(61)	Egypt	1998–2005	Retrospective	Electronic records screened for women attending the endoscopy unit at the obstetrics and gynecology department in a University hospital	2,493	26.8 ± 5.3 (Not reported)	Endometriosis	Laparoscopy
(62)	Egypt	2012–2014	Cross-sectional	Adolescent girls with severe dysmenorrhea	220	15.2 ± 3.53 (Not reported)	Endometriosis	Laparoscopy
(63)	Egypt	2011–2012	Cross-sectional	Infertile women visiting a specialized infertility clinic	3,900	27.9 ± 4.9 (Not reported)	PCOS	Rotterdam criteria
(64)	Egypt	2010–2011	Cross-sectional	Infertile women visiting an outpatient clinic in a University hospital	830	26.8 ± 5.4 (18.0–37.0)	PCOS	Rotterdam criteria
(65)	Egypt	2001–2010	Retrospective	Electronic records screened for the investigation of infertility in a University hospital	4,103	27.6 ± 4.8 (Not reported)	Endometriosis; PCOS	Laparoscopy; Rotterdam criteria
(66)	Iran	2012–2013	Cross-sectional study	Women referred for a laparoscopy due to unexplained infertility	383	30.9 ± 5.3 (Not reported)	Endometriosis	Laparoscopy
(67)	Iran	2001–2003	Retrospective	Electronic records screened for women presenting with hirsutism to the dermatology clinic in a University hospital	790	25.9 ± 5.7 (10.0–45.0)	PCOS	Rotterdam criteria
(68)	Iran	2011–2013	Retrospective	Electronic records screened for women who underwent laparoscopy for the investigation of infertility in a hospital	1,282	32.4 ± 4.9 (16.0–46.0)	Endometriosis	Laparoscopy
(69)	Iran	2009	Cross-sectional study	Female high school students	1,850	17.2 ± 0.70 (17.0–18.0)	PCOS	NIH Criteria
(70)	Iran	Not reported	Cross-sectional study	Female high school students	1,549	17.3 ± 0.9 (16.0–20.0)	PCOS	Rotterdam criteria
(71)	Iran	Not reported	Cross-sectional study	Female high school students	1,000	16.0 ± 1.9 (16.0–20.0)	PCOS	NIH criteria
(72)	Iran	2001–2011	Retrospective	Women attending a hospital for a hysterectomy	191	51.6 ± 12.5 (23.0–85.0)	Adenomyosis	Hysterectomy
(73)	Iran	2007–2008	Retrospective	Women attending a hospital for a hysterectomy	100	46.8 ± 7.8 (21.0–75.0)	Adenomyosis; uterine fibroids	Hysterectomy
(74)	Iran	2009	Cross-sectional study	Mandatory pre-marriage screening clinic	820	29.1 ± 7.6 (Not reported)	PCOS	Rotterdam/NIH criteria
(75)	Iran	Not reported	Cross-sectional study	Multi-stage random sampling of random household lists of premenopausal women available in the health department	602	33.2 ± 3.6 (18.0–45.0)	PCOS	Rotterdam/NIH criteria
(76)	Iran	2005–2006	Cross-sectional study	Multistage random sampling of high school students in Tehran	1,430	15.8 ± 1.1 (15.0–18.0)	PCOS	Rotterdam criteria
(77)	Iran	Not reported	Cross-Sectional Study	Random sampling method of participants selected from the Tehran lipid and glucose study	1,002	29.2 ± 8.7 (18.0–45.0)	PCOS	NIH criteria
(78)	Iran	Not reported	Cross-sectional study	Random household lists of premenopausal women available in the health department	929	34.4 ± 7.6 (18.0–45.0)	PCOS	Rotterdam/NIH criteria
(79)	Iraq	2020	Cross-sectional study	Cluster sampling method from young adolescent girls at high schools	900	15.96 ± 0.91 (14.0–18.0)	PCOS	NIH criteria

(Continued)

TABLE 2 | Continued

References	Country	Study period	Study design	Participant ascertainment	Sample size	Age Mean ± Sd (Range)	Gynecological condition	Diagnostic method/criteria
(80)	Iraq	2017	Cross-sectional study	Women attending an infertility center in a hospital	100	Not reported (21.0–44.0)	PCOS	Rotterdam criteria
(81)	Iraq	2007–2008	Retrospective	Women attending a hospital for a hysterectomy	391	46.6 ± 4.2 (40.0–49.0)	Adenomyosis; uterine fibroids	Hysterectomy
(82)	Israel	1998–2015	Retrospective	Performed from the Maccabi healthcare service database	570,781	40.4 ± 8.0 (15.0–55.0)	Endometriosis	Laparoscopy
(83)	Israel	Not reported	Cross-sectional study	Post-menopausal women attending an out-patient clinic	104	56.3 ± 5.5 (47.0–64.0)	PCOS	Rotterdam criteria
(84)	Jordan	2015	Cross-sectional study	Self-administered questionnaire from random women selected at universities, schools, and shopping centers	1,772	27.9 ± 5.7 (15.0–45.0)	Endometriosis	Laparoscopy
(85)	Jordan	2008–2009	Retrospective	Women attending hospital for hysterectomy	148	46.6 ± 5.7 (35.0–76.0)	Adenomyosis; uterine fibroids	Hysterectomy
(86)	Lebanon	1979–1981	Retrospective	Women who have undergone gynecological laparoscopy in a University hospital	862	31.5 ± 4.7 (17.0–52.0)	Endometriosis	Laparoscopy
(87)	Lebanon	Not reported	Retrospective	Electronic records screened for women presenting with hirsutism to the endocrinology clinic	146	22.0 ± 5.1 (Not reported)	PCOS	Rotterdam criteria
(88)	Middle Eastern women in Sweden	1990–2004	Retrospective	The total population register, Swedish national hospital discharge register, and the national cause of death register (only middle eastern population was extracted)	46,384	Not reported (20.0–41.0)	Endometriosis	Laparoscopy
(89)	Oman	2006–2010	Retrospective	Electronic records screened for premenopausal women presenting to gynecology outpatients in a University hospital	3,644	24.2 ± 5.4 (15.0–45.0)	PCOS	Rotterdam criteria
(90)	Oman	2007–2009	Retrospective	Women attending a hospital	3,560	Not reported (18.0–45.0)	PCOS	Rotterdam criteria
(91)	Palestine	2011–2012	Cross-sectional	Random sample of students selected from An-Najah National University	137	20.2 ± 1.40 (18.0–24.0)	PCOS	NIH criteria
(92)	Qatar	Not reported	Cross-sectional study	Eligible participants from the Qatar Biobank	720	27.2 ± 2.68 (18.0–40.0)	PCOS	NIH criteria
(93)	Qatar	2011	Cross-sectional study	Random sample of students from University	120	21.0 ± 2.00 (18.0–30.0)	PCOS	NIH criteria
(94)	Saudi Arabia	1990–2002	Retrospective	Women attending a hospital for an ultrasound	1,111	Not reported (15.0–79.0)	Uterine fibroids	Ultrasound
(95)	Saudi Arabia	1995–1999	Retrospective	Women attending a hospital for a hysterectomy	108	49.8 ± 8.2 Not reported	Uterine fibroids	Hysterectomy
(96)	Saudi Arabia	2000–2005	Retrospective	Women presenting with hirsutism to the endocrinology clinic in a University hospital	101	24.5 ± 6.6 (Not reported)	PCOS	Rotterdam criteria
(97)	Saudi Arabia	2008–2013	Retrospective	Women who have undergone gynecological laparoscopy in a University hospital	190	33.8 ± 8.9 (Not reported)	Endometriosis	Laparoscopy

(Continued)

TABLE 2 | Continued

References	Country	Study period	Study design	Participant ascertainment	Sample size	Age Mean ± Sd (Range)	Gynecological condition	Diagnostic method/criteria
(98)	Saudi Arabia	1990–2002	Retrospective	Women attending a hospital for a hysterectomy	251	Not reported (18.0–60.0)	Uterine fibroids	Hysterectomy
(99)	Turkey	2017–2019	Retrospective	Women attending infertility polyclinics	3,033	Not reported	PCOS	Rotterdam criteria
(100)	Turkey	2009–2014	Retrospective	Women attending a hospital for a hysterectomy due to heavy bleeding	129	49.0 ± 3.1 (Not reported)	Adenomyosis; uterine fibroids	Hysterectomy
(101)	Turkey	2003–2004	Retrospective	Women attending a hospital for a hysterectomy	298	50.0 ± 4.1 (38.0–86.0)	Adenomyosis	Hysterectomy
(6)	Turkey	2009–2010	Cross-sectional study	Female staff of a governmental institute	392	33.0 ± 7.30 (18.0–45.0)	PCOS	Rotterdam/NIH criteria
(102)	UAE	2016	Cross-sectional study	Self-administered questionnaire from random women selected at a University	3,572	24.9 ± 5.2 (18.0–55.0)	Endometriosis	Laparoscopy
(103)	UAE	1990–1994	Retrospective	Women attending an endocrine clinic for hirsutism	102	22.0 ± 5.1 (14.0–37.0)	PCOS	Rotterdam criteria
(104)	UAE	2012–2015	Retrospective	Women who have undergone gynecological laparoscopy in an endometriosis clinic in a hospital	5,881	32.1 ± 5.8 (15.0–59.0)	Endometriosis	Laparoscopy
(105)	UAE	2012	Cross-sectional study	Random sample of students selected from Ras Al Khaimah Medical University	250	19.7 ± 1.68 (18.0–24.0)	PCOS	NIH Criteria
(106)	Yemen	2006–2012	Retrospective	Women attending a hospital for a hysterectomy	2,544	47.6 ± 5.0 (16.0–80.0.0)	Adenomyosis; uterine fibroids	Hysterectomy

NIH, National Institute of Health; PCOS, polycystic ovary syndrome.

TABLE 3 | Summary of the quality assessment of the studies reporting the outcomes of interest included in the meta-analyses.

Study outcome	No. of studies	Grade score	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Uplifting factors
Polycystic ovary syndrome									
Population-based study: NIH criteria	12	Very low	2; non-RCT	−1; Six studies with high risk of bias (unrepresentative sample of population; did not specify recruitment strategy)	−1; high heterogeneity due to inconsistency in recruitment strategy and target population	0; all studies demonstrated directness of evidence	−1; two studies with imprecision (sample size not statistically significant)	0; none	2; Four studies with representative sample and similar direction of effect; four studies with large sample size
Population-based study: Rotterdam criteria	6	Low	2; non-RCT	0; five studies with low risk of bias (all samples were selected from the same country)	−1; high heterogeneity due to inconsistency in recruitment strategy and target population	0; all studies demonstrated directness of evidence	0; all studies demonstrated precision in sample	0; None	1; three studies with representative sample and similar direction of effect; two studies with large sample size
Hospital-based study: any indication via Rotterdam criteria	3	Low	2; non-RCT	0; two studies with low risk of bias (retrospective studies that identifies prevalence within a defined group)	0; no heterogeneity	0; all studies demonstrated directness of evidence	−1; one study with imprecision (sample size not statistically significant)	0; none	1; two studies with large sample size, adequate disease ascertainment
Hospital-based study: infertility via Rotterdam criteria	5	Very low	2; non-RCT	−1; three studies with high risk of bias (unrepresentative of control group and whole study population)	−1; high heterogeneity due to inconsistency in recruitment strategy and target population with inadequate sample ascertainment	0; all studies demonstrated directness of evidence	0; all studies demonstrated precision in sample	0; none	1; three studies with large sample size
Endometriosis									
Population-based study	4	Very low	2; non-RCT	−1; two studies with high risk of bias (unrepresentative of control group or whole population; self-reported outcomes)	−1; high heterogeneity due to inconsistency in recruitment strategy and target population	0; all studies demonstrated directness of evidence	−1; two studies with imprecision (recruited a younger sample group)	0; none	2; two studies with representative sample and similar direction of effect
Hospital-based study: any indication	4	Very low	2; non-RCT	0; two studies with low risk of bias (retrospective studies that identifies prevalence within a defined group)	−1; high heterogeneity due to inconsistency in recruitment strategy and target population	−1; two studies demonstrated indirectness of evidence (did not report total sample size in manuscript)	−1; one study with imprecision (sample size not statistically significant)	0; none	1; two studies with large sample size, adequate disease ascertainment
Hospital-based study: infertility	3	Low	2; non-RCT	0; two studies with low risk of bias (unrepresentative of population)	−1; high heterogeneity due to inconsistency in recruitment strategy and target population	0; all studies demonstrated directness of evidence	0; all studies demonstrated precision in sample	0; None	1; two studies with large sample size, adequate disease ascertainment
Uterine fibroids									
Hospital-based study: any indication	6	Low	2; non-RCT	−1; five studies with high risk of bias (unrepresentative of control group and whole study population; retrospective studies)	−1; high heterogeneity due to inconsistency in recruitment strategy and target population	0; all studies demonstrated directness of evidence	0; all studies demonstrated precision in sample	0; none	2; two studies reported adequate disease ascertainment and high sample size

(Continued)

TABLE 3 | Continued

Study outcome	No. of studies	Grade score	Study design	Risk of bias	Inconsistency	Indirectness	Impredsion	Publication bias	Uplifting factors
Hospital-based study: abnormal uterine bleeding	2	Very low	2; non-RCT	−1; two studies with high risk of bias (unrepresentative of control group and whole study population; retrospective studies)	−1; high heterogeneity due to inconsistency in recruitment strategy and target population	0; all studies demonstrated directness of evidence	−1; two studies with imprecision (sample size not statistically significant)	0; none	1; one study reported adequate disease ascertainment and significant sample size
Adenomyosis									
Hospital-based study: any indication	4	Low	2; non-RCT	−1; three studies with high risk of bias (unrepresentative of control group and whole study population; retrospective studies)	−1; high heterogeneity due to inconsistency in recruitment strategy and target population	0; all studies demonstrated directness of evidence	0; all studies demonstrated precision in sample	0; none	2; two studies reported adequate disease ascertainment and significant sample size
Hospital-based study: abnormal uterine bleeding	2	Very low	2; non-RCT	−1; two studies with high risk of bias (unrepresentative of control group and whole study population; retrospective studies)	0; no heterogeneity	0; all studies demonstrated directness of evidence	−1; two studies with imprecision (sample size not statistically significant)	0; none	1; one study reported adequate disease ascertainment and significant sample size

at the lower range of the scale with 6.3% (95% CI: 4.4–8.6; range: 6.1–7.3%) (6, 91) and 6.7% (95% CI: 4.6–9.1; range: 3.0–11.3%) (69, 71, 74, 75, 77–79), respectively, whereas prevalence estimates in the Gulf Arab states were 18.8% (95% CI: 9.5–30.3; range: 12.0–27.6%) (92, 93, 105). The population-based pooled prevalence according to the Rotterdam criteria was 11.9% (95% CI: 7.1–17.6; range: 3.4–19.9%) but only included studies from Iran and Turkey, from the Persian and Levant regions (**Figure 2B**). Among post-menarche adolescent women (<18 years of age), the pooled prevalence was 5.6% (95% CI: 1.8–11.3; range: 3.0–8.3%) (76, 107), whereas among pre-menopausal adult women (>18 years of age), it was much higher, at 15.6% (95% CI: 13.6–17.7; range: 14.1–19.9%) (6, 74, 75, 78).

The hospital-based prevalence studies of PCOS were categorized into (i) women presenting to obstetrics and gynecology clinics with any indication: 6.8% (95% CI: 6.3–7.4; range: 6.7–7.0%) (**Figure 2C**) and (ii) infertile women: 23.4% (95% CI: 15.6–32.2; range: 10.4–37.4) (**Figure 2D**). The three hospital-based studies estimated lower prevalence rates, but one of the studies only recruited post-menopausal women (6.7%, 95% CI: 3.3–13.2) (83), and the other two analyzed medical records retrospectively (7.0%, 95% CI: 6.2–7.9 and 7.0%, 95% CI: 6.1–7.8) (89, 90). The high heterogeneity ($I^2 = 99\%$) that was observed for the infertile pooled prevalence estimate is likely due to the fact that two of the studies were recruiting participants from a specialized infertility clinic (10.4%, 95% CI: 9.5–11.44 and 23.4%, 95% CI: 21.9–24.9) (63, 99), whereas the other three studies were recruiting infertile women that were visiting the obstetrics and gynecology department in a University hospital (18.5%, 95% CI: 17.3–19.7; 37.4%, 95% CI: 34.1–40.8 and 33.0%, 95% CI: 23.9–43.1) (64, 65, 80). Hence, the former group may be women with severe PCOS phenotype that require specialized fertility services and assistive reproductive technology, whereas the latter group may be women who require fertility medical treatment. Since hyperandrogenism is part of the Rotterdam criteria, and hirsutism is caused by increased androgenicity in the pilosebaceous gland, the pooled prevalence within the hirsute patients diagnosed with PCOS was very large, at 70.2% (95% CI: 57.7–81.7; range: 62.5–82.1%; $I^2 = 96\%$) (67, 87, 96, 103, 108).

Endometriosis

Twelve studies reported prevalence estimates of endometriosis diagnosed via laparoscopic surgical visualization, and four out of these 12 reported additional histological confirmation (**Figure 3**). The pooled prevalence for surgically confirmed endometriosis in population studies, which were validated through surgical records, was estimated at 1.2% (95% CI: 0.9–1.6, range: 0.8–2.4%) (**Figure 3A**). Two of these studies retrospectively extracted data from large-scale population-based databases in Israel (82) and Middle Eastern women living in Sweden (88). Two further cross-sectional studies in Jordan (84) and the U.A.E. (102) assessed women attending universities who could be affected but given the younger age may not have undergone laparoscopic intervention or sought medical help.

The hospital-based prevalence for studies of endometriosis among women undergoing laparoscopy for unspecified indication was 12.9% (95% CI: 4.1–25.4, range: 4.2–21.0%).

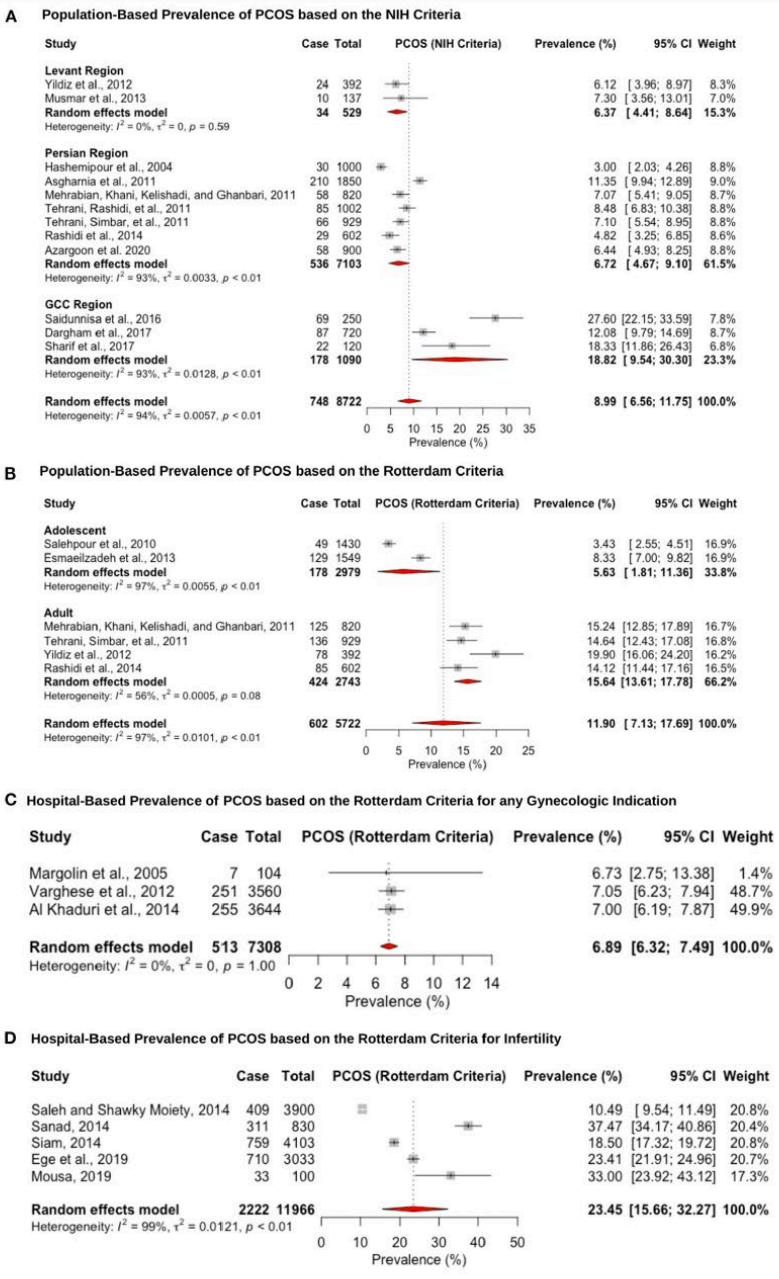


FIGURE 2 | Forest plot of the pooled prevalence estimates of PCOS: **(A)** population-based study based on the NIH criteria, **(B)** population-based study based on the Rotterdam criteria, **(C)** hospital-based study (obstetrics and gynecology department) based on the Rotterdam criteria, and **(D)** hospital-based study (presenting with infertility) based on the Rotterdam criteria.

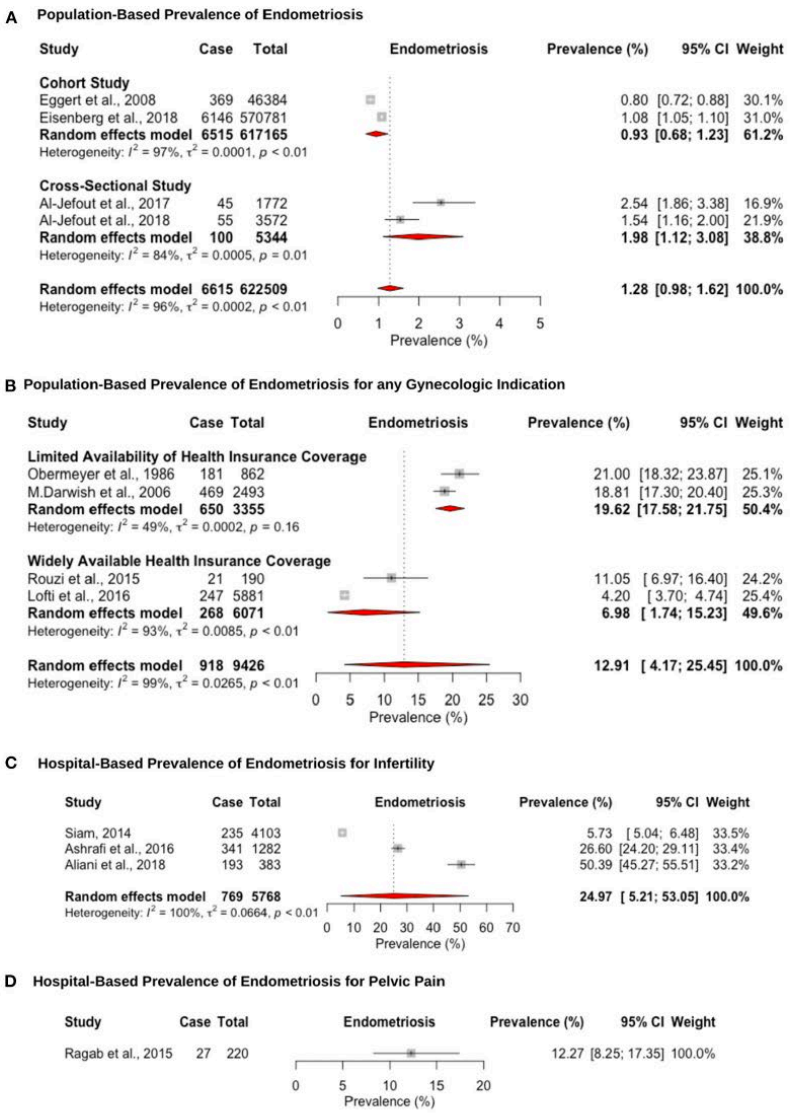


FIGURE 3 | Forest plot of the pooled prevalence estimate of surgically confirmed endometriosis: **(A)** population-based study, **(B)** hospital-based study (undergoing laparoscopy for any reason), **(C)** hospital-based study (presenting with infertility), and **(D)** hospital-based study (presenting with pelvic pain).

However, differences in prevalence estimates were observed based on the availability of healthcare insurance coverage (**Figure 3B**). Despite the importance of healthcare insurance coverage to provide cost-effective, quality healthcare services, most of the region did not provide or implement insurance coverage for the citizens and residents until the World Health Assembly passed a resolution in 2005 (30, 109, 110). Articles from countries that were published before 2006 had limited healthcare insurance coverage with a pooled prevalence estimate of 19.6% (95% CI: 17.5–21.7; range: 18.8–21.0%) (61, 86), as opposed to a prevalence estimate of 6.9% (95% CI: 1.7–15.2; range: 4.2–11.0%) (84, 102) for articles in countries published after

2007 with highly available private healthcare insurance coverage. Wider healthcare insurance coverage may reflect the lower prevalence estimate for surgically confirmed endometriosis, due to more accessibility to surgical procedures (111). The pooled hospital-based prevalence of endometriosis among infertile women undergoing laparoscopy was higher than for any indication, at 24.9% (95% CI: 5.2–53.0), although study estimates varied widely (range: 5.7–50.3%) (65, 66, 68) (**Figure 3C**). One large prospective study in Egypt ($N = 2,493$) showed that infertility is the primary reason for laparoscopic surgery in 80.9% of surgeries, followed by chronic pelvic pain in 12.2% and other indications in 14.5%. Endometriosis was diagnosed in 38.8, 46.6, and 14.5% of these three groups, respectively (61). This suggests that patients are more likely to seek medical treatment due to infertility compared to pelvic pain or other indications, which may be due to limited access of unmarried women to gynecology clinics. The hospital-based prevalence of endometriosis among women undergoing laparoscopy for pelvic pain was only estimated in a single study, at 12.2% (95% CI: 8.2–17.3) (62) (**Figure 3D**). The prevalence of endometriosis is likely overestimated among women undergoing surgery for pain symptoms and/or infertility; hence, there is an inherent selection bias in these groups compared to the general population.

Endometriosis was staged laparoscopically according to the four stages of the American Society of Reproductive Medicine (ASRM) staging system in 4 out of 12 studies (61, 68, 104, 112). The laparoscopic presentation of stage I/II vs. stage III/IV endometriosis was noted in one study (66). The endometriosis stage was not mentioned in eight of the 12 studies. Pooled prevalence of endometriosis for patients undergoing laparoscopy for any indication, according to the ASRM staging system, was 21.7% (95% CI: 13.8–30.8, $I^2 = 92.8\%$) for stage I, 34.1% (95% CI: 25.3–43.4, $I^2 = 73.7\%$) for stage II, 26.1% (95% CI: 14.9–39.1, $I^2 = 96.1\%$) for stage III, and 15.3% (95% CI: 8.03–24.3) for stage IV. Only one study reported the prevalence of endometriosis, according to ASRM criteria, for patients undergoing laparoscopy for infertility: 15.3% (52/341) for stage I, 24.9% (85/341) for stage II, 32.5% (111/341) for stage III, and 24.6% (84/341) for stage IV (68), and one study for patients undergoing laparoscopy for pelvic pain: 44.4% (12/27) for stage I, 25.9% (7/27) for stage II, and 29.6% (8/27) for stage III (62). Stage was not correlated with pelvic pain or infertility, as reported in previous studies (113).

Uterine Fibroids

Eight hospital-based studies estimated the prevalence of uterine fibroids by retrospectively screening electronic medical records of women (**Figure 4**). Seven studies utilized hysteroscopy as the diagnostic tool, and only one study utilized imaging and clinical assessment to diagnose uterine fibroids. The pooled hospital-based prevalence of uterine fibroids in women undergoing hysterectomy or ultrasound was 30.6% (95% CI: 24.9–36.6; range: 18.5–42.6%) for any indication (**Figure 4A**). The pooled hospital-based prevalence of uterine fibroids in women undergoing hysterectomy for abnormal uterine bleeding was 57.1% (95% CI: 45.5–68.4; range: 51.0–62.7%) (**Figure 4B**), while the prevalence of uterine fibroids diagnosed by ultrasound was 21.2% (95% CI: 18.8–23.7).

Adenomyosis

Five hospital-based studies reported the prevalence of adenomyosis by retrospectively screening electronic medical records of women attending a hospital for a hysterectomy (**Figure 5**). The hospital-based prevalence of adenomyosis in women undergoing hysterectomy for any indication was 30.8% (95% CI: 27.1–34.6, range: 25.5–37.7%) (**Figure 5A**) and 47.2% (95% CI: 40.7–53.7, range: 45.7–49.0%) for heavy menstrual bleeding (**Figure 5B**). Women diagnosed with adenomyosis often have other associated gynecological diseases, such as endometriosis or uterine fibroids, which complicates differential diagnosis and attribution of symptoms. In addition, no study provided an imaging-based diagnosis that could provide a more representative population-based estimate. While the gold standard for diagnosis has been histopathologic examination of the uterus after hysterectomy, the prevalence may be underestimated due to missed adenomyosis from cases that are not managed by hysterectomy (114).

DISCUSSION

Main Findings

We conducted the first systematic review and meta-analysis of pooled prevalence of PCOS, endometriosis, uterine fibroids, and adenomyosis in women from the Middle East, a region representing 6.8% of the world's population but underserved in clinical science (28–31). Much of the scientific research featured poorly designed studies and methodological and statistical heterogeneity. The region lacks reliable, population-based data on the major causes of women's health diseases due to limited reporting regulations and lack of national registries (29, 31).

Our findings indicate that the population-based prevalence of PCOS according to NIH and Rotterdam diagnostic criteria in the Middle Eastern populations is estimated at 8.9% (95% CI: 6.5–11.7) and 11.9% (95% CI: 7.1–17.6), respectively, which are similar to the estimated global prevalence (5–9% and 10–20%, respectively) (2). However, among women from the Gulf Region, there was a substantially higher prevalence of PCOS (18.8%; 95% CI: 9.5–30.3) in comparison to women from the Levant (6.3%; 95% CI: 4.4–8.6) and Persian Region (6.7%; 95% CI: 4.6–9.1), based on the NIH criteria. Obesity rates in the Arab Gulf countries exceed those of the remaining Middle Eastern region, with a gender disparity among women, for all age groups (115), where the prevalence of overweight and obesity among adults is 35–48 and 24–40%, respectively (116). Obesity is a common clinical feature in women affected by PCOS, due to its association to the onset of oligomenorrhea and hyperandrogenism (117). Comorbid conditions of PCOS, such as hyperinsulinemia, type 2 diabetes mellitus, cardiovascular disease, and dyslipidemia, have also been reported to have the highest prevalence in the Arab Gulf countries (118–120). Hence, it is likely that the prevalence differences of PCOS between the regions are at least in part due to the pathogenetic role on obesity in the subsequent development of PCOS (117). Analysis of a genome-wide association study (GWAS) on PCOS demonstrated that the relative severity of the PCOS phenotypes, in particular severe hirsute-hyperandrogenism, may

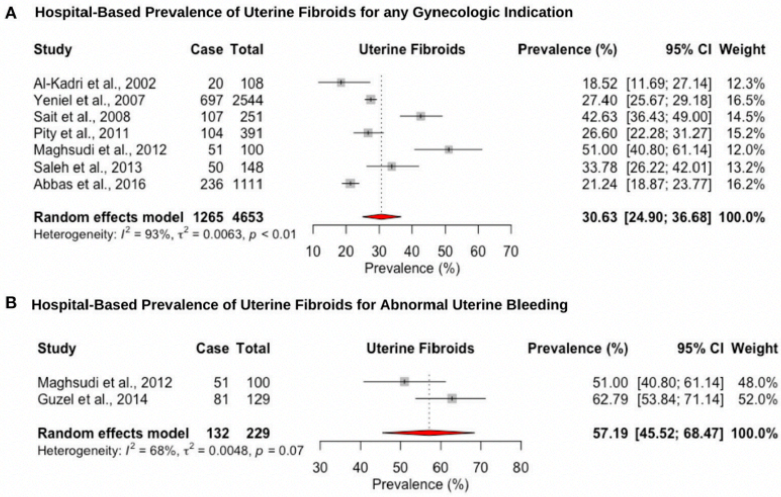


FIGURE 4 | Forest plot of the pooled prevalence estimate of hysterectomy-confirmed uterine fibroids: **(A)** hospital-based study (undergoing hysteroscopy in a period of time) and **(B)** hospital-based study (presenting with abnormal uterine bleeding).

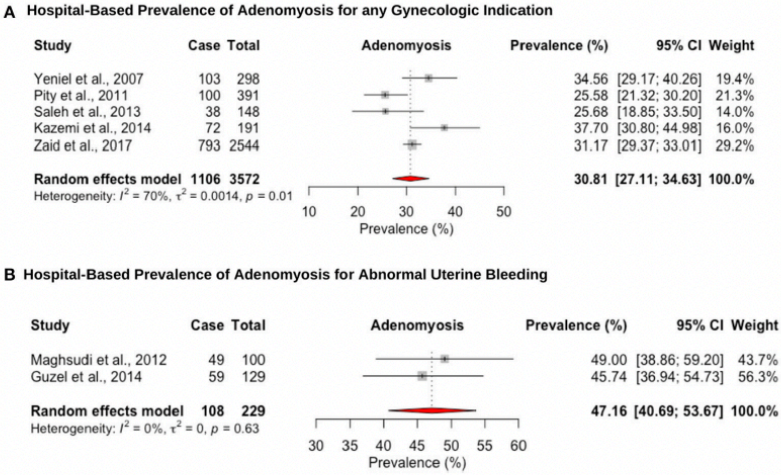


FIGURE 5 | Forest plot of the pooled prevalence estimate of hysterectomy-confirmed adenomyosis: **(A)** hospital-based study (undergoing hysteroscopy in a period of time) and **(B)** hospital-based study (presenting with abnormal uterine bleeding).

result from different combinations of SNPs more commonly present in women of Middle Eastern origin. This may be a basis for the higher prevalence of PCOS that is dominated by obesity, high blood pressure, diabetes mellitus, and hirsutism (121, 122). Genetic influences in populations of diverse origin are important to study alongside environmental influences, to understand the effect of their interaction in causing different PCOS phenotypes (123). Additionally, high heterogeneity was reported due to variability of age group of the participants among studies, where post-menarche adolescent women and post-menopausal women reported a lower prevalence of PCOS compared to pre-menopausal adult women. Adolescents with PCOS manifest similar clinical, metabolic, and endocrine features to adult women (124); hence, the significant difference could be

attributed to delayed diagnosis of the condition among young, single women who are unable to access reproductive health care due the hegemony of traditions that may prevent them from discussing their symptoms and seeking care.

Prevalence for surgically confirmed endometriosis (12.9% among women undergoing laparoscopy for any indication; 24.% among infertile women; 12.2% among women hospitalized for pelvic pain; 1.28% in a population-based setting) was similar to European ancestry populations (5–10% among women undergoing laparoscopy; 5–50% among infertile women; 5–21% among women hospitalized for pelvic pain; 2–43% among asymptomatic women seeking tubal ligation) (4, 17, 125). However, the reliance on surgical confirmation of endometriosis, access to clinics that is mostly limited to married women, and consequent selection biases affect these estimates, as is demonstrated by the heterogeneity estimates in our meta-analyses. As the main presenting symptomatology of endometriosis and mode of diagnosis are both influenced by psychosocial factors, women of different cultural backgrounds may present with different clinical phenotypes. Further epidemiological studies must be conducted among women of different populations, to explore the diagnostic pathways for women with endometriosis and be able to obtain an accurate prevalence estimate for the population. In addition, given that endometriosis has an estimated heritability of ∼50% and the region has an estimated consanguinity rate of 20–50%, increased prevalence of endometriosis may be mediated by numerous deleterious recessive alleles due to increased homozygosity levels (126–128). Most GWAS datasets have been generated from women of European ancestry, with only two in women of East Asian ancestry. It is important to define the extent of the effects of specific risk alleles in different ethnic groups and conduct trans-ethnic mapping to restrict signal to causal variants of endometriosis (129–131).

The hospital-based pooled prevalence of uterine fibroids for women was estimated at 28.2% (95% CI: 20.4–36.7), vs. 57.1% (95% CI: 45.5–68.4) among women with heavy menstrual bleeding, which are on the high end of the estimated global prevalence 5–30% (3) and 37–59% (132), respectively. Detection bias may explain the overestimation of uterine fibroid prevalence as nearly all studies were from women presenting for hysterectomy. Considering the consistently observed greater risk of uterine fibroids among black women, it is important to conduct further more robust epidemiological and genetic studies in women of Middle Eastern origin, to investigate whether they also exhibit a higher prevalence and whether this is associated with certain risk factors (3, 132, 133). The hospital-based prevalence of adenomyosis for women undergoing hysterectomy was high (any indication: 31.7% [95% CI: 20.6–43.9; for heavy menstrual bleeding: 47.2% (95% CI: 40.7–53.7)], but within the range previously reported for studies assessing prevalence at hysterectomy (14–57%) (21). The restriction of hospital-based studies to women undergoing hysterectomy for adenomyosis likely underestimates the prevalence as tissue may not have been routinely investigated for the condition. In addition, prevalence studies of uterine fibroids and adenomyosis all recruited multiparous women in their fourth and fifth decades of life, making comparison of estimates with global figures difficult. The lack of well-conducted, population-based studies limits the understanding of the public health impact of these conditions and prioritize diagnostic and management pathways.

Limitations and Strengths

This is the first systematic review of the prevalence of common gynecological conditions in Middle Eastern women. Study and reporting quality were generally low; however, the moderate/high heterogeneity that were present in the pooled data was reduced after completing subgroup analysis using relevant variables to limit bias. Potential explanations of residual heterogeneity among the studies are likely due to differences in study populations, sampling schemes, and study designs (case definition and ascertainment). Most of the studies selected women through convenience sampling, from hospitals, which may either overestimate the prevalence of the diseases or underestimate the disease risk due to missed asymptomatic cases. Prevalence estimates from retrospectively screened medical records are potentially affected by selection and information biases, as well as methodological issues, such as a lack of specific inclusion and exclusion criteria and data abstraction protocols. Beyond the limitations of the existing literature, there are fundamental issues with the diagnostic method used for the gynecological conditions, which hinders derivation of true population prevalence. The heterogeneous nature of PCOS in terms of its definition, diagnostic criteria, and ethnic variability likely leads to variable PCOS prevalence estimates in different populations. The lack of a non-invasive diagnostic modality for endometriosis creates diagnostic bias for those that are unable to access surgical evaluation. In addition, much of the information available on uterine fibroids and adenomyosis prevalence came from hospital-based studies that lacked imaging and symptomatology-based diagnosis and were not representative of the general population.

Social and cultural factors play a role in diagnostic bias. Given that women in the region will more likely consult a physician for fertility-related issues, as opposed to pain or menstrual irregularities (61), the studies conducted in a hospital-based setting are based on highly selected populations that cannot be generalized broadly. In addition, gynecological conditions and associated clinical phenotypes may present differently in various populations. Given the lack of epidemiological studies in the region focusing on symptomatology and phenotypes, the standard clinical definitions based on mainly Western population health data may not adequately capture the symptom presence and severity affecting diagnostic pathways of these heterogeneous conditions (134, 135). In fact, treatment regimens and responses vary widely between regions and among ethnic groups (136). There is an underrepresentation of studies from low- and middle-income regions in the Middle East that have been subject to war and political instability (Iraq, Syria, Libya, Sudan, Lebanon, Yemen, and Palestine), as opposed to higher-income regions, such as the Gulf countries, Turkey, and Egypt, where women have greater access to health care and may be more intensively screened.

This review highlights the importance of investigating gynecological health in the Middle East, and the need for well-designed studies that address both prevalence and the impact of gynecological condition on women's lives. An extensive search was conducted in two languages, to avoid missing any relevant information. We performed a broad search, including manuscripts from gray literature. Potential sources of bias were identified, and significant clinical and statistical heterogeneity was discussed to indicate considerable variability in the data due to residual confounding and study design. It is essential to prioritize improved and unbiased quantification of gynecological condition prevalence and incidence extrapolation, to improve generalizability and improve public health focus.

Further epidemiological studies must be conducted to investigate symptomatology and risk factors in women of this region, to deliver more culturally sensitive healthcare (137). Specific areas in need of attention include improving the clinical definition, diagnostic techniques, and treatment methods to provide the best practice for this diverse patient population. More generally, given the potential effects of these common chronic conditions on personal lives, economies, healthcare systems, and global community, it must be a public health priority to advance our understanding of the complex pathways leading to diagnosis, develop targeted prevention, and provide early detection guidelines in different populations (138–143). Key to this endeavor is advancing our understanding of how genetic and non-genetic factors interplay to disease predisposition and mechanisms in different populations (144).

CONCLUSION

To our knowledge, this is the first systematic review study to investigate the prevalence of common gynecological diseases in women in Middle Eastern populations, highlighting a paucity in reliable data. With 200 million women in the region, the importance of conducting more research in the area of women's health is clear and is needed to serve as a benchmark for evaluation of future research activities and comparative purposes with Middle Eastern immigrants and other populations. A gynecology clinic in the Middle East remains the realm mostly of married women. Young women may suffer from chronic pain and menstrual irregularities, but the hegemony of traditions may prevent them from discussing these and thus prolong suffering. To continue to decrease health disparities, researchers should acknowledge the limitations in scientific research that investigate the health disparities in women of Middle Eastern region. Robust data will urge policymakers in the Middle East to invest in health information systems to better identify risk factors for gynecology diseases, help set targets for policymaking, impact public awareness, and enable educational and evaluation strategies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

MM and NR were involved in all parts of the study: conception, study design, acquisition of data, information extraction, quality assessment, analysis, meta-analysis plots, interpretation, drafting of manuscript, and final approval. KZ and CB were responsible for conception, study design, analysis methods, interpretation, drafting of manuscript, and final approval. SK identified the search terms, developed the search strategies, conducted the search on each database to find relevant studies, reviewed the literature search method section of the manuscript, and did the final approval. MA-J, HA, CL, and SM were involved in study design, interpretation, reviewing of the manuscript, and final approval. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/frph.2021.661360/full#supplementary-material

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Appendix II

frontiers in Global Women's Health

ORIGINAL RESEARCH
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Impact of Endometriosis in Women of Arab Ancestry on: Health-Related Quality of Life, Work Productivity, and Diagnostic Delay

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Introduction: Endometriosis has a negative effect on health-related quality of life (HRQoL), wellbeing and daily functioning. Endometriosis is an under-researched condition within non-western populations. Cultural representations are needed to understand the relative roles of societal norms, traditional factors, and religious sensitivities on the impact of endometriosis on HRQoL in various populations. In particular, there is a lack of emphasis placed in understanding the association of HRQoL on endometriosis in Arab women.

Method: In this prospective case-control study, 2,610 Arab ancestry women in the United Arab Emirates were recruited to investigate the impact of endometriosis on HRQoL, diagnostic delay, psychological co-morbidities, work productivity, and physical activity. Participants completed the following standardized, validated questionnaires: Short Form-36 version 2 questionnaire, the World Endometriosis Research Foundation EPHect minimum clinical questionnaire version, and Work Productivity and Activity Impairment questionnaire. Translations to the Arabic language, validated using the forward-backward translation method, of the questionnaires were utilized.

Results: HRQoL scores were significantly impaired in women with endometriosis, as demonstrated in the Physical Composite Scores and Mental Composite Scores in the symptomatic control group ($p = 0.001$; $p = 0.003$, respectively) and the asymptomatic control group ($p < 0.001$; $p < 0.001$, respectively). Susceptibility and severity of multiple pain syndromes and infertility in women with endometriosis was the main indicator of lower HRQoL. Anxiety ($p = 0.007$) and depression ($p = 0.005$) were significantly associated with endometriosis, in comparison to symptomatic controls. The average diagnostic delay was 11.61 years, however single women experience 15.81 years of diagnosis delay, with approximately 18% ($n = 15$) of the single women experiencing more

than a 20-year delay in diagnosis. The intensity of physical activity was not associated with endometriosis, when compared to symptomatic ($p = 0.405$) or asymptomatic controls ($p = 0.144$).

Conclusion: For the first time, we provide evidence from a combined hospital, clinic, and population-based study that Arab women with endometriosis experience significant impacts on HRQoL, substantial diagnostic delay after the onset of symptoms, significant association to psychological disorders (anxiety and depression), and a negative impact on work productivity. Future research must focus on understanding the personal and culturally centered beliefs of Arab women to ensure a positive HRQoL trajectory by improving diagnosis and management strategies.

Keywords: quality of life, endometriosis, global health, women's health, Middle East, Arab women, diagnostic delay, work productivity and activity impairment

INTRODUCTION

Endometriosis is a chronic gynecological condition that is characterized by endometrium-like tissue located outside the uterine cavity (1). Prevalence rates in the general population are unknown, however, when considering evidence derived from population-based studies of the prevalence of symptoms and findings at laparoscopy, an estimated 10% of premenopausal women have endometriosis, with clinical studies showing that 40–80% of women with endometriosis experience chronic pelvic pain, and 20–50% infertility (1–3). Common symptomatology includes dysmenorrhea, dyspareunia, dyschezia, dysuria, chronic pelvic pain, and infertility (4). Treatment of endometriosis is focused on the amelioration of symptoms, and is limited to repeated surgical removal of lesions, hormonal interventions, such as oral contraceptives, progestin, or GnRH analogs, often with many side effects, and assisted reproduction for infertility (1, 3). The current clinical requirement of surgical visualization to establish a diagnosis means diagnostic delay typically span 7 years (1, 5).

Given the chronic nature of endometriosis, range of pain symptoms, and potential impact on fertility, diagnosis of endometriosis is often delayed, which negatively affects patients' quality of life (5–11). The increased risk of psychological disorders among endometriosis patients interrupts one's regular life, for almost all women in multiple life domains, such as education, work, and intimate relationships (11, 12). The Global Study of Women's Health (GSWH), a cross-sectional study conducted in 10 countries among women undergoing their first laparoscopy for symptoms suggestive of endometriosis, demonstrated a negative impact of endometriosis on HRQoL and work productivity. Absenteeism ($p = 0.019$), presenteeism ($p = 0.033$), and overall work productivity losses ($p = 0.014$) were reported more frequently by women with endometriosis when compared with symptomatic controls (5). Women who experienced longer diagnostic delays reported greater impairment in HRQoL (5). Country-specific differences were observed in the GSWH study, specifically for the duration of diagnostic delay (3–10 years), diagnostic incidence rates (34.8–100%), prevalence of moderate/severe disease stage (American Society of Reproductive Medicine, ASRM, staging; 30–40% in most centers, but nearly 90% in other countries), and monetary loss from endometriosis-associated work absenteeism and presenteeism (varying from US$208 to US$23,712). While the GSWH study included a variety of countries and ethnicities, Middle Eastern countries were not part of the study. Existing research on endometriosis has limited generalizability to the Middle Eastern population where a knowledge gap exists on the differential impact of endometriosis on quality of life. Collecting comprehensive data from all patient populations is critical to understand if there are intrinsic differences in the pathophysiology of endometriosis, in terms of race, genetics, environmental and socioeconomic factors.

In a systematic review with meta-analysis, the pooled prevalence of endometriosis was estimated to be 12.9% (95% CI: 4.2–25.4) in Middle Eastern women undergoing laparoscopy, for any indication (13). While the findings of this review demonstrated that the region lacks reliable, population-based data on the symptomatology and risk factors of endometriosis, there are inherent difficulties in the universal application of symptom and phenotype-based criteria across different countries and cultures, as demonstrated for polycystic ovary syndrome among Arab women (13–17). No studies have assessed the diagnostic delay, work productivity or activity impairment among Middle Eastern women with endometriosis. To the best of our knowledge, only one study utilized a validated quality of life tool (World Health Organization Quality of Life Assessment–BREF) in Middle Eastern women with endometriosis, demonstrating that dysmenorrhea severity is negatively correlated with physical, social and environmental domains ($p = 0.028$; $p = 0.013$; $p = 0.033$, respectively) (18).

Polygamous marriages, strong patriarchal cultures, reticence in disclosing personal matters to the public, and reluctance in seeking care to limit community censorship and victimization is common in the Arab population. These cultural issues limit Arab women's autonomy and may contribute to reproductive and mental health disparities (19–22). In addition, inadequate knowledge on reproductive health literacy and restricted access to mental health services are neglected public health issues in this region, likely to impact women's wellbeing and quality of

life (23–25). Given the potential effects of this chronic disease on personal lives, health care systems, and the global community, cross-cultural studies are needed to understand the roles of cultural sensitivities, traditions, and religious norms in the impairment of HRQoL to overall disease burden in Arab women with and without endometriosis pathology.

The Middle Eastern Women Research Association (MAR'A) Project is the first epidemiological study on women's health conditions and related co-morbidities in the Middle East that aims to develop a better understanding of cultural and regional women's health patterns. The findings presented in this study are based on the analyses of data collected within the MAR'A Project, which recruited Arab ancestry women from population and hospital-based settings in the United Arab Emirates (UAE). In this study, we investigated the impact of endometriosis on HRQoL, work productivity, activity impairment and physical activity in Arab ancestry women living in the UAE and evaluated symptoms that may significantly influence HRQoL, adopting the use of standardized, validated questionnaires. Furthermore, we estimated diagnostic delay of endometriosis from onset of symptoms to diagnosis by laparoscopy and prevalence of psychological co-morbidities.

METHODS

Sample

The Arab region consists of 22 countries located in the Middle East, a transcontinental region that includes the Gulf Cooperative Council region (Bahrain, Kuwait, Oman, Saudi Arabia, Qatar, United Arab Emirates, Yemen), the Levant region (Iraq, Jordan, Lebanon, Palestine, Syria), and the North African region (Algeria, Comoros, Djibouti, Egypt, Libya, Mauritania, Morocco, Somalia, Sudan, and Tunisia) (26). The Arab population are unified by ancestral, ethnic, familial or heritage ties, with common cultural practices, social linguistic influences and traditional norms (27–30).

The UAE is situated in the Middle East, located at the southeastern Arabian Peninsula. Its pivotal geographic position allowed an influx of Arab tribes and foreign expats from the region, providing a representation of the middle eastern population (31). Admixture analysis has shown consistent patterns of the ethnicities and populations of different parts of the Middle East, demonstrating that the contemporary populations of the UAE is suitable to conduct representative epidemiological studies of the Arab population (31, 32).

Ethical approval was obtained from the research ethics committee within the University of Oxford (OXTREC: 25–18) and the Ministry of Health in the UAE (MOHAP/DXB-REC-25/2018). The study followed the General Data Protection Regulation, and adult participants provided written consent to participate in the study after reading the participant information sheet.

Recruitment and Study Participants

The MAR'A Project is a prospective case-control study with multiple recruitment sites across the UAE, including: four hospitals and clinics (women who attended the hospitals for laparoscopic surgery or for diagnostic, therapeutic and/or screening tests), and six population-based sites (women who attended public health seminars organized within the same geographic catchment areas as the participating hospitals and clinics). The participants were approached in the waiting room in the hospitals and clinics, or at the end of the public seminars, and asked if they were interested in learning more about this research study. Between August 2018 and August 2019, we recruited 2,610 participants, using the following criteria: 1) premenopausal women, 2) aged 18–50 years, 3) self-reported ethnically Arab, and 4) no previous diagnosis of endometriosis. Exclusion criteria were: 1) pregnant women, 2) women with special needs, and 3) women who were illiterate, and were unable to comprehend and provide informed consent. Participants who met the inclusion criteria were invited to participate in the study and given the consent form and participant information sheet in their preferred language (English or Arabic), which had been professionally translated using the forward-backward translation methods and approved by the ethics committee. The recruitment flow chart is demonstrated in **Figure 1**.

The case group were incident endometriosis cases who attended the hospital scheduled to undergo a diagnostic and/or therapeutic laparoscopy or laparotomy for any indication (pelvic pain, subfertility, pelvic mass, adnexal torsion, infection or to be sterilized) by visual confirmation as is the current golden standard (33, 34), and classified into four grades, based on the revised American Society for Reproductive Medicine (rASRM) (35).

The control group comprised three distinct groups: 1) hospital controls who had undergone laparoscopic surgery showing that they were endometriosis-free, 2) clinic controls who were screened using therapeutic/diagnostic tests (such as monitoring for other gynecological conditions or pre-marital screening, ovulation monitoring, cosmetic gynecology, reproductive cancer screening and/or gynecological health check-up), and 3) population controls recruited during organized public seminars. The control groups were sub-divided into symptomatic and asymptomatic controls (**Figure 1**), to explore sensitivity of results to control definition. Symptomatic controls were defined as: 1) women who experienced chronic pelvic pain, dysmenorrhea, dyspareunia, dyschezia, dysuria for at least 6 months duration with a numerical rating scale (NRS) (36, 37) score greater than four (38), and/or 2) women who were infertile defined as unprotected intercourse in the fertile phase of the menstrual cycles for 12 months (39). Women who did not report the above symptoms were categorized into the asymptomatic control group.

In analysis, comparisons were made between 1) women with endometriosis vs. symptomatic controls, and 2) women with endometriosis vs. asymptomatic controls. The symptomatic control group allowed us to investigate whether observed associations relate to endometriosis *per se*, and not the presence of symptoms. The asymptomatic control group allowed investigation of factors associated with symptoms with or without endometriosis. To quantify hidden bias, such as the possibility of undiagnosed endometriosis cases in the control group, sensitivity analysis was conducted

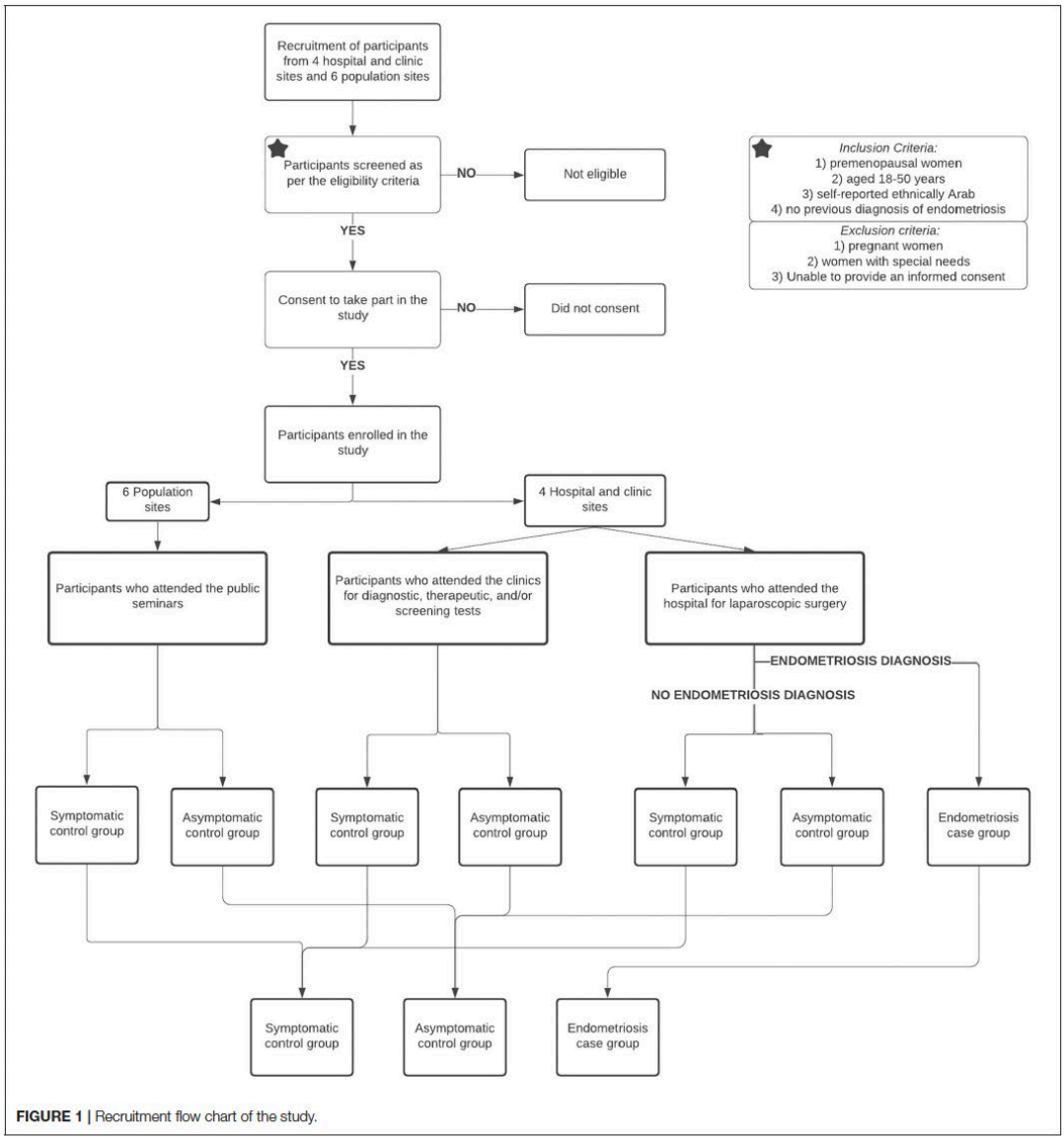


FIGURE 1 | Recruitment flow chart of the study.

between HRQoL dimensions from the symptomatic controls with surgical confirmation vs. symptomatic controls with no surgical confirmation.

Questionnaire and Data Collection

Participants completed the following standardized, validated questionnaires and instruments: Short Form-36 version 2 (SF36v2) (40, 41) questionnaire, the World Endometriosis Research Foundation EPHect (WERF-EPHect) minimum clinical questionnaire (EPQ-M) version (42), and Work Productivity and Activity Impairment (WPAI) (43, 44) questionnaire. Translations to the Arabic language, validated using the forward-backward translation method, of the questionnaires were utilized. SF36v2 was used to measure HRQoL and is constructed to measure concepts relating to functional health, well-being, relative burden of the disease,

TABLE 1 | Demographic details of the participants based on endometriosis cases vs. symptomatic controls and asymptomatic controls.

	Endometriosis cases (n = 518)	Symptomatic controls (n = 1,331)	p-value	Asymptomatic controls (n = 761)	p-value
Age (y) [Mean (SD)]	34.04 (4.81)	35.36 (8.01)	<0.001	32.22 (8.54)	<0.001
Body mass index (kg/m^2) [mean (SD)]	26.10 (4.55)	27.08 (5.68)	<0.001	27.48 (5.59)	<0.001
Higher education	66.2% (343)	61.9% (824)	0.085	56.9% (433)	0.001
Employment	61.0% (316)	62.0% (825)	0.697	68.2% (519)	0.009
Married	76.3% (395)	79.2% (1,054)	0.169	81.3% (619)	<0.001
Parous	52.1% (270)	62.1% (827)	<0.001	78.6% (598)	<0.001
Parity (Number of children) [mean (SD)]	2.16 (0.94)	2.64 (1.39)	<0.001	3.18 (2.12)	<0.001
Age at Menarche [mean (SD)]	13.12 (1.34)	13.56 (2.57)	<0.001	13.60 (1.19)	<0.001
Menstrual Irregularity	31.3% (162)	27.2% (362)	0.082	20.0% (152)	<0.001
Menstrual Duration [mean (SD)]	5.75 (1.57)	5.35 (1.41)	<0.001	5.51 (1.30)	0.003
Chronic Pelvic Pain	67.0% (347)	57.6% (766)	<0.001	NA	NA
Dysmenorrhea	88.2% (457)	79.0% (1,052)	<0.001	NA	NA
Dysuria	27.0% (140)	16.2% (215)	0.002	NA	NA
Dyschezia	30.1% (156)	18.8% (250)	<0.001	NA	NA
Infertility*	64.9% (281/433)	55.2% (624/1,130)	0.001	NA	NA

*NA, Not Applicable, SD: Standard Deviation. *When investigating fertility characteristics, only ever married women (married, widowed, divorced) were included because single women are unable to seek fertility care in the UAE.*

TABLE 2 | Association of endometriosis and HRQoL in comparison to symptomatic controls and asymptomatic controls, measured using the SF36v2 dimensions and composite scores.

	Endometriosis cases (n = 518) Mean (±SD)	Symptomatic controls (n = 1,331) Mean (±SD)	Adjusted p-value	Asymptomatic controls (n = 761) Mean (±SD)	Adjusted p-value
Physical function	62.38 (22.59)	66.95 (25.07)	0.001	73.75 (23.40)	<0.001
Role-physical	58.03 (27.06)	64.62 (27.66)	0.001	71.48 (27.65)	<0.001
Body pain	53.77 (29.09)	63.00 (24.35)	<0.001	71.36 (22.15)	<0.001
General health	51.46 (19.41)	55.08 (20.90)	0.003	61.75 (20.63)	<0.001
Vitality	45.15 (17.08)	50.01 (19.07)	0.001	58.88 (20.43)	<0.001
Social functioning	61.12 (23.39)	66.46 (25.11)	0.001	72.66 (24.37)	<0.001
Role emotional	56.39 (22.15)	59.16 (25.49)	0.009	66.55 (25.79)	<0.001
Mental function	52.64 (16.77)	56.58 (17.68)	0.002	64.84 (16.44)	<0.001
PCS	43.60 (8.19)	46.02 (8.43)	0.001	48.28 (7.77)	<0.001
MCS	41.35 (6.83)	42.70 (7.63)	0.003	46.32 (7.43)	<0.001

MCS, Mental Component Score; PCS, Physical Component Score; SD, Standard Deviation. Adjusted p-values for age (continuous), current BMI (underweight, normal weight, overweight, obese), civil status (married, not married), educational status (up to high school level, up to postgraduate level), and work status (working, not working).

objective and subjective ratings, and self-evaluation of general health status (40, 41). WERF-EPHect questionnaire (EPQ-M) were used to collect demographic information, measure the presence and severity of symptoms, risk factors, phenotypic profile and physical activity assessment (42, 45). WPAI was used to measure absenteeism and presenteeism in employed women, and the impact of symptoms on activities (43, 44).

Data were collected and managed in a web-based research electronic data capture (REDCap) (46) database, with 10% of the questionnaires inputted by two independent data processers to find discrepancies. The following basic anthropometric measurements were collected: (1) weight and height using calibrated digital scaling instruments, and (2) waist and hip circumference using the WHO guidelines (47). After data checking and validation, 2,610 questionnaires were used for data analyses in this study. Pairwise deletion was utilized for variables where data were not missing at random; where reliability of data could not be confirmed by participant, the variable was dropped from the multivariate analysis to minimize the risk of bias.

Analyses

Health Related Quality of Life

The SF-36v2 questionnaire (Cronbach alpha: English language (0.78–0.93) (40, 48–51), Arabic language (0.72–0.94) (41) was analyzed as per the developers' guidelines (40, 41, 48, 50–53). The SF-36 eight dimensions are physical functioning, role limitation-physical, bodily pain, general health, vitality, social functioning, role limitation-emotional, and mental health. Due to the lack of Middle Eastern normative values scores for the general population, the USA population normative values were

utilized in this study as a reference population, to allow a meaningful comparison of the data when conducting cross-cultural comparisons (48, 49, 53, 54). The raw score of each of the eight SF-36 dimensions was constructed using the Likert method of summated ratings and each of the eight domains transformed scale was standardized using a z-score transformation. The subscale factor score coefficient for physical component summary (PCS) and mental component summary (MCS) were aggregated using factor analysis. The PCS correlates with physical functioning, role-physical and bodily pain, and the MCS correlates with mental health, role-emotional, and social function. Vitality, general health, and social functioning correlate with both components. T-scores linear transformation is calculated by centering the obtained PCS and MCS sums to get a mean of 50 and a standard deviation (SD) equal to 10 (48, 49). A validated, Arabic translated version was utilized for this study (41).

Means and standard deviations for each of the eight-dimension scales are presented, ranging from 0 to 100, and two composite scores above the normative value (mean of 50 and a SD of 10) demonstrates a healthy QoL. The missing values in the SF-36 dimensions were imputed as recommended by the developer (48, 49): if 50% or more items in one dimension were completed, the mean value of the total completed items were imputed in each missing value; if more than 50% of the items were missing, the dimension score was excluded. In our survey, the item response rate of the 36 items in the SF-36 was 99.77%.

Endometriosis Symptomatology, Disease Stage, Comorbidities, and Demographics

The two-composite quality of life scores (PCS and MCS) were compared with pelvic pain severity, presence of endometriosis-associated symptoms, four grade classification based on the revised American Society for Reproductive Medicine (rASRM) (35), and length of time between symptom onset and diagnosis. Pelvic pain severity was reported using the numerical rating scale (NRS) (37), a subjective measure in which individuals rate their pain on an eleven-point numerical scale [score from 0 to 10; Cronbach alpha: English language (0.86–0.95) (37, 55, 56), Arabic language (0.84–0.92) (45)]. Endometriosis-associated symptoms included presence of dysmenorrhea, chronic pelvic pain, dysuria, dyschezia and infertility, and were obtained from the minimal WERF-EPHect questionnaire (EPQ-M). Disease stage was classified according to the rASRM stage 1–4 system using the WERF EPHect minimal surgical form (MSF) and abstracted from the operative notes within the medical records. Participants were asked to report demographic information, past medical history, and lifestyle factors. To assess the impact of endometriosis and associated psychological disorders, participants were asked if they received a clinical diagnosis for anxiety and/or depression.

Diagnostic Delay of Endometriosis

Diagnostic delay of endometriosis was quantified by averaging the self-reported earliest age of symptom onset (dysmenorrhea, chronic pelvic pain, dyschezia, dysuria, and infertility) and age of first contact seeking gynecological consultation, and then subtracting from this the age at surgically confirmed diagnosis of endometriosis. Due to societal norms that delay single women from seeking gynecological help, the diagnostic delay of the onset of pelvic pain symptoms was compared between single women and married women. Infertility was not included in the subtype analyses for marital status because single women are prohibited from seeking fertility services.

Work Productivity and Activity Impairment

The Work Productivity and Activity Impairment Questionnaire [WPAI; Cronbach alpha: English language (0.77–0.82) (43, 57), Arabic language (0.71–0.76) (44)] is a validated instrument that measures the effect of symptoms and disease on work productivity and daily tasks. The impact of the symptoms is measured by absenteeism (hours of missed work), presenteeism (perceived impairment of work tasks), work productivity loss (perceived loss in productivity levels) and activity impairment (impairment of patient's daily life activities). Higher WPAI percentages indicate a greater impairment and less productivity.

Physical Activity Assessment

Physical activity was assessed using a validated measure from the EPQ-M. Participants were asked about their recent physical activity exposure by reporting the average time spent per week during the past year on each of the following activities: walking, jogging, running, bicycling, racquet sports, lap swimming, calisthenics, and other aerobic activity. A metabolic equivalent (MET) score was assigned to each of the eight activities above) to assess the amount of energy the body uses per minute, using the Compendium of Physical Activities (58). The reported minutes per week engaged in each activity was multiplied by the MET score, and the summed value for the individual activities creates the MET/wk. Light-intensity activities are those with <3.0 METs, moderate-intensity activities are those between 3.0 and 6.0 METs, and vigorous-intensity activities score more than 6.0 METs.

Statistical Methods

The data were analyzed using Statistical Package for Social Science (SPSS) version 20 (SPSS Inc., Chicago, IL) and R (Version 3.4.1). A power calculation determined that a minimum of 1,500 (number of cases = 500; number of controls = 1,000) would need to be recruited to detect an average effect size of 1.15 with a power of 0.8, at a significance level of 0.05. Reporting of the study design was done in adherence to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (59). Sensitivity analysis was assessed using a non-parametric Wilcoxon Signed Ranks Test to quantify hidden bias between the HRQoL dimensions from the symptomatic controls with surgical confirmation vs. symptomatic controls with no surgical confirmation.

The descriptive variables were verified using frequency analysis. Chi-square and Fisher's exact test were used to study categorical variables. Independent sample *t*-test or nonparametric Mann-Whitney *U*-test were used to study continuous variables. Kruskal-Wallis or ANOVA tests were used to verify the association between the HRQoL domains and the clinical aspects of endometriosis. The chi-squared test was

TABLE 3 | Association between endometriosis symptomatology and SF-36 composite scores for endometriosis cases and symptomatic controls.

	Endometriosis		Symptomatic controls		Endometriosis vs. symptomatic controls	
	PCS (A) Mean* (±SD)	MCS (B) Mean* (±SD)	PCS (C) Mean* (±SD)	MCS (D) Mean* (±SD)	A vs. C *p*-value	B vs. D *p*-value
Dysmenorrhea	42.93 (8.12)	41.03 (6.83)	44.95 (8.51)	41.74 (7.75)	<0.001	0.090
Chronic Pelvic Pain	42.11 (8.14)	40.71 (6.95)	44.53 (8.51)	41.52 (7.81)	<0.001	0.100
Dyschezia	41.26 (7.32)	40.05 (6.35)	43.11 (7.85)	40.20 (7.28)	0.019	0.862
Dysuria	41.64 (7.08)	40.01 (6.61)	42.89 (7.46)	40.11 (7.01)	0.118	0.428
Infertility	43.38 (8.24)	40.93 (6.75)	45.52 (8.36)	41.63 (7.60)	0.001	0.016

*MCS, Mental Component Score; PCS, Physical Component Score; SD, Standard Deviation. *Adjusted mean and p-values for age (continuous), current BMI (underweight, normal weight, overweight, obese), married (married, not married), educational status (up to high school level, up to postgraduate level), and work status (working, not working).*

TABLE 4 | Symptom onset and diagnostic delay of endometriosis from age at time of diagnosis [years: 34.04 (SD: 4.81)].

			Delay intervals		
	Age at symptom onset (Years) Mean (±SD)	Age at first gynecological consultation (Years) Mean (±SD)	Onset of symptoms to first gynecological consultation (Years) Mean (±SD)	First gynecological consultation to diagnosis (Years) Mean (±SD)	Total diagnostic delay (Years) Mean (±SD)
Dysmenorrhea	17.10 (3.85)	24.02 (5.87)	6.92 (4.86)	9.92 (4.81)	16.83 (5.65)
Chronic Pelvic Pain	20.14 (3.20)	26.57 (5.20)	6.43 (4.20)	7.37 (4.65)	13.80 (5.36)
Dyschezia	23.76 (2.76)	28.92 (4.69)	5.52 (3.98)	5.16 (3.77)	10.33 (5.24)
Dysuria	23.39 (2.80)	28.91 (5.17)	5.16 (3.73)	5.40 (4.10)	10.94 (4.87)
Infertility	NA	26.06 (2.77)	NA	7.32 (4.53)	7.32 (4.53)
Total	21.10 (3.15)	26.90 (5.78)	6.01 (4.19)	6.96 (4.33)	11.61 (5.59)

NA, Infertility is often diagnosed by a physician, and women are unaware of their age at infertility onset, thus we have included the age at first diagnosis of infertility.

TABLE 5 | Anxiety and depression in women with endometriosis vs. symptomatic controls and asymptomatic controls.

	Endometriosis cases vs. Symptomatic controls				Endometriosis cases vs. Asymptomatic controls			
	Odds ratio (95% CI)	*p*-value	Adjusted odds ratio (95% CI)	Adjusted *p*-value	Odds ratio (95% CI)	*p*-value	Adjusted odds ratio (95% CI)	Adjusted *p*-value
Anxiety								
No	1.00	0.006	1.00	0.007	1.00	<0.001	1.00	<0.001
Yes	1.40 (1.11, 1.78)		1.38 (1.09, 1.74)		6.04 (4.24, 8.61)		6.46 (4.47, 9.35)	
Depression								
No	1.00	0.003	1.00	0.005	1.00	<0.001	1.00	<0.001
Yes	1.44 (1.15, 1.82)		1.41 (1.11, 1.78)		5.06 (3.57, 7.16)		5.43 (3.77, 7.83)	

Adjusted odds ratio and p-values for age (continuous), current BMI (underweight, normal weight, overweight, obese), civil status (married, not married), educational status (up to high school level, up to postgraduate level), and work status (working, not working).

also used to associate the profile of the participants with the staging of endometriosis. Spearman correlation were calculated to establish bivariate relationships between pain severity and HRQoL scores. Multivariate linear regression models tested multivariate relationships between endometriosis-associated symptoms (dysmenorrhea, chronic pelvic pain, dyschezia, dysuria and infertility) and HRQoL scores. Multiple logistic regression analysis was used to study associations between depression and anxiety within the endometriosis and control groups. All regression models accounted for age (continuous), current BMI (underweight, normal weight, overweight, obese), civil status (married, not married), educational status (up to high school level, up to postgraduate level), and work status (working, not working). The significance level adopted for all analyses was $p \leq 0.05$.

RESULTS

In total, 3,062 women were approached to participate in this study, however 402 (13.1%) participants declined, leaving 2,660

TABLE 6 | Work productivity and activity impairment in women with endometriosis and symptomatic controls.

	Endometriosis cases $n = 518$ %, mean (±SD)	Symptomatic controls $n = 1,331$ %, mean (±SD)	Unadjusted *p*-Value	Adjusted *p*-Value
Absenteeism	16.74 (12.69)	14.76 (12.61)	0.002	0.001
Presenteeism	22.68 (23.06)	18.67 (22.58)	<0.001	0.006
Overall work productivity loss	34.32 (25.11)	29.67 (24.14)	<0.001	0.002
Activity impairment	36.87 (21.56)	33.98 (23.77)	0.008	0.059

Absenteeism: Time absent from work due to symptoms.
Presenteeism: Reduced Effectiveness while on the job due to symptoms.
Overall Work Productivity Loss: Combination of Absenteeism and Presenteeism.
Activity Impairment: Reduced effectiveness while doing non-work-related activities.
Adjusted Odds Ratio and P-Values for age (continuous), current BMI (underweight, normal weight, overweight, obese), civil status (married, not married), educational status (up to high school level, up to postgraduate level), and work status (working, not working).

(86.9%) women in the study. Fifty questionnaires (1.6%) had more than 50% missing data, hence these questionnaires were rejected because they were not completed in line with the study protocol, leaving complete data for 2,610 (85.2%) women. All dyspareunia-related variables were excluded from the analysis, because 96% of the questionnaires had missing data. In view of the conservative social values and cultural beliefs in the region, reluctance among women to report sexual problems was anticipated.

Of the 2,610 women who participated in the study, 518 had surgically-confirmed endometriosis and 2,092 were controls. The recruitment population of the controls were (population-based sample, $n = 842$; hospital-based laparoscopic confirmation, endometriosis-free, $n = 474$; hospital and clinic-based sample, $n = 776$), and were grouped according to presence of symptoms [symptomatic control sample ($n = 1,331$); asymptomatic control sample ($n = 761$)]. Most endometriosis cases had rASRM stage I and II endometriosis at the time of their surgical diagnosis [stage I: 129 (24.9%); stage II: 191 (36.8%); stage III: 109 (21.0%); stage IV: 89 (17.2%)].

The mean age of participants was 34.18 (SD ± 7.77) and the mean body mass index (BMI) was 27.00 (SD ± 5.46). Most of the women were married (79.2%, $n = 2,068$), with a higher education (61.3%, $n = 1,600$) and were working (63.6%, $n = 1,660$), which aligns with the annual census data (60). Comparison of the demographic, menstrual history, and prevalence of symptoms in endometriosis cases vs. symptomatic controls and asymptomatic controls is given in **Table 1**. In comparison to symptomatic and asymptomatic controls, women with endometriosis had a lower BMI ($p < 0.001$; $p < 0.001$), and lower parity ($p < 0.001$; $p < 0.001$). Higher educational achievement and employment rate was not significant between endometriosis cases vs. symptomatic controls ($p = 0.085$; $p = 0.697$). Menstrual irregularity was not associated with endometriosis vs. symptomatic controls ($p = 0.082$); however, a significant difference was present for earlier age at menarche ($p < 0.001$) and longer duration of menstruation ($p < 0.001$). Women with endometriosis had a higher prevalence of being affected by chronic pelvic pain ($p < 0.001$), dysmenorrhea ($p < 0.001$), dysuria ($p = 0.002$), dyschezia ($p < 0.001$), and infertility ($p = 0.001$), in comparison to symptomatic controls. Even with a high prevalence of chronic pain symptoms among the endometriosis cases, the chief clinical complaint and primary reason for surgical investigation was infertility (61.8%, $n = 320$), with only 36.8% ($n = 191$) agreeing to surgical intervention due to their pain symptoms and 1.4% ($n = 7$) proceeding with tubal ligation.

Health-Related Quality of Life

Prior to investigating the impact of HRQoL on endometriosis, a sensitivity analysis was conducted to quantify hidden bias between the HRQoL dimensions of symptomatic controls with laparoscopic confirmation vs. symptomatic controls with no surgical confirmation. The assessment of robustness between the HRQoL dimensions for the two symptomatic controls (surgical investigation vs. no surgical investigation) demonstrated no statistically significant differences in the HRQoL dimensions (physical function, $p = 0.335$; role-physical, $p = 0.160$; body pain, $p = 0.055$; general health, $p = 0.852$; vitality, $p = 0.615$; social functioning, $p = 0.266$; role-emotional, $p = 0.115$; mental health, $p = 0.862$; PCS, $p = 0.147$; MCS, $p = 0.551$), suggesting that results were not dependent on definition of symptomatic control group. Given that we found no change in our effect estimates, this suggests that the potential presence of undiagnosed cases in our symptomatic control group had little impact on the results of the analyses we present.

Compared with symptomatic and asymptomatic women, mean HRQoL scores were significantly lower in the endometriosis case group in all eight dimensions and two composite scores (**Table 2**). Using the US standardized scores for the calculation of HRQoL, all groups (endometriosis cases, symptomatic controls and asymptomatic controls) had a lower PCS and MCS score than the US normative general population (mean of 50) (49). After adjustment for demographic factors, the HRQoL scores were significantly impaired in women with endometriosis, as demonstrated in the PCS and MCS scores in symptomatic control group ($p = 0.001$; $p = 0.003$, respectively) and asymptomatic control group ($p < 0.001$; $p < 0.001$, respectively).

TABLE 7 | Physical activity, measured by MET-minutes/week, in women with endometriosis vs. symptomatic controls and asymptomatic controls.

	Endometriosis cases $n = 518$ Mean (±SD)	Symptomatic controls $n = 1,331$ Mean (±SD)	*p*-value	Asymptomatic controls $n = 761$ Mean (±SD)	*p*-value
Light MET	46.68 (44.16)	46.22 (44.16)	0.839	48.49 (45.57)	0.481
Moderate MET	102.85 (183.62)	118.86 (186.07)	0.101	121.46 (201.73)	0.109
Vigorous MET	182.61 (285.08)	186.14 (243.06)	0.790	203.33 (282.97)	0.200
Total MET	332.15 (486.99)	351.22 (423.63)	0.405	373.28 (498.45)	0.144

MET, Metabolic equivalent.
Light-intensity MET: Activities that are those with less than 3.0 METs.
Moderate-intensity MET: Activities are those between 3.0 and 6.0 METs.
Vigorous-intensity MET: Activities that score more than 6.0 METs.

There was a significant negative correlation between the subjective NRS rating of pain severity and HRQoL, when conducting a Spearman correlation test. Severity of pelvic pain was inversely correlated with PCS score (correlation coefficient: −0.256, $p < 0.001$) and MCS score (correlation coefficient: −0.116, $p < 0.001$) among endometriosis cases, and among symptomatic controls (correlation coefficient: −0.229, $p < 0.001$, correlation coefficient: −0.136, $p < 0.001$; respectively). However, endometriosis staging was not associated with physical ($p = 0.815$) or mental ($p = 0.737$) component scores, when stratified into the rASRM four-stage system.

After stratifying endometriosis cases and symptomatic controls by pain symptoms (dysmenorrhea, chronic pelvic pain, dyschezia and dysuria) and infertility, and adjusting for demographic factors, all symptomatic women had impaired PCS and MCS, regardless of presence of endometriosis (**Table 3**). Endometriosis and symptomatic controls could not be distinguished by MCS (**Table 3**; comparison between B vs. D). This is consistent with other comparative studies that women with and without pathology, matched for presence of pain symptoms, showed no difference on their MCS score (61). However, PCS was significantly lower when comparing the endometriosis cases to symptomatic controls, except for dysuria ($p = 0.118$), which may be because women with endometriosis experience multiple pain symptoms with a greater severity that hinders their physical and daily activities.

Diagnostic Delay of Endometriosis

Dysmenorrhea had the earliest symptom onset in the study population, and infertility the latest onset. The delay intervals from the onset of symptoms to first gynecological consultation, and intervals from first gynecological consultation to confirmed diagnosis are depicted in **Table 4**. Considering the average age at diagnosis was 34.04 (SD: 4.81) years for women with endometriosis, the interval between symptom onset and laparoscopic diagnosis of disease was on average 11.61 (SD: 5.59) years. Within this, the interval from the first onset of symptoms to first gynecological consultation was 6.01 (SD: 4.19) years, and the interval between first gynecological consultation to diagnosis was 6.96 (SD: 4.33) years.

The delay from symptom onset to diagnosis varied from 7.32 years among women with infertility to 12.44 among those with pelvic pain. Arab women were more likely to seek surgical confirmation of endometriosis when they suffered from infertility, as opposed to pain, hence the shorter diagnostic delay when including infertility confirmation. This is also demonstrated when participants were asked for their chief clinical complaint and primary reason for surgical investigation (infertility, 61.8%; pain, 36.8%).

When investigating the diagnostic delay of pain symptoms, married women experience 10.78 years of delay and single women experience 15.81 years of delay. There was a significant correlation between longer diagnostic delay of endometriosis and reduced HRQoL (PCS: correlation coefficient: −0.233. $p > 0.001$; MCS: correlation coefficient: −0.374, $p < 0.001$).

Psychological Disorders

Participants were asked to report if they have been clinically diagnosed with anxiety and/or depression disorders. Of endometriosis cases, 28.0% ($n = 145$) reported anxiety, 21.9% ($n = 292$) of symptomatic controls and 6.0% ($n = 46$) of asymptomatic controls. For depression disorder the numbers were 26.3% ($n = 136$), 20.0% ($n = 266$), and 6.6% ($n = 50$), respectively. After adjustment for demographic factors, there was a significant association between endometriosis status both when comparing with symptomatic and asymptomatic controls (**Table 5**).

Work Productivity and Activity Impairment

Participants were asked to rate the impact of their symptoms on work productivity and daily life using a 10-point scale in the WPAI questionnaire. Most women in the study population were employed (63.6%, $n = 1,660$), and those who did not work were mostly housewives or carers (75.3%; $n = 716$). Of the symptomatic women who were not in employment, approximately one in six (18.0%; $n = 171$) reported that they did not work because of the symptoms for which they underwent surgery. Work productivity was significantly impaired among women in the endometriosis group (**Table 6**), in comparison to the symptomatic group, for absenteeism ($p = 0.001$), presenteeism ($p = 0.006$), and overall work productivity loss ($p = 0.002$). No significant difference ($p = 0.059$) of impact on

non-work-related activities between the endometriosis cases and symptomatic controls was present.

Physical Activity

The intensity of physical activity was based on a MET score, measured to assess the amount of energy the body uses per minute, using the Compendium of Physical Activities (58). We did not observe any significant association between exercise activity and endometriosis (**Table 7**). However, all groups (endometriosis cases, symptomatic controls and asymptomatic controls) performed less exercise than the recommended guidelines of at least 500 MET-minutes per week (62). The prevalence of physical inactivity was 67.2% (n = 1,754) in the study.

DISCUSSION

For the first time, we provide evidence from a combined hospital, clinic, and population-based study that Arab women with endometriosis experience significant impacts on HRQoL, substantial diagnostic delay after the onset of symptoms, significant association to psychological disorders (anxiety and depression), and a negative impact on work productivity.

All women in the study population (endometriosis, symptomatic controls, and asymptomatic controls) had poorer mental HRQoL than the normative population. To interpret mental health and illness among Arab women, it is important to understand how Arab women perceive their role in their social, cultural, and religious context. The collectivist society emphasizes interdependence, where their role as custodians of community culture is to protect their family from any emotional harm. Emphasis is placed upon family privacy, reputation and solidarity, where women may feel reluctant to seek help due to shame and risk of harming the reputation and honor of the family (22, 63, 64). Therefore, the cultural expectation for Arab women to conceal mental distress may contribute to poor mental HRQoL and increased risk of developing psychological disorders (22, 65).

Physical and mental HRQoL scores were significantly impaired in women with endometriosis, in comparison to symptomatic control group ($p = 0.001$; $p = 0.003$, respectively) and asymptomatic control group ($p < 0.001$; $p < 0.001$, respectively). The effect of endometriosis on physical and mental HRQoL of women was substantial, with SF36v2 scores similar to those reported in Arab women with breast cancer (66). In comparison to the GSWH, the PCS and MCS scores were lower among women of Arab ancestry in endometriosis patients (PCS: 45.1, MCS: 42.2 vs. PCS: 43.6, MCS: 41.3) and symptomatic control group (PCS: 47.6, MCS. 43.5 vs. PCS: 46.0, MCS: 42.7). Susceptibility of multiple pain symptoms and infertility in women with endometriosis was the main indicator of a lower HRQoL. Arab women find it difficult to cope with society, friends, and family's negative reactions to their illness, where they may be blamed for the pain as a sign of punishment or uncontrolled anger, leading to social humiliation and ridicule (20, 64, 67–69).

The impact of pelvic pain severity, with or without surgically confirmed endometriosis pathology, demonstrated a similar direction of effect on PCS score ($p < 0.001$) and MCS score ($p < 0.0001$). The lack of statistical significance in MCS score, when comparing the effect of HRQoL composite scores on endometriosis-associated symptoms, between endometriosis cases and symptomatic controls, demonstrates that the presence, duration and severity of the pain state might be a driving force in the development of sensitization (70, 71). This may suggest that reduced HRQoL is associated with the coexistence of multiple pelvic pain symptoms, as opposed to endometriosis *per se*, although more detailed studies would need to be conducted to relate these causally. Arab women who suffer from chronic pain are subjected to pressure because of the transition from care-provider to care-receiver when suffering from debilitating, symptomatic episodes (72). Due to the burden to their commitments of their roles as mothers and housewives, it may be pain typology and severity that is associated with HRQoL, and not the presence of endometriosis *per se*.

Surgical staging of endometriosis in the present sample was not associated with a difference in the physical ($p = 0.815$) or mental ($p = 0.737$) component scores. This is consistent with previous studies where rASRM surgical staging was not associated with susceptibility or severity of pain or infertility of endometriosis (73). This suggests, perhaps not surprisingly, that the reduction of the HRQoL in women with endometriosis is related to symptomatology rather than rASRM stage.

In this study, only 4% of the women answered questions relating to dyspareunia due to the social taboo of discussing sexual relations and other private affairs. The lack of data in this topic demonstrates that Arab women with sexual pain may suffer in silence, and the impact of psychosocial expectations to prioritize privacy over their quality of life and wellbeing. Further understanding of the type and severity of dyspareunia phenotype may lead to a more personalized treatment approach. To study this sensitive topic among Arab women, sex education and psychosexual therapy must be easily accessible to be able to tackle cultural taboos and social pressures regarding dyspareunia.

Infertility has psychological effects in terms of anxiety, stress, depression and self-esteem, mostly affecting mental health (6). While this association is common across different populations, it may be intensified in this ethnic group because childlessness strongly influences marital life, and unfortunately may lead to divorce, or becoming a second wife in a polygamous marriage (74, 75). Divorced women in Arab societies suffer emotionally and socially, especially when they are infertile. In this study, 88.2% of the divorced women were infertile. Hence, infertility has a significant impact on the mental health components in our study because Arab women are often blamed when conception does not occur, and feel pressure from their husband as if they are not fulfilling their reproductive responsibility (76). This is demonstrated by the particularly low MCS score among infertile women, in both endometriosis and symptomatic control groups.

The diagnostic delay from first onset of symptoms to diagnosis was 11.61 years among Arab women. Within this, the interval from the first onset of symptoms to first gynecological consultation was 6.01 years, and between first gynecological consultation to diagnosis was 6.96 years. The diagnostic delay of 11.61 years among Arab women is approximately 5 years

greater than what was reported in the GSWH study (6.7 years), mainly driven by the delay in seeking the first gynecological consultation from symptom onset (6 years among Arab women vs. 1 year in the GSWH study) (5). Due to cultural stigma, it is not common for single women to visit a gynecologist when experiencing chronic pain or menstrual irregularities, hence prolong suffering, as demonstrated in our study where only <20% of the women were single. This is also reflected in the delay of diagnosis by 15.81 years among single women, with approximately 18% ($n = 15$) of the single women experiencing more than a 20-year delay in diagnosis due to chronic pain. Single Arab women were found to have fewer affirming attitudes toward seeking medical care, as they may endanger future marital prospects (77). Additionally, women are often told that their debilitating menstrual pain is normal or unexplained. Hence, the greater delay of diagnosis when suffering from pelvic pain (12.44 years) vs. infertility (7.32 years). Chronic peripheral pain stimulation followed by sensitization of the central nervous system can result in irreversible damage (70, 71). The diagnostic delay that is evident in this study suggests a critical window for attention and early intervention among women with symptoms suggestive of endometriosis. An increased diagnostic delay was associated with poorer HRQoL, due to a longer duration of painful symptoms without an accurate diagnosis and adequate treatment, worsening of the prognosis for fertility and pain, and increasing the risk for repeated operative procedures. The consequence of persistent pain emphasizes that women with endometriosis and symptomatic women with no endometriosis pathology need to consult immediately after symptom onset and be treated actively when they first seek medical care (70, 71, 78–80). This may minimize the development of a state that can cause long-term suffering and reduced HRQoL. Early diagnosis is likely crucial for the effective treatment and prevention of disease progression, as symptoms related to endometriosis can present immediately upon onset of menarche. Arab women may feel reluctant to seek help for their symptoms and sacrifice their own needs and welfare for the sake of the family unit (63, 64). Therefore, in additional to diagnostic delay among the physicians and referral patterns, cultural issues may contribute to the delay in seeking gynecological help.

Anxiety ($p = 0.007$) and depression ($p = 0.005$) were significantly associated with endometriosis, in comparison to symptomatic controls. The overlapping impacts of endometriosis on different aspects of life (physical, psychological, reproductivity, economical, and quality of life), as well as the early onset of symptoms and later diagnosis of the disease, collectively, have a considerable impact on mental health (6, 81, 82). There is a stigma and shame of receiving psychiatric treatment among Arab women to limit community censorship and victimization (77, 83). Rigid cultural norms and expectations oblige Arab women to accept and conceal mental distress and physical pain, which may contribute to an elevated risk of developing psychiatric disorders (77). The prolonged period of the unknown cause of the exacerbating symptoms has a critical impact on a woman's illness trajectory. Endometriosis is a condition that is misdiagnosed, mismanaged, and ignored; in addition to the need for increased health literacy among the population, there is also a lack of proper recognition by health professionals of the symptoms and psychological and interpersonal impact associated with endometriosis. Improving women's health and their HRQoL requires a multi-disciplinary team with a culturally relevant approach to create a suitable environment for providing better psychological care.

Women with endometriosis-related symptoms are negatively affected in a variety of ways relating to work productivity. When comparing the impact of endometriosis-associated symptoms on work productivity and activity impairment, women with endometriosis reported a greater impairment in terms of absenteeism ($p = 0.001$), presenteeism ($p = 0.006$) and overall work productivity loss ($p = 0.002$). However, no significant difference was observed in activity impairment between symptomatic women with and without endometriosis. Greater prevalence of empirical, over-the-counter medication usage by affected women leads to unsuccessful attempts to mitigate this pain, impacting their work productivity (84). Presence and severity of multiple pelvic pain symptoms are the major drivers of work productivity loss in endometriosis (5, 85, 86).

Inconsistent associations were observed between various types of physical activity and endometriosis in published literature (2, 86–89). In this study, the intensity of physical activity was not associated with endometriosis, when compared to symptomatic or asymptomatic controls. The prevalence of physical inactivity in the study was very high, at 67.2%, which aligns with published manuscripts in the region (90–95). There are various personal and environmental factors that act as barriers for Arab women to participate in physical activity: cultural normal and practices of public modesty, lack of accessible environments and fitness facilities for women to feel comfortable to exercise, lack of supportive social milieu for women, conservative dress that is not suitable for physical activity, and lack of information on the importance of physical activity in schools (96, 97). Thus, both general and gender norms are a barrier to physical activity among Arab women, and as such programmes aimed at increasing physical activity are difficult to implement.

Strengths of our study include its large sample size, surgically-confirmed incident endometriosis cases, and the selection of multiple control groups facilitating analyses comparing the contribution of control group selection to the results. Restricting our endometriosis cases to incidental cases diagnosed by laparoscopy decreased misclassification. However, the need for laparoscopy to diagnose endometriosis demonstrates the risk of including women with undiagnosed endometriosis in population-based control groups, resulting in indication biases. Until a non-invasive sample test is available that may be applied at a population level, critical care is needed on the selection of the control group to reduce ascertainment bias. Choosing an appropriate control group for endometriosis cases is complex, and multiple groups sampled from population and hospital based settings, as we used in this study, allow the testing of sensitivity of results to control group choice (98). The control group was recruited from community sites and hospitals/clinics from which the cases were enrolled. Although controls did not report a prior endometriosis diagnosis, some

were likely to have undiagnosed endometriosis, meaning our estimates may be affected by misclassification of endometriosis among the controls. This would have driven the associations observed to the null hypothesis of no difference, rather than creating spurious associations. Nevertheless, the prevalence of undiagnosed moderate-severe endometriosis in the general population group is likely to be low (<2%), therefore the control group is unlikely to contain many undiagnosed cases, especially if they were screened for moderate to severe pelvic symptoms (98). In addition, we found no significant magnitude of effect on the distribution of HRQoL dimensions among symptomatic controls (endometriosis-free) with laparoscopic confirmation vs. symptomatic controls with no surgical diagnosis. Women with infertility, or moderate/severe pain symptoms were over-represented in our patient sample because cases were enrolled in hospitals (which are typically more complex and severe cases of endometriosis), when compared to those with asymptomatic or mild symptoms that avoid seeking care from a gynecologist.

In order to compare the quality of life of women with endometriosis with the general population, the official norm-based scores derived from the 1998 USA general population by Quality metric Incorporated were used (49). The reason for choosing this normative population was to allow cross-cultural comparisons, however, the US general population may not be representative of the general Middle Eastern population, for which normative scores have not been published. Higher US scores would lead to a conservative estimation of the decreased quality of life in women with endometriosis. A SF-36 norm-based score must be developed from the Middle Eastern population to utilize for future HRQoL studies. Even though the participants were asked to report clinically diagnoses of anxiety and depression disorders, this information is self-reported and due to the lack of national health registries across the country, we were unable to verify this information. In addition, women are likely to seek treatment from nonpsychiatric specialist, such as general practitioners and gynecologist, for their mental illness due to the associated stigma, therefore this would have driven the associations observed to the null hypothesis (99). HRQoL and symptom severity may be hampered by recall bias because it was collected retrospectively. However, to limit information bias, we restricted our study to women undergoing a first laparoscopy for symptoms suggestive of endometriosis. There are methodological drawbacks with case-control studies, such as uncertain temporal relationships between HRQoL and endometriosis, therefore, a longitudinal cohort study would be more suited to investigate these associations.

It should be noted that the findings may not be generalisable to women who currently reside in countries that are exposed to war (Iraq, Palestine, Syria, Lebanon, Yemen) due to the lack of access to healthcare, low standard of care, low accessibility to adequate medical supplies, lack of qualified medical staff, mental health impact and the lack of attention for women's health due to high mortality and morbidity directly due to war and conflict. In addition, while the study findings may not be generalisable to Arab women residing in countries outside the Middle Eastern region, because they are likely to encounter a different set of social and cultural factors, these findings could be used to make cross-cultural comparisons. For instance, investigating the quality of life of Arab women residing in Western societies can be compared with those in this study, to elucidate similarities and differences among cultures, as well as the genetic and non-genetic underpinnings on HRQoL outcomes. This will increase the likelihood of a positive HRQoL trajectory, improve health and wellness among Arab women, and tackle disparities in the representation of Arabs in endometriosis research, globally. This may also enable an exploration of geographical variations in healthcare provisions for women with endometriosis.

It is important to acknowledge the influence of cultural sensitivities, traditions, and religious heterogeneity in different aspects of reproductive health disparities in healthcare that can act as barriers and directly impact Arab women. HRQoL associated with endometriosis is a growing concern, increasingly voiced by patients and health professionals. Women with endometriosis-associated symptoms should be referred to centers of expertise, led by those with training in complex benign gynecology and referred to a multi-disciplinary team that includes a psychologist, gynecology radiologist, pain specialist and with support from patient organizations. The significantly lower quality of life scores in women with endometriosis and symptomatic control group demonstrate that medical care should also address the emotional and social problems that come with endometriosis. Further research should identify symptom control strategies that target those pathways to improve the outlook for affected women. Our study will enable the establishment of communities for ongoing support and intends to build on the strength of women-centered networks for Arab women.

CONCLUSION

The chronicity and severity of pain and infertility associated with endometriosis have a negative impact upon HRQoL, psychological wellbeing and daily functioning. To improve the quality of life in women affected by endometriosis, medical care should address emotional, social and well-being aspects of the disease. The scientific and medical professional need an informed understanding of the heterogenous array of religious beliefs, cultural norms, and traditional expectations in the community, to ensure they are providing culturally sensitive, comprehensive care. There is a need to conduct an in-depth understanding of the personal and culturally centered beliefs of Arab women within the realms of their lives as young adolescents and adults, and how their HRQoL is impacted with endometriosis. Such understanding will allow policymakers, stakeholders, and medical physicians to improve management and develop targeted health education awareness campaigns for Arab women that struggle with endometriosis, which will differ from the current, more western-centric approaches. Additional support is required to target younger Arab women in this region to advance their understanding of reproductive health literacy and increase awareness of the severe impact of this condition and associated symptoms.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research Ethics Committee within the University of Oxford (OXTREC: 25-18) Ministry of Health in the UAE (MOHAP/DXB-REC-25/2018). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MM, NR, KZ, and CB were involved in all parts of the study conception, study design, analysis methods, interpretation, drafting of manuscript, and final approval. MA-J and HA were involved in study design, interpretation, reviewing of the manuscript, and final approval. All authors contributed to the article and approved the submitted version.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix III

V1.0 04/04/2018

OxTREC Ref: 25-18



PARTICIPANT INFORMATION SHEET

The MAR'A Project: Middle Eastern Women Research Association

Dear Participant,

Invitation

You are being invited to take part in the above named research study. Taking part in this study is voluntary. Before you decide if you wish to take part, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this information sheet.

What is the study about?

We will be conducting a study of 1,680 women in the United Arab Emirates from the Oras Medical Centre in Sharjah and Al Tawam Hospital in Al Ain. We are going to estimate the number of women affected by endometriosis, polycystic ovary syndrome (PCOS) and uterine fibroids in the Middle East. These gynaecological diseases cause infertility and pain. We will investigate the rate of women affected by these women's health conditions with associated lifestyle factors (diet and physical activity), reproductive factors (fertility history and pain history), and other related diseases. This is the first study to look into factors that could cause womens health diseases in the Middle East. By learning about these factors, we can understand the cause of these diseases, and learn about different ways we can treat it.

For the genetic study, we will need a saliva sample from the participants so that we could look at the inherited factors that are linked with endometriosis. Saliva contains genes, and everyone's genes are a little different. So by getting the DNA of women with and without endometriosis, we can compare the genes between the women and see which gene causes the disease by using a method called 'genome-wide association study.' By locating a specific gene that causes endometriosis, we can target it and this will allow use to make new drugs to treat diseases. If you have decided to undergo a laparoscopy, as it is thought you might have endometriosis you could participate as an endometriosis patient. If you have decided to undergo laparoscopic tubal sterilisation, as we do not expect you to have endometriosis you could participate as a control patient.

Why have I been invited to take part?

We are inviting all women who are 1) ethnically Arab, 2) ages between 18-50 and 3) have an ability to give a informed consent.

What's involved for me?

We will ask you to complete a questionnaire, and if applicable, a saliva sample collection. We estimated that it would take approximately one hour and a half for you to complete this study: 45 minutes to discuss the consent form and patient information sheet, giving you an appropriate amount of time to ask questions and to discuss with family, friends and Chief Investigator whether you would like to participate, 35 minutes for the questionnaire completion, 5 minutes for basic anthropometric measurements, and 5 minutes for saliva collection where you have to spit 2 ml of saliva into a tube. There are no other commitments or lifestyle restrictions associated with participating. No private medical record or personal information will be collected from you. Data obtained will be self-reported history that you will complete in the participant questionnaire.

What will happen to my data/sample?
After we collect the data, they will be stored in a secured, locked cabinet in United Arab Emirates University. Your questionnaire data will be entered in an electronic secure cloud-based database that will be transferred to a password-protected encrypted device. Your DNA saliva samples will be analysed by professionals in the laboratory in Khalifa University of Biotechnology, for one year. After the analysis, your remaining DNA saliva samples will be disposed, and the informed consent form/participant questionnaire will be archived for an additional 5 years in a secured, locked cabinet at United Arab Emirates University. Data analysis will be conducted by authorized representatives (such as study staff and co-investigators of the study) in the University of Oxford and Harvard University whilst ensuring compliance with regulation. All will have a duty of confidentiality and we will anonymise any documents that are sent to host institutions (University of Oxford and Harvard University), so that you cannot be identified from them. The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki and relevant regulations of Good Clinical Practice. All documents will be held in complete confidence and we will follow ethical and legal practice in relation to all study procedures. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

Are there any risks in taking part?
Participating in the research is not anticipated to cause disadvantages or discomfort. In the questionnaire, you will be asked to recall medical problems which maybe discomforting for some. However, none of these questions or test have adverse effects or any risks for you, and you do not have to answer all of them if you don't want to. The saliva samples will be a painless and non-invasive method. An inconvenience would be that we would require approximately one hour and a half of your time.

What are the benefits of taking part?
You will receive no medical or financial benefits from taking part in this study. However, the information from this study may help us in the development of future treatments for endometriosis.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. You can ask any questions about the study before decideing whether to take part. If you decide to take part you are still free to withdraw at any time and without giving a reason. If you would like to withdraw from the study, you will be asked if we can keep/use the data that you have given to us, if data is completely anonymised. If you want to exclude all the data from the study, all the information collected will be destroyed.

How will you intend to report and disseminate the results of the study?
To ensure results are available to you, they will be published in open access journals and present it to local policymakers, physicians and the public. You will not be identified in any reports/publications resulting from this research and those reading them will not know who has contributed to it. Genetic findings will not be fed back to you because the conditions under investigation are common complex conditions for which the genetic findings have no clinical value.

Has the study been reviewed by an ethics committee?
Your records obtained while you are in this study will remain strictly confidential and anonymous at all times. We have ethical approval for this study from University of Oxford (Oxford Tropical Research Ethics Committee) and the UAE (UAE University Research Committee, Dubai Research Ethics Committee of Ministry of Health and Prevention, and Health Authority Abu Dhabi Department). All results are anonymised before analysis, and the link between samples/data and participants will be destroyed at the end of the project. Your name will never be used on any forms, reports or publications

about the study. All information about you and your samples will be given a study identity number. Therefore, all information concerning you and your participation in this study will always remain strictly confidential and anonymous. The investigator will be responsible for the samples and will ensure they are kept securely.

What if I have any questions or want to raise a concern?
Mira Mousa, Chief Investigator, University of Oxford, +971 50 990 4455, mira.mousa@wrh.ox.ac.uk

Dr. Moamar Al-Jefout, Local Principal Investigator, United Arab Emirates University, +971 54 370 1543, drmoamar@uaeu.ac.ae

If you have any ethical complaints about the project in the first instance you can contact the Dubai Research Ethics Committee, Ministry of Health and Prevention, **Ms. Yusra Abdulrahman on 04-7078538, Yusra.swaidal@moh.gov.ae**

If you decide to take part in the study you will be asked to sign a consent form. A copy is attached for your information. Before you sign the consent form, you should ask questions about anything that you do not understand. You will be given a copy of the information sheet and a signed consent form to keep. Once you have signed the consent form you can still change your mind and withdraw from the study at any time and without giving a reason; this will not affect your medical care.

Data Protection

The University of Oxford is responsible for ensuring the safe and proper use of any personal information you provide, solely for research purposes.

Thank you for taking part in this research.

V1.0 04/04/2018

OxTREC Ref: 25-18

CONSENT FORM

The MAR'A Project: Middle Eastern Women Research Association

	Initials
1. I confirm I am over 18 and have read and understood the patient information sheet version 3.0 dated 28th June 2018 for the above study and have had the opportunity to ask questions and had them answered satisfactorily.	
2. I agree that my participation is voluntary and that I am free to withdraw without giving any reason, without any medical care or legal rights being affected.	
3. I agree that others working on the investigator's behalf need my permission to look at my anonymised health records collected during the current study both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw. I agree to this access.	
4. I agree to donate a saliva sample (2mls) to allow genetic studies to be performed	
5. I agree that my given samples taken for the purposes of research are a gift to the University of Oxford. If a commercial product were developed as a result of this study, I, nor my heirs would not profit financially.	
6. I understand that the saliva samples are for research purposes and are not intended to be diagnostic in any way.	
7. I agree to take part in this study and have my collected samples used in this study.	
8. . I agree that data collected during the study will be stored in the United Arab Emirates University and genetic analysis will be conducted in Khalifa University of Biotechnology laboratory.	
9. I agree that data analysis may be looked at by authorized representatives (such as study staff and co-investigators of the study) from the University of Oxford, United Arab Emirates University, and Khalifa University of Biotechnology, whilst ensuring compliance with regulation. I give permission for these individuals to have access to the data collected material and data analysis.	
10. I agree that my saliva samples will be disposed after analysis.	
11. I agree that my consent form and participant questionnaire will be archived for 5 years after data analysis in a locked, secured cabinet at United Arab Emirates University.	

Printed name of patient	Date	Signature of patient
Printed name of Investigator	Date	Signature of Investigator

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PARTICIPANT QUESTIONNAIRE

Overall Health

A1. In general, would you say your health is:

- ☐ Excellent
- ☐ Very good
- ☐ Good
- ☐ Fair
- ☐ Poor

A2. Compared to one year ago, how would you rate your health in general now?

- ☐ Much better than one year ago
- ☐ Somewhat better than one year ago
- ☐ About the same
- ☐ Somewhat worse now than one year ago
- ☐ Much worse now than one year ago

A3. The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
Vigorous activities, such as running, lifting heavy objects	☐	☐	☐
Moderate activities, such as moving a table, pushing a vacuum, bowling or playing golf	☐	☐	☐
Lifting or carrying groceries	☐	☐	☐
Climbing several flights of stairs	☐	☐	☐
Climbing one flight of stairs	☐	☐	☐
Bending, kneeling or stooping	☐	☐	☐
Walking more than a mile	☐	☐	☐
Walking half a mile	☐	☐	☐
Walking 100 yards	☐	☐	☐
Bathing and dressing yourself	☐	☐	☐

A4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	Yes	No
Cut down on the amount of time you spent on work and other activities	☐	☐
Accomplished less than you would like	☐	☐
Were limited in the kind of work or other activities	☐	☐
Had difficulty performing the work or other activities (e.g. it took more effort)	☐	☐

A5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
Cut down on the amount of time you spent on work and other activities	☐	☐
Accomplished less than you would like	☐	☐
Did work less carefully than usual	☐	☐

A6. During the past 4 weeks, to what extent have your physical health or emotional problems interfered with your normal social activities with family, neighbours or groups?

☐ Not at all ☐ Slightly ☐ Moderately ☐ Quite a bit ☐ Extremely

A7. How much bodily pain have you had during the past 4 weeks?

☐ None ☐ Very mild ☐ Mild ☐ Moderate ☐ Severe ☐ Very severe

A8. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give one answer that comes closest to the way you have been feeling.

How much time during the last 4 weeks…..:

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
Did you feel full of life?	☐	☐	☐	☐	☐
Have you been very nervous?	☐	☐	☐	☐	☐
Have you felt so down in the dumps that nothing would cheer you up?	☐	☐	☐	☐	☐
Have you felt calm and peaceful?	☐	☐	☐	☐	☐
Did you have a lot of energy?	☐	☐	☐	☐	☐
Have you felt downhearted and low?	☐	☐	☐	☐	☐
Did you feel worn out?	☐	☐	☐	☐	☐
Have you been happy?	☐	☐	☐	☐	☐
Did you feel tired?	☐	☐	☐	☐	☐

A9. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Not sure	Mostly false	Definitely false
I seem to get ill more easily than others	☐	☐	☐	☐	☐
I am as healthy as anybody I know	☐	☐	☐	☐	☐
I expect my health to get worse	☐	☐	☐	☐	☐
My health is excellent	☐	☐	☐	☐	☐

Menstrual history and hormones

B1. How old were you when you had your first menstrual period? ____

B2. Have you had any periods in the last 3 months?

☐ No → continue with question B2.1

☐ Yes → skip to question B2.4

B2.1. What was the reason for not having periods?

☐ Taking hormones continuously (e.g. the Pill, injections, Mirena, HRT)

☐ Pregnant/breastfeeding

☐ Menopause (stopped having periods)

B2.2. Approximately how many periods have you had over the last 12 months? _____

B2.3. When was your last period? _____

B2.4. Were your periods in the last 3 months natural or hormone-induced (e.g. on the Pill, injections, Mirena or HRT)?

☐ Natural ☐ Hormone induced

B2.5. When was the first day of your last menstrual period (LMP)?

LMP___/___/_____ ☐ Uncertain

DD MM YYYY

B2.6. Were your periods in the last 3 months regular? (expected date – every 28 days?)

- ☐ extremely regular (period starts 1-2 days before or after it is expected)
- ☐ very regular (period starts 3-4 days before or after it is expected)
- ☐ regular (period starts 5-7 days before or after it is expected)
- ☐ somewhat irregular (period starts 8-20 days before or after it is expected)
- ☐ irregular (period starts more than 20 days before or after it is expected)

B2.7. How many days of bleeding did you usually have each period in the last 3 months? (Not counting discharge/spotting for which you need a panty liner only)

_____ days or ☐ Too irregular to say

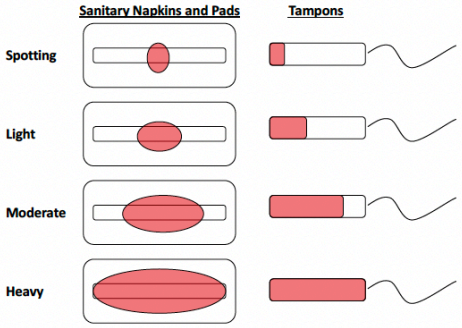
B2.8. The figure below shows examples of the amount of bleeding you can experience every four hours during your period. Please describe the amount of bleeding you typically experience four-hourly during your period at its heaviest, and on average.

At its heaviest?

- ☐ Spotting
- ☐ Light
- ☐ Moderate
- ☐ Heavy

On average?

- ☐ Spotting
- ☐ Light
- ☐ Moderate
- ☐ Heavy



B3. Please list below all hormones you have ever used for any reason (acne, bad cramping, irregular periods, birth control, fertility treatments).

Name of hormone	Age started	Used within the last 3 months?	Total time used
1.	.....	☐ No ☐ Yes	..... months ..... years
2.	.....	☐ No ☐ Yes	..... months ..... years
3.	.....	☐ No ☐ Yes	..... months ..... years

B4. Have you ever used emergency contraception?

- ☐ No
- ☐ Yes → If yes:

B4.1. Have you used emergency contraception in the last 3 months?

- ☐ No
- ☐ Yes

B5. What are/were your reasons for using hormones? (Tick all that apply).

- ☐ Birth control / pregnancy prevention
- ☐ Irregular periods
- ☐ Heavy periods
- ☐ Acne
- ☐ Endometriosis

☐ Polycystic ovarian syndrome (PCOS)
☐ Ovarian cyst
☐ Pelvic pain or pain with periods
B5.1. Did hormones help with the pain? ☐ Yes ☐ No
B5.2. Did you ever discontinue or change hormones because they were not effective enough at controlling pain? ☐ Yes ☐ No

B6. Have you ever used a non-hormonal coil/IUD?
☐ No
☐ Yes → If yes: B6.1. At what age did you first use a non-hormonal coil/IUD? ____

Pregnancy and fertility

C1. Have you ever been pregnant (confirmed by a positive pregnancy test, including miscarriages, ectopic pregnancies or terminations)?
☐ No ☐ Yes, please complete the table below.

	Pregnancy							
	1st	2nd	3rd	4th	5th	6th	7th	8th
How old were you at the start of the pregnancy?								
(Please write your age at each pregnancy)	.....	.....	.....	.....	.....	.....	.....	.....
What fertility treatment was used, if any, for this pregnancy?								
Natural conception: no fertility treatment	☐	☐	☐	☐	☐	☐	☐	☐
Fertility drugs by pills to stimulate ovulation (clomid, clomiphene)	☐	☐	☐	☐	☐	☐	☐	☐
Intrauterine insemination (IUI)	☐	☐	☐	☐	☐	☐	☐	☐
In vitro fertilization (IVF/ICSI)	☐	☐	☐	☐	☐	☐	☐	☐
What was the outcome of this pregnancy? (Please tick ✓ all that apply)								
Single live birth	☐	☐	☐	☐	☐	☐	☐	☐
Twins or triplets	☐	☐	☐	☐	☐	☐	☐	☐
Miscarriage	☐	☐	☐	☐	☐	☐	☐	☐
Stillbirth	☐	☐	☐	☐	☐	☐	☐	☐
Tubal or pregnancy in other location outside the uterus	☐	☐	☐	☐	☐	☐	☐	☐
Molar	☐	☐	☐	☐	☐	☐	☐	☐
Currently pregnant	☐	☐	☐	☐	☐	☐	☐	☐
How many weeks were you pregnant?								
Less than 24 weeks	.....	.....	.....	.....	.....	.....	.....	.....
24-28 weeks	.....	.....	.....	.....	.....	.....	.....	.....
29-32 weeks	.....	.....	.....	.....	.....	.....	.....	.....
33-36 weeks	.....	.....	.....	.....	.....	.....	.....	.....
37 or more weeks	.....	.....	.....	.....	.....	.....	.....	.....
If this pregnancy was a miscarriage, tubal/ectopic, or if you had a termination, how was this managed?								
Surgically (D&C, ERPC)	☐	☐	☐	☐	☐	☐	☐	☐
Medically (with tablets either orally and/or vaginally)	☐	☐	☐	☐	☐	☐	☐	☐
No management was needed	☐	☐	☐	☐	☐	☐	☐	☐
If this pregnancy resulted in a birth, was the delivery vaginal or via Caesarean section?								

Vaginal birth	☐	☐	☐	☐	☐	☐	☐	☐
Caesarean section	☐	☐	☐	☐	☐	☐	☐	☐
Did you go into labour and if so, was it induced or did it begin on its own?								
No labour	☐	☐	☐	☐	☐	☐	☐	☐
Spontaneous labour	☐	☐	☐	☐	☐	☐	☐	☐
Induced labour	☐	☐	☐	☐	☐	☐	☐	☐

Did you have any of the following complications related to pregnancy?								
Gestational diabetes	☐	☐	☐	☐	☐	☐	☐	☐
Pregnancy-related high blood pressure	☐	☐	☐	☐	☐	☐	☐	☐
Pre-eclampsia Toxemia	☐	☐	☐	☐	☐	☐	☐	☐
Mastitis/breast infection	☐	☐	☐	☐	☐	☐	☐	☐
HELLP syndrome	☐	☐	☐	☐	☐	☐	☐	☐
Hyperemesis gravidarum	☐	☐	☐	☐	☐	☐	☐	☐
Pre-term birth (birth before 37 weeks)	☐	☐	☐	☐	☐	☐	☐	☐

C2. Have you ever tried to get pregnant for more than 6 months in a row without succeeding?

☐ No

☐ Yes → If yes: C2.1. What was the longest amount of time that you tried, whether or not you actually got pregnant? _____ months

C3. Have you or your partner ever had any tests/investigations to find out why you were not getting pregnant?

☐ No

☐ Yes → If yes: C3.1. What were the results of these tests? (Please tick ✓all that apply)

☐ Endometriosis
☐ Adhesions
☐ Blocked tubes
☐ Polycystic ovary syndrome (PCOS)
☐ Pelvic inflammatory disease
☐ No/irregular ovulation
☐ Poor sperm count/quality
☐ Uterine fibroids
☐ No cause was found
☐ I can't remember
☐ Other……

C4. Did you ever seek treatment for infertility in any clinic?

☐ No

☐ Yes → If yes: C4.1. Please tell us about any fertility treatment you have used.

	Never used	Used in the last three months	Used, but not within the last three months	Number of cycles (if applicable)
Intercourse timed specifically to conceive	☐	☐	☐	……..
Fertility-focused intercourse	☐	☐	☐	……..
Fertility drugs by pills to stimulate ovulation (clomid, clomiphene or any other drug in pill form)	☐	☐	☐	……..
Fertility drugs by Injection (gonadotropins, HCG, or any other drug by injection)	☐	☐	☐	……..
Progesterone (vaginal or intramuscular injection)	☐	☐	☐	……..
Insemination with your partner's semen	☐	☐	☐	……..
In vitro fertilization (IVF)	☐	☐	☐	……..
In vitro fertilization with intracytoplasmic sperm injection (ICSI)	☐	☐	☐	……..

Pain

D1. Using the scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

	Not at all	To a slight degree	To a moderate degree	To a great degree	All the time
I worry all the time about whether the pain will end	☐	☐	☐	☐	☐
I feel I can't go on	☐	☐	☐	☐	☐
It's terrible and I think it's never going to get any better	☐	☐	☐	☐	☐
It's awful and I feel that it overwhelms me	☐	☐	☐	☐	☐
I feel I can't stand it anymore	☐	☐	☐	☐	☐
I become afraid that the pain will get worse	☐	☐	☐	☐	☐
I keep thinking of other painful events	☐	☐	☐	☐	☐
I anxiously want the pain to go away	☐	☐	☐	☐	☐
I can't seem to keep it out of my mind	☐	☐	☐	☐	☐
I keep thinking about how much it hurts	☐	☐	☐	☐	☐
I keep thinking about how badly I want the pain to stop	☐	☐	☐	☐	☐
There's nothing I can do to reduce the intensity of the pain	☐	☐	☐	☐	☐
I wonder whether something serious may happen	☐	☐	☐	☐	☐

The following questions ask about pelvic pain with your periods (including irregular bleeding or bleeding while on hormonal treatments, but not spotting). By 'pelvic pain' we mean any type of pain (cramping, shooting, stabbing, etc.) in the lower part of your belly, as shown by the shaded area in this picture:

D2. Have you ever had pain during your periods?

☐ No pain → Skip to question D12
☐ Mild cramps (medication never or rarely needed)
☐ Moderate cramps (medication usually needed)
☐ Severe cramps (medication and bed rest needed)

D2.1 At what age did you start having period pain? ___ years

If you have had a period in the last 3 months, please complete the following questions, otherwise, please tick here ___ and continue to question D12

D3. How much pelvic pain did you have during your last period?

☐ No pain → skip to question D10
☐ Mild cramps (medication never or rarely needed)
☐ Moderate cramps (medication usually needed)
☐ Severe cramps (medication and bed rest needed)

D4. Did you take any medications for period pain during your last period? (Please tick all that apply)

☐ No
☐ Yes, pain-killers that were prescribed by a doctor
☐ Yes, pain-killers bought over-the-counter without prescription (e.g. aspirin, ibuprofen, paracetamol/acetaminophen, naproxen)
☐ Yes, hormones, but pain was not alleviated
☐ Yes, hormones, pain was at least somewhat alleviated

D5. During your last period, did your period pain prevent you from going to work or school or carrying out your daily activities (even if taking pain-killers)?

☐ No ☐ Yes

D6. Please rate how severe your period pain was at its worst during your last period using a scale from 0 to 10 where 0=no pain and 10=worst imaginable pain.

No pain **Worst imaginable pain**

0 1 2 3 4 5 6 7 8 9 10

D7. The following questions are about your bowel movements/stool when you had period pain in the last 3 months.

When you had period pain in the last 3 months, how often…	Never/ Rarely	Some-times	Often	Most of the time	Always
…did this pain get better or stop after you had a bowel movement?	☐	☐	☐	☐	☐
…did this pain get worse after you had a bowel movement?	☐	☐	☐	☐	☐
…did you have more frequent bowel movements when the pain started?	☐	☐	☐	☐	☐
…did you have less frequent bowel movements when the pain started?	☐	☐	☐	☐	☐
…were your stools looser when the pain started?	☐	☐	☐	☐	☐
…were your stools harder when the pain started?	☐	☐	☐	☐	☐

D8. How old were you when your pelvic pain during your period was at its worst? _____

D9. Please rate how severe your period pain was at its worst in the last 12 months using a scale from 0 to 10 where 0=no pain and 10=worst imaginable pain.

0 1 2 3 4 5 6 7 8 9 10

If you are married, or have ever been married, please answer questions D10-D15. If you are single, please skip to D16.

The following questions are about pain during or after vaginal intercourse or penetration. By 'pelvic pain' we mean any type of pain (cramping, shooting, stabbing, etc.) in the lower part of your belly, as shown by the shaded area in this picture:

We remind you that any information you give will be treated in complete confidence.

If however you do not wish to answer these questions, please tick here ___ and skip to question D16. If you have never had intercourse, please check here ___ and skip to question D16.

D10. Have you ever had pain during intercourse or in the 24 hours following vaginal sexual intercourse/penetration?

☐ No → Please skip to question D27

☐ Yes → If yes: E15.1. At what age did this pain start? ___

D11. When you last had vaginal intercourse/penetration, where did you feel the pain? (Tick all that apply)

☐ At the entrance of the vagina

☐ Deep inside the vagina

☐ In the abdomen/pelvis

☐ Other location → If yes: E18.1. Please describe: _____

D12. Please rate how severe your pain was at its worst during the last time you had vaginal intercourse/penetration using a scale from 0 to 10 where 0=no pain and 10=worst imaginable pain.

0 1 2 3 4 5 6 7 8 9 10

D13. During times you had vaginal intercourse/penetration in the last 12 months, how often did you have pelvic pain during or in the 24 hours after intercourse?

- ☐ Never
- ☐ Occasionally (less than a quarter of times)
- ☐ Often (a quarter to half of the times)
- ☐ Usually (more than half of the times)
- ☐ Always (every time)

D14. In the last 12 months, was there a time of the month in which vaginal intercourse/penetration was more painful than at other times? Tick all that apply)

	Was intercourse/vaginal penetration attempted during this time frame?			If yes, was it more painful at this time than other times?	
D15.1. During a period?	☐ No	☐ Yes	→	☐ No	☐ Yes
D15.2. A few days before a period	☐ No	☐ Yes	→	☐ No	☐ Yes
D15.3. A few days after a period	☐ No	☐ Yes	→	☐ No	☐ Yes
D15.4. At mid cycle (around ovulation)	☐ No	☐ Yes	→	☐ No	☐ Yes

D15. In the last 12 months, did you ever interrupt/avoid vaginal intercourse/penetration because of pelvic pain?

- ☐ No
- ☐ Yes

The questions in this section ask about pelvic/lower abdominal pain in general.
By 'pelvic pain' we mean any type of pain (cramping, shooting, stabbing, etc.) in the lower part of your belly, as shown by the shaded area in this picture

D16. Have you ever experienced pelvic pain in general? Do not count: pain caused by menstrual cramps, intercourse, surgery, pregnancy, childbirth, sports-related or other injury, food poisoning, or stomach flu.

- ☐ No → skip to D25
- ☐ Yes → D16.1 At what age did you start having this pelvic pain? ___ years
  D16.2 When did you last have this pain?
  - ☐ In the last month
  - ☐ 1-3 months ago
  - ☐ 4-6 months ago
  - ☐ 7-12 months ago
  - ☐ longer than 12 months ago

D17. To what extent has your pain interfered with your normal social activities with each of the following activities in the last 3 months:

Work or school:	☐ Not at all	☐ Slightly	☐ Moderately	☐ Quite a bit	☐ Extremely
	☐ Not applicable				
Daily activities at home:	☐ Not at all	☐ Slightly	☐ Moderately	☐ Quite a bit	☐ Extremely
Sleep:	☐ Not at all	☐ Slightly	☐ Moderately	☐ Quite a bit	☐ Extremely
Sexual intercourse:	☐ Not at all	☐ Slightly	☐ Moderately	☐ Quite a bit	☐ Extremely
	☐ Not applicable				
Exercise/sports:	☐ Not at all	☐ Slightly	☐ Moderately	☐ Quite a bit	☐ Extremely
	☐ Not applicable				
Social activities:	☐ Not at all	☐ Slightly	☐ Moderately	☐ Quite a bit	☐ Extremely
	☐ Not applicable				

D18. Approximately how long in total did you have this pain for in the last 3 months?

- ☐ Less than one day
- ☐ One day
- ☐ Two to three days
- ☐ One day a week
- ☐ More than one day a week
- ☐ Every day

D19. Do you usually have this pain at about the same time in your cycle? (Please tick ✓ all that apply)

- ☐ No
- ☐ Yes: a few days before a period
- ☐ Yes: a few days after a period
- ☐ Yes: at mid cycle (around ovulation)
- ☐ Yes, other……

D20. Have you taken any medication to help alleviate this pain in the last 3 months? (Please tick all that apply)

- ☐ No
- ☐ Yes, pain-killers that were prescribed by a doctor
- ☐ Yes, pain-killers bought over-the-counter without prescription (e.g. aspirin, ibuprofen, paracetamol/acetaminophen, naproxen)
- ☐ Yes, hormones, but pain was not alleviated
- ☐ Yes, hormones, pain was at least somewhat alleviated

D21. When you had pelvic pain in the last 3 months, what did it feel like?

Throbbing	☐ None	☐ Mild	☐ Moderate	☐ Severe
Shooting	☐ None	☐ Mild	☐ Moderate	☐ Severe
Stabbing	☐ None	☐ Mild	☐ Moderate	☐ Severe
Sharp	☐ None	☐ Mild	☐ Moderate	☐ Severe
Cramping	☐ None	☐ Mild	☐ Moderate	☐ Severe
Hot-Burning	☐ None	☐ Mild	☐ Moderate	☐ Severe
Aching	☐ None	☐ Mild	☐ Moderate	☐ Severe
Heavy	☐ None	☐ Mild	☐ Moderate	☐ Severe
Tender	☐ None	☐ Mild	☐ Moderate	☐ Severe
Tiring-Exhausting	☐ None	☐ Mild	☐ Moderate	☐ Severe
Sickening	☐ None	☐ Mild	☐ Moderate	☐ Severe
Fearful	☐ None	☐ Mild	☐ Moderate	☐ Severe
Punishing-Cruel	☐ None	☐ Mild	☐ Moderate	☐ Severe

D22. What makes your pelvic pain worse? Please tick all that apply.

☐ Full bladder or urinating	☐ Stress
☐ Sitting	☐ Time of day
☐ Bowel movement	☐ Full meal
☐ Constipation	☐ Weather
☐ Intercourse or orgasm	☐ Coughing/sneezing
☐ Standing or walking	☐ Exercise
☐ Nothing makes my pain worse	☐ Other, please specify: _____

D23. What helps your pelvic pain? (Please tick ✓ all that apply)

- ☐ Pain medication
- ☐ Relaxation
- ☐ Lying down
- ☐ Music
- ☐ Massage
- ☐ Ice
- ☐ Hot bath
- ☐ Meditation
- ☐ Laxatives / enema
- ☐ TENS Unit
- ☐ Emptying bladder
- ☐ Hot water bottle

☐ Heating pad
☐ Bowel movement
☐ Nothing helps
☐ Other: .....

The following questions are about the time in your life when your pelvic/lower abdominal pain was at its worst. Please do not count: pain related to periods or intercourse, pregnancy or childbirth, any surgery, sports-related or other injury, food poisoning or stomach flu.

D24. How old were you when your pelvic/lower abdominal pain was at its worst? ..... years old

D25. Please rate how severe your pelvic/lower abdominal pain was when it was at its worst using a scale from 0 to 10 where 0=no pain and 10=worst imaginable pain.

0 1 2 3 4 5 6 7 8 9 10

D26. Have you ever received a diagnosis for the pain from a doctor?

☐ No
☐ Yes (tick all that apply):
☐ Irritable Bowel Syndrome
☐ Inflammatory bowel disease (e.g. Crohn's or Ulcerative Colitis)
☐ Endometriosis
☐ Fibroid(s)
☐ Ovarian cyst
☐ Pelvic inflammatory disease/infection
☐ Painful bladder/interstitial cystitis (NOT a bacterial bladder infection)
☐ Stress
☐ Other: ..... (please describe)

D27. Please indicate whether you have (had) the following other types of pain in the last 12 months:

Low back pain	☐ No	☐ Yes, in last month	☐ Yes, more than 1 month ago
Back pain that goes away with exercise	☐ No	☐ Yes, in last month	☐ Yes, more than 1 month ago
Back pain that does not go away with exercise	☐ No	☐ Yes, in last month	☐ Yes, more than 1 month ago
Muscle/joint pain unrelated to a viral infection or (sports) injury	☐ No	☐ Yes, in last month	☐ Yes, more than 1 month ago
Pain at ovulation (mid cycle)	☐ No	☐ Yes, in last month	☐ Yes, more than 1 month ago
Pain in legs	☐ No	☐ Yes, in last month	☐ Yes, more than 1 month ago
Pain with urination	☐ No	☐ Yes, in last month	☐ Yes, more than 1 month ago
Pain with bowel movement	☐ No	☐ Yes, in last month	☐ Yes, more than 1 month ago

D28.Have you ever been significantly bothered by recurrent headaches?

☐ No ☐ Yes

D29. Have you ever had any other type of chronic pain lasting at least six months?

☐ No ☐ Yes

If yes: Which type of pain have you had, for how long (either continuously or on and off), and how severe was the pain typically

Type of Pain	Duration			Typical Severity		
	Less than 1 year	1-5 years	More than 5 years	Mild	Moderate	Severe
Back Pain						
Neck Pain						
Post-Surgical Pain (including scar pain)						
Other (Please specify):						

D.30 Are you extremely sensitive to cold temperatues?

☐ No ☐ Yes

Medical history

E1. Have had any medical conditions and at what age you were first diagnosed by a doctor.

Medical Condition	Age of Diagnosis

E2. Have you been told that you were born with a structural problem / birth defect of your uterus, cervix, or vagina?

☐ No

☐ Yes → If yes: E2.1. Did you have surgery for this issue?

☐ No

☐ Yes → If Yes: E2.2. Was the problem improved or corrected after surgery?

☐ No

☐ Yes

E3. Have you ever been diagnosed by a doctor with cancer or a malignancy of any kind?

☐ No ☐ Yes

If Yes: E3.1. What type(s) of cancer (primary location) have you been diagnosed with, and when were you first diagnosed? (Please write below)

Type of Cancer	**Age first diagnosed (years)**

E4. Have you had any surgical procedures during your life? If so, at approximately what age(s) did you have the procedure(s), how many have you had in total, and what was the reason for the surgery?

Surgical Condition	**Age of Surgery**

E5. Have you experienced unusual or excessive hair growth on your face or body that is not a side effect of a medication?

☐ No ☐ Yes

If Yes: E5.1. Where have you experienced such hair growth? On your:

Upper lip	☐ Yes	☐ No
Chin	☐ Yes	☐ No
Upper back	☐ Yes	☐ No
Lower back	☐ Yes	☐ No
Upper arms	☐ Yes	☐ No
Thighs	☐ Yes	☐ No

Chest	☐ Yes	☐ No
Upper abdomen	☐ Yes	☐ No
Lower abdomen	☐ Yes	☐ No

E6. Have you had acne after the age of 18 (adult acne)?

☐ No ☐ Yes

E6.1. Have you had acne after the age of 25 (adult acne)?

☐ No ☐ Yes

E6.1.1. Where have you had acne? (please respond for each item)

Face or throat	☐ Yes	☐ No
Chest or back	☐ Yes	☐ No
Upper arms	☐ Yes	☐ No

E7. Have you experienced thinning or loss of your hair (not including hair-thinning side-effects of medications or treatments)?

☐ No ☐ Yes

E8. Do you have darkening of the skin around your neck, under your arms, on your hands or in your groin?

☐ No ☐ Yes

E12. Has a doctor or other health care provider ever diagnosed you with endometriosis?

☐ No
☐ Yes

If Yes,

E12.1. How was the diagnosis made? (Tick all that apply)

☐ laparoscopy or other surgical procedure
☐ ultrasound/MRI scan
☐ based on symptoms
☐ other, please describe: _____

E12.2. If you have had surgery for endometriosis, during your most recent surgery was your endometriosis treated (i.e. was it removed or burnt away)?

☐ No
☐ Yes
☐ Unsure
☐ Have not had surgery for endometriosis

E12.3. How old were you when you first had symptoms?_____ years old

E12.4. What symptoms, if any, prompted you to see a health care provider before your diagnosis with endometriosis? (please tick all that apply)

☐ Pain
☐ Infertility
☐ Pain and Infertility
☐ No symptoms
☐ Other (please specify): _____

E12.5. How old were you when you were diagnosed with endometriosis? _____ years old

E13. Have you ever had surgery to look for endometriosis and none was found?

☐ No ☐ Yes

If yes: E13.1. What symptoms prompted the surgery? (please tick all that apply)

☐ Pain
☐ Infertility
☐ Pain and Infertility
☐ Other (please specify): _____

E14. Have any of your blood relatives been diagnosed with any of the conditions below?
(Please tick all that apply)

Condition	Mother	Father	Sister	Brother	Daughter	Son	Grandparents, aunt, uncle, cousin	
							Mother's side	Father's side
Endometriosis	☐		☐		☐		☐	☐
Chronic pelvic pain	☐		☐		☐		☐	☐
Polycystic Ovary Syndrome (PCOS)	☐		☐		☐		☐	☐
Uterine Fibroids	☐		☐		☐		☐	☐
Heavy vaginal bleeding	☐		☐		☐		☐	☐
Thyroid disease	☐	☐	☐	☐	☐	☐	☐	☐
Cardiovascular disease	☐	☐	☐	☐	☐	☐	☐	☐
Diabetes	☐	☐	☐	☐	☐	☐	☐	☐
Dementia	☐	☐	☐	☐	☐	☐	☐	☐
Clinical obesity	☐	☐	☐	☐	☐	☐	☐	☐
Cancer	☐	☐	☐	☐	☐	☐	☐	☐

E15. At what age did your biological mother reach the menopause (stop having periods) naturally?

..... years or: E15.1. ☐ She has not reached the menopause yet, aged ..... years

E15.2. ☐ Don't know / her periods did not stop naturally

Medication history

F1. Please tell us about any pain medications, over-the-counter or prescription, that you have used at least once a week for a period of 3 months or longer.

PAIN RELIEF DRUG TABLE

Type of drug	Ever used? ✓ if yes	Currently taking? ✓ if yes	At what age did you first take this drug regularly?	For what pain was this medication used?	How many days per week?	How many tablets per week?	In total, how long have you used this drug?
Paracetamol/acetaminophen	☐	☐	____	☐ Pelvic pain ☐ Other pain ☐ Both	☐ 1 ☐ 2-3 ☐ 4-5 ☐ 6+	☐ 1-2 ☐ 3-5 ☐ 6-14 ☐ 15+	____ months ____ years
Aspirin (325 mg or more/tablet)	☐	☐	____	☐ Pelvic pain ☐ Other pain ☐ Both	☐ 1 ☐ 2-3 ☐ 4-5 ☐ 6+	☐ 1-2 ☐ 3-5 ☐ 6-14 ☐ 15+	____ months ____ years
Ibuprofen (e.g., Brufen)	☐	☐	____	☐ Pelvic pain ☐ Other pain ☐ Both	☐ 1 ☐ 2-3 ☐ 4-5 ☐ 6+	☐ 1-2 ☐ 3-5 ☐ 6-14 ☐ 15+	____ months ____ years

Celebrex, Vioxx (COX-2 inhibitors)	☐	☐	____	☐ Pelvic pain ☐ Other pain ☐ Both	☐ 1 ☐ 2-3 ☐ 4-5 ☐ 6+	☐ 1-2 ☐ 3-5 ☐ 6-14 ☐ 15+	____ months ____ years
Other anti-inflammatory analgesics (naproxen, mefanamic acid, Aleve, Naprosyn, Relafen, Ketoprofen, Anaprox)	☐	☐	____	☐ Pelvic pain ☐ Other pain ☐ Both	☐ 1 ☐ 2-3 ☐ 4-5 ☐ 6+	☐ 1-2 ☐ 3-5 ☐ 6-14 ☐ 15+	____ months ____ years
Strong (narcotic) analgesics (hydrocodone +paracetamol, codeine+paracetamol, morphine, codeine, oxycodone, hydrocodone, Demerol)	☐	☐	____	☐ Pelvic pain ☐ Other pain ☐ Both	☐ 1 ☐ 2-3 ☐ 4-5 ☐ 6+	☐ 1-2 ☐ 3-5 ☐ 6-14 ☐ 15+	____ months ____ years
Other pain-killing drugs aimed at the nerves/central nervous system (amitriptyline, nortryptilline, gabapentin, pregabalin, lamotrogine)	☐	☐	____	☐ Pelvic pain ☐ Other pain ☐ Both	☐ 1 ☐ 2-3 ☐ 4-5 ☐ 6+	☐ 1-2 ☐ 3-5 ☐ 6-14 ☐ 15+	____ months ____ years
Muscle relaxants (diazepam/temazepam, buscopan)	☐	☐	____	☐ Pelvic pain ☐ Other pain ☐ Both	☐ 1 ☐ 2-3 ☐ 4-5 ☐ 6+	☐ 1-2 ☐ 3-5 ☐ 6-14 ☐ 15+	____ months ____ years
Herbal medicines	☐	☐	____	☐ Pelvic pain ☐ Other pain ☐ Both	☐ 1 ☐ 2-3 ☐ 4-5 ☐ 6+	☐ 1-2 ☐ 3-5 ☐ 6-14 ☐ 15+	____ months ____ years

F2. Have you EVER taken prescription drugs for more than 3 months, excluding hormone treatments and pain medications?

☐ Yes → please fill out the Prescription Drug Table below before proceeding to the next section

☐ No → please skip to I1

PRESCRIPTION DRUG TABLE

Type of drug	Have you ever taken this drug every day for over a month?	At what age did you first take this drug every day for over a month?	In total, how many years you have taken this drug? Please estimate, and enter "0 total years" if less than 1 year.	Are you currently taking this drug every day?	Please write down the specific name of the drug you have used most recently if known:
	✓ if yes	Age 1st	Years taken:	✓ if yes	Name of drug:
a. Diuretic (water pill)	☐	__ __	__ __	☐	
b. Diabetic tablets	☐	__ __	__ __	☐	
c. Insulin	☐	__ __	__ __	☐	
d. Thyroid drugs	☐	__ __	__ __	☐	

e. Drugs for epilepsy	☐	__ __	__ __	☐	
f. Sleeping tablets / tranquilisers	☐	__ __	__ __	☐	
g. Anti-depressants	☐	__ __	__ __	☐	
h. Other drugs to treat mental illness	☐	__ __	__ __	☐	
i. Drugs for osteoporosis ("brittle bones")	☐	__ __	__ __	☐	
j. Drugs for rheumatoid arthritis	☐	__ __	__ __	☐	
k. Antibiotics for a month or more	☐	__ __	__ __	☐	
l. Antacids	☐	__ __	__ __	☐	
m. Drugs for stomach ulcer / gastritis	☐	__ __	__ __	☐	
n. Drugs for high cholesterol	☐	__ __	__ __	☐	
o. Drugs for allergies (antihistamines)	☐	__ __	__ __	☐	
p. Steroids (oral, inhaled, or nasal)	☐	__ __	__ __	☐	
q. Chemotherapy for cancer	☐	__ __	__ __	☐	
r. Tamoxifen for cancer	☐	__ __	__ __	☐	
s. Blood pressure drugs	☐	__ __	__ __	☐	
t. Drugs for angina (chest pain)	☐	__ __	__ __	☐	
u. Other drugs for a heart condition	☐	__ __	__ __	☐	
v. Inhaler for asthma	☐	__ __	__ __	☐	
w. Warfarin / heparin to thin blood	☐	__ __	__ __	☐	
x. Migraine tablets/injections	☐	__ __	__ __	☐	
Other 1: ……	☐	__ __	__ __	☐	
Other 2: ……..	☐	__ __	__ __	☐	
Other 3: ……..	☐	__ __	__ __	☐	
Other 4: ……..	☐	__ __	__ __	☐	
Other 5: ……..	☐	__ __	__ __	☐	

Personal Information and lifestyle

G1. What is your date of birth? __ __ / __ __ / __ __ __ __
DD MM YYYY

G2. How would you describe your ethnic origin?

☐ Arab

☐ Where are you from: _____

G3. What is your major ancestry? (Please tick one).

☐ African ☐ Middle Eastern ☐ Asian

☐ Southern European / Mediterranean ☐ Persian ☐ Baluch

☐ Don't know ☐ Other (Please specify): _____

G4. Are your parents first or second-degree relatives? ___

G5. Are your grandparents first or second-degree relatives? ___

G6. What is your marital status?

☐ Single ☐ Married ☐ Divorced ☐ Widowed

G7. Are you currently in school?

☐ No ☐ Yes

G8. What is the highest level of education you have attained (with certificate)?

☐ Primary school ☐ Post-secondary not university / some college or vocational school

☐ Middle school ☐ University

☐ High school ☐ Postgraduate

G9. What is your current height? _____ cm

G10. What is your current weight? _____ kg

G11. Since 18 years of age, what is the most that you have weighed (not including pregnancy and the 12 months following pregnancy)? _____ kg

G11.1 How old were you when you weighed that amount? _____

G12. Since 18 years of age, what is the least that you have weighed? _____ kg

G12.1. How old were you when you weighed that amount? _____

G13. During the last 12 months, what was your average time per week spent on each of the following recreational activities?

	Zero	1-4 min	5-19 min	20-59 min	One hour	1-1.5 hours	2-3 hours	4-6 hours	7-10 hours	11+ hours
Walking or hiking outdoors (include walking to work)										
Jogging (slower than 10 minutes/mile or 1.5 km)										
Running (10 minutes/mile or 1.5 km)										
Bicycling (include stationary machine)										
Calisthenics/aerobics/aerobic dance/rowing machine										
Tennis, squash, racquetball										
Lap swimming										
Other aerobic recreation (e.g., lawn mowing)										

G14. Have you smoked more than 100 cigarettes *(1-hour consecutive shisha/hookah smoking session)* during your lifetime?

☐ No ☐ Yes

If yes:

G14.1. How old were you when you first started smoking? _____ years old

G14.2. Do you smoke currently?

☐ No, I stopped smoking at age _____

☐ Yes, and I smoke about _____ cigarettes per week

G15. What term best describes your current work status?

☐ Working in a paid job, as an employee

☐ Self-employed

☐ Not in paid work force: (Please tick ✓ all that apply)

- ☐ Homemaker
- ☐ In full time education
- ☐ Doing voluntary work
- ☐ Unable to work because of the symptoms for which I am undergoing surgery
- ☐ Unable to work for other reasons
- ☐ Other (Please describe)

……

G16. During the past four weeks, how much did your symptoms affect your productivity while you were working?

0 1 2 3 4 5 6 7 8 9 10

G17. During the past four weeks, how much did your symptoms affect your ability to do your regular daily activities, other than work at a job?

0 1 2 3 4 5 6 7 8 9 10

G18. . During the past four weeks, how many days or hours did you miss from work because of problems associated with your symptoms?

……hours

G19. . During the past four weeks, how many days or hours did you miss from work because of problems associated with your symptoms

……hours

G20. How many hours a week do you get paid to work? (If self-employed, specify the number of hours a week that your work on average)

……hours

G21. At what age did you first visit a gynaecologist?

____ years old.

G22. Have you ever been exposed to war? (Including exposure to: to smoke and oil cloud, chemical warfare agents including nerve gas and mustard gas, wearing chemical protective clothing, depleted uranium, and smoke from burned excrement and exhaust fumes)

Yes No

G23.What is your nationality? _____

Thank you for your time and cooperation in answering these questions.
If you have comments or questions about any part of this survey, please explain here.

Appendix IV

V1.0 04/04/2018; OxTREC Ref: 25-18

ورقة معلومات المشارك
مرآة: جمعية بحوث المرأة في الشرق الأوسط

أعزاءي المشاركين في البحث
تحياتي، وفائق تقديري،

أنتم مدعون للمشاركة في البحث أعلاه، ولكن قبل إبداء موافقتك بالمشاركة الطوعية لإنجاح هذا البحث عليك بمعرفة كل ما يتعلق بهذا البحث ولديكم المزيد من الوقت للاطلاع على أسباب إجراء هذا البحث وعلى جميع المعلومات المتعلقة بذلك، ونحن نبذل أقصى الجهود من جانبنا في التعاون التام معكم للإجابة على أي استفسارات تتعلق بجوانب إجراء هذه الدراسة البحثية، حتى يساعدك ذلك في النهاية على اتخاذ قرار المشاركة من عدمها في هذا البحث. نشكركم على الاطلاع على جميع محتويات الدراسة البحث أعلاه.

بماذا تتعلق هذه الدراسة البحثية؟
وقد ارتئينا أن تشتمل الدراسة بمشاركة ما يقرب من ٢٣٠٠ أمرأه من مركز اوراس في الشارقة و مستشفى توام في العين .الا على أن تكون مشاركة المرأة العربية في جوانب البحث من الأهمية القصوى في انجاح وترسيخ هذه الدراسة البحثية للتوصل إلى حلول تشخيصية وعلاجية لفهم شريحة واسعة من النساء ذات الأصول العربية بعد الكشف عن الأسباب البيئية والجينية في نشؤ بعض الأمراض النسائية لديهن ، من المعروف أن بعض الأمراض النسائية لها دور في تأخير فرص الحمل والانجاب لدى العديد من النساء والتي قد تنتهي بالعقم وفقدان القدرة على الانجاب إذا لم يتم تشخيصها مبكرا لما لها من تأثيرات عديدة أخرى كالشعور بالآلام في منطقة الحوض والتأثيرات النفسية المرافقة لتأخر الحمل والانجاب لدى المرأة وأهم تلك الأمراض هو ما يعرف بمرض بطانة الرحم المهاجرة، وتكيسات المبيض المتعددة(PCOS) والأورام الرحمية. ونحن إذ ندعوكم للتعاون معنا من خلال مشاركتكم لتفهم الأسباب البيئية منها والجينية (الوراثية) المتعلقة بصحة المرأة بعد أن أصبح من الواضح من تأثير العوامل البيئية والوراثية في نشؤ بعض الأمراض النسائية الخاصة بالمرأة وحالما يتم التوصل إلى معرفة تلك الأسباب فإن ذلك سيكون له تأثير في التشخيص المبكر للمرض واستحداث الطرق العلاجية لها مستقبلاً.

الجزء الأساسي في الدراسة البحثية هذه هو إجراء دراسة وتقييم حدوث فرص اصابة المرأة في دولة الإمارات العربية ودراسة جميع الأسباب المتعلقة بنشوئها بدءاً من طريقة الحياة اليومية للمرأة هنا والممارسات الشخصية مرورا بالعوامل البيئية والجغرافية كأسباب لنشؤ هذا المرض. حاليا ليس هناك دراسة بحثية دقيقة بهذا المجال تخص أسباب نشؤ بعض الأمراض النسائية في عالمنا العربي. لذلك يبقى الهدف الأساسي الذي نصبو إليه هو إمكانية زيادة الوعي لدى شريحة واسعة من النساء للمساعدة على تشخيص وعلاج العديد من الأمراض النسائية والتي بدأت تشكل عبئاً كبيرا على المجتمع لما لها من تأثير مباشر على الحمل والانجاب لدى المرأة العربية. مع العلم ان هذه الدراسة البحثية ستكون الأولى في الشرق الأوسط. اذ لم تكن هناك أي دراسة بحثيه دقيقة بهذا المجال تخص معرفه أسباب نشوء بعض الامراض النسائية في عالمنا العربي.

في حالة عدم التأكد من الجواب على بعض الأسئلة المتعلقة بالبحث حاولي التفكير مليا لبعض الوقت على أن تكون الإجابة أكثر دقة حيث أنه على ضوء الإجابة يتم تقييم نتائج البحث ، حيث سيتم كذلك إجراء الفحوصات الجينية (فحص DNA) على نماذج اللعاب والتي يتم جمعها ومقارنة نتائج فحص (DNA) عند النساء الاتي لم يصبن بمرض بطانة الرحم المهاجرة، على أن يتم اختيار النساء الاتي تم تشخيصهن جراحيا بأنهن مصابات بمرض بطانة الرحم المهاجرة، وأن تحديد هذه الاختلافات الجينية سيساعد بالتأكيد الباحث على التوصل إلى أفضل الطرق العلاجية للسيطرة على مرض بطانة الرحم المهاجرة، ومتى نتمكن من تحقيق ذلك ؛ سنقوم بإجراء دراسة بحثية موسعة لجزيئات (DNA) ومن ثم التوصل إلى تحديد الجين المسؤول عن نشؤ مرض بطانة الرحم المهاجرة.

لماذا تمت دعوتي للمشاركة في البحث؟
نحن في هذه الدراسة البحثية المهمة ندعو جميع النساء ذات الأصول العربية والبالغات في العمر بين سن 18 – 55 سنة ولديهن القدرة على المشاركة بهذا البحث المهم من الناحية العلمية البحثية والطبية.

ما الذي ينطوي عليه عمله في هذه الدراسة بالنسبة لي؟
سوف نطلب منك إكمال الاستبيان، وإذا لزم الأمر، جمع نماذج من اللعاب. فأن الأمر سيستغرق ما يقرب من ساعة واحدة لاستكمال هذه الدراسة: 30 دقيقة لمناقشة نموذج الموافقة وما يتعلق بالمعلومات الطبية، مما يوفر لك الوقت المناسب لطرح الأسئلة ومناقشة الأمر مع العائلة والأصدقاء، قد نحتاج إلى 20 دقيقة لاستكمال الاستبيان، و5 دقائق لقياسات الطول والوزن وكتله الجسم، و5 دقائق أخره لجمع نماذج اللعاب ما يقارب 2 مل من اللعاب في أنبوب خاص.

ماذا سيحدث لبياناتي ونماذج اللعاب الخاصة بي؟
بعد أن يتم جمع البيانات الخاصة بالبحث سيتم تخزين وحفظ نماذج اللعاب الخاصة بكي في جامعة الإمارات العربية المتحدة وضمن سريه تامة. حيث سيتم بعده استحداث دراسة جينية من قبل مختصين في البحث الجيني في جامعة خليفة للتكنولوجيا الحيوية. وقد يتم حفضها لمدة عام واحد. وبعد الانتهاء من دراسة نماذج سيتم اتلافها مع الإبقاء على جميع البينات المتعلقة بالدراسة الجينية لتلك النماذج وقد يتم الإبقاء عليها وحفظها لما يقرب من 5 سنوات وسيتم حفظها بطريقة ذات سريه عالية في قسم البحوث (جامعة الإمارات العربية المتحدة). وسيتم مشاركة تلك البينات المتعلقة بالدراسة البحثية مع المختصين في جامعة أكسفورد وجامعة هارفارد مع ضمان الامتثال

لجميع القوانين المعمول بها حتى تكون مطابقة للوائح البحوث هناك. سيتحمل الجميع المسؤولية لحفظ هذه البينات بسرية تامة حيث سيتم إخفاء هوية المشاركين بالبحث عندما يتم إرسال تلك الدراسة البحثية إلى المؤسسات البحثية (جامعة أكسفورد وجامعة هارفارد)، بحيث لا يمكن التعرف على هوية المشاركين في الدراسة. وسيضمن الباحث إجراء هذه الدراسة وفقًا لمبادئ إعلان هلسنكي واللوائح ذات الصلة للممارسات الطبية السريرية. جميع الوثائق ستحفظ بسرية عالية طبقا للممارسات الأخلاقية والقانونية فيما يتعلق بجميع إجراءات الدراسة. وستلتزم هذه الدراسة بقانون حماية البيانات الخاصة بالمشاركين بهذه الدراسة والذي يتطلب إخفاء هوية البيانات الخاصة وحفظها بسرية عالية.

هل هناك أي مخاطر في المشاركة في هذه الدراسة البحثية؟
من غير المتوقع أن تكون المشاركة بالبحث تحمل أي مخاطر وعيوب للشخص المشارك في الاستبيان. ومع ذلك فإن لديك الحق في عدم الإجابة على أي من هذه الأسئلة أو الاختبارات المتعلقة بالاستبيان إذا لم ترغبي بذألك، كما ليس عليك الإجابة عنها جميعًا. فيما يتعلق بجمع نماذج اللعاب فهي طريقة سهلة ولا تسبب اي إزعاج للمشارك في البحث.

هل المشاركة بالبحث يعود لي بالمنفعة؟
بالحقيقة المشاركة في البحث هي طوعية ولا تعود باي فوائد من الناحية المادية أو العلاجية للأشخاص المشاركين بالبحث. ولكن بالتأكيد مشاركتكم بالدراسة سيدعم جهودنا في الوصول إلى فرص التشخيص المبكر لتلك الأمراض النسائية ومن ثم ستسرع في أمكانية زيادة فرص العلاج لتلك الأمراض.

هل يجب على المشاركة بهذه الدراسة البحثية؟
وكما ذكرنا سابقا من ان المشاركة انما هي طوعية لذألك لديك الحق بالمشاركة من عدمها لذألك فأن الأمر متروك لك لتقرري ما إذا كنت ترغبين بالمشاركة أم لا. فإذا قررت المشاركة، سيتم إعطاؤك ورقة خاصة بالمعلومات المتعلقة حيث يتم الاحتفاظ بها ومن ثم يطلب منك التوقيع على نموذج الموافقة. وحينها يمكنك طرح أي أسئلة حول الدراسة قبل اتخاذ قرار بشأن المشاركة. وحتى إذا قررت المشاركة، فلا يزال لديك الحرية في الانسحاب في أي وقت ودون إبداء سبب. إذا كنت ترغبين في الانسحاب من الدراسة، فسوف يتم سؤالك عما إذا كان بإمكاننا الاحتفاظ / استخدام البيانات الخاصة بكي، ولك الحق في أي مرحلة من البحث في الطلب منا بإلغاء هذا الاستبيان وعدم أكماله أو حفضه فسيتم ذلك وحسب رغبتك.

هل سيتم مراجعة الدراسة البحثية من قبل لجنة أخلاقيات المهنة (Ethics Committee)؟
ستظل سجلاتك التي تم الحصول عليها أثناء وجودك في هذه الدراسة ذات سرية عالية وفي جميع الأوقات حيث لم يتمكن الباحثون خلال مراحل دراسة الاستبيان أو نماذج الخاصة بكي من معرفة أي شيء يتعلق بهويتك الشخصية كاسمك أو اسم عائلتك في أي نماذج أو تقارير حيث سيتم الاحتفاظ بها بالسرية عالية وبشكل امن. ولدينا موافقة مسبقة لهذه الدراسة من جامعة أكسفورد (OXTREC) والإمارات العربية المتحدة (لجنة البحوث بجامعة الإمارات، ولجنة أخلاقيات البحوث في دبي التابعة لوزارة الصحة، وهيئة الصحة في أبو ظبي). وحيث انه لن يتم الإعلان عن اسمك في أي مرحلة من البحث وسيتم استبدال الاسم برقم محدد يتم تداوله بدلا استخدام اسمك الشخصي. لذألك فان جميع المعلومات المتعلقة بالدراسة ونماذج الخاصة سيتم التعامل معها بالسرية العالية طوال فترة البحث.

ماذا إذا كان لدي أي سؤال او استفسار؟
نعم يمكنك توجيه أي سؤال او استفسار خاص بالدراسة البحث:
ميرا موسى، جامعة أكسفورد: mira.mousa@wrh.ox.ac.uk - 050-9904455
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إذا كان أي شكاوى أخلاقية حول المشروع في المقام الأول، ارجوا الاتصال بلجنة أخلاقيات البحث في دبي، وزارة الصحة والوقاية، السيدة يسرى عبد الرحمن على، Yusra.swaidal@moh.gov.ae - 04-7078538

حيث أن جميع المعلومات التي يتم الحصول عليها كنتيجة لهذا البحث سيكون لها بالتأكيد فوائد مستقبلية كبيرة في ايجاد الطرق العلاجية لهذا المرض. موافقتك بالمشاركة بهذه الدراسة البحثية سيتم توثيقها بموافقتك وتوقيعك على نموذج نصوص إجراء البحث. موافقتك الأولية وتوثيقك ذلك بالتوقيع على نماذج نصوص هذه الدراسة البحثية لا يمنعك في أي وقت أثناء إجراء هذه الدراسة بالانسحاب أو التوقف عن إكمالها دون أي توضيح لأسباب ذلك.

للمزيد من المعلومات الخاصة بهذه الدراسة البحثية المهمة يمكنك الاتصال بالباحثة المختصة:

ولكم جزيل الشكر والتقدير لتعاونكم معنا في إتمام هذه الدراسة البحثية والتي بالتأكيد سيكون لها أثر إيجابي كبير في زيادة فرص التشخيص والعلاج للعديد من الامراض النسائية مستقبلا

نموذج الموافقة
مرآة: جمعية بحوث المرأة في الشرق الأوسط

1- أؤكد أنني أبلغ من العمر أكثر من 18 عاماً، وكنت قد قرأت وبدقة جميع الصفحات المتعلقة بالدراسة البحثية أعلاه من طرح الأسئلة والإجابة عليها بدقة عالية.
2- أؤكد كذلك على أن دوري هنا هو تطوعي، ويمكنني التوقف أينما شئت دون الحاجة إلى توضيح الأسباب، ودون أن يكون هناك أي تبعات من الناحية الطبية أو القانونية.
3- أوافق على التبرع نماذج اللعاب التي يتم جمعها أثناء البحث لغرض إجراء الدراسة الجينية عليها.
4- أؤكد على أن جميع النماذج التي يتم جمعها هي لغرض البحث وليس ليس لها دور في التشخيص المرضي.
5- أوافق على أن أكون مشاركة في هذا البحث، وعلى أن تكون نماذج اللعاب التي يتم جمعها جزءاً مكملا للبحث.
6- أوافق على اكمال الدراسة البحثية المتعلقة بالبحث.
7- أوافق على أنني لن أتلقى أي فوائد أو تعويض من هذه الدراسة.
8- أوافق على أنه سيتم تخزين البيانات التي تم جمعها أثناء الدراسة في جامعة الإمارات العربية المتحدة وسيتم إجراء التحليل الوراثي في مختبر جامعة خليفة للتكنولوجيا الحيوية.
9- أوافق على أنه يمكن النظر في تحليل البيانات الخاصة بالدراسة البحثية وبمشاركة المؤسسات البحثية في جامعة أكسفورد وجامعة هارفارد، وجامعة الإمارات العربية المتحدة، وجامعة خليفة للتكنولوجيا الحيوية. وحيث أعطي الإذن بالموافقة لهؤلاء الأفراد للوصول إلى البيانات التي تم جمعها وتحليلاها.
10- أوافق على انه يتم التخلص من نماذج اللعاب الخاصة بي بعد الانتهاء من التحليل.
11- أوافق على أنه سيتم حفظ استمارة الموافقة الخاصة بي والاستبيان لمدة قد تصل الى 5 سنوات بعد تحليل البيانات حيث سيتم حفضها في خزانة مؤمنة ومغلقة وذات سرية عالية في جامعة الإمارات العربية المتحدة.

توقيع المريض ..... التاريخ ..... اسم المريض .....

توقيع الشاهد ..... التاريخ ..... اسم الشاهد .....

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جامعة الإمارات العربية المتحدة
United Arab Emirates University

الأسئلة المتعلقة بالصحة العامة

A1- بصورة عامة، ماذا تقولين عن صحتك؟

- ☐ رائعة
- ☐ جيدة جدا
- ☐ جيدة
- ☐ مقبولة
- ☐ غير جيدة

A2- مقارنة بالسنة الماضية، كيف يمكنك تقييم صحتك حاليا؟

- ☐ أفضل بكثير من السنة الماضية
- ☐ أفضل بقليل من السنة الماضية
- ☐ لا يوجد تغير عن السنة الماضية
- ☐ أحسست بالتدهور الصحي مقارنة بالسنة الماضية
- ☐ تدهور صحي كبير مقارنة بالسنة الماضي

A3- الأسئلة التالية تتعلق بالنشاط اليومي:

هل أن صحتك تمنعك من اجراء الأعمال اليومية والموضحة أدناه؟ وكم هي النسبة التقريبية لذلك؟

		نعم بشكل كبير	نعم بشكل محدود	لا لم تتأثر
1	عند ممارسة الأعمال المرهقة كالركض السريع، أو رفع أوزان كبيرة، أو المشاركة في الفعاليات الرياضية العنيفة.	☐	☐	☐
2	عند ممارسة الأعمال المتوسطة الشدة كما في تحريك طاولة من مكانها،أو استخدام المكنسة الكهربائية للتنظيف،أو لعب الجولف.	☐	☐	☐
3	حمل أغراض التسوق.	☐	☐	☐
4	صعود الدرج لعدة درجات.	☐	☐	☐
5	صعود الدرج (لبعض الدرجات).	☐	☐	☐
6	الانحناء لألتقاط بعض الأشياء.	☐	☐	☐
7	المشي لأكثر من ميل.	☐	☐	☐
8	المشي لحوالي نصف ميل.	☐	☐	☐
9	المشي لمسافة لاتزيد عن 100 قدم.	☐	☐	☐
10	استخدام الحمام (الاستحمام)، ولبس الملابس الخاصة بك.	☐	☐	☐

A4- خلال الأسابيع الأربعة الماضية، كم من المرات تعرضت لبعض الصعوبات أدناه، والمتعلقة بلياقتك ونشاطك اليومي سواء في العمل أو في منزلك؟

		نعم	لا
1	هل حصل أن أقتطعت بعضا من وقت عملك سواء في المنزل أو العمل ؟	☐	☐
2	هل انجازك للأعمال اليومية أصبح أقل قدرة وكفاءة؟	☐	☐
3	هل هناك أعمال معينة أصبحت لاتستطيعين انجازها؟	☐	☐
4	هل تعانين من صعوبة في انجاز بعض الأعمال سواء في العمل أو المنزل؟	☐	☐

A5- خلال الأسابيع الأربعة الماضية، كم مرة كنت تعانين من امكانية انجاز عملك سواء في العمل أو المنزل نتيجة لتأثير الضغوط والعوامل النفسية (كالقلق والتوتر)؟

		نعم	لا
1	هل ذلك أدي إلى تقليل ساعات عملك اليومي؟	☐	☐
2	هل شعرت بصعوبة في انجازك اليومي للأعمال؟	☐	☐
3	هل شعرت بأن عليك بذل جهد أكبر لانجاز أعمالك اليومية؟	☐	☐

A6- خلال الأسابيع الأربعة الماضية، لأي درجة أصبحت تشعرين بأن لياقتك الصحية، وحالتك النفسية بدأت تؤثر على انجاز نشاطاتك الاجتماعية؟

☐ لم تتأثر ☐ بشكل بسيط ☐ بشكل متوسط ☐ بشكل واضح ☐ بشكل كبير جدا

A7- خلال الأسابيع الأربعة الماضية، هل كنت تشتكين من آلام في الجسم؟

☐ لا ☐ بسيطة جداً ☐ بسيطة ☐ متوسطة ☐ شديدة ☐ شديدة جداً

A8- الأسئلة أدناه تتعلق بما كنت تشعرين به خلال الأسابيع الأربعة الماضية، يرجى اختيار الإجابة المناسبة لكل سؤال:

	جميع الأوقات	معظم الأوقات	بعض الأحيان	أوقات قليلة	ليس في أي وقت
هل تشعرين بالسعادة المطلقة؟	☐	☐	☐	☐	☐
هل أنت عصبية المزاج؟	☐	☐	☐	☐	☐
هل تشعرين بالإحباط وتشعرين أنه لايوجد شئ يمكن أن يسعدك؟	☐	☐	☐	☐	☐
هل تشعرين بالهدوء والاستقرار النفسي؟	☐	☐	☐	☐	☐
هل تشعرين أنك تمتلكين طاقة داخلية قوية؟	☐	☐	☐	☐	☐
هل تعانين من الشعور بالإحباط واليأس؟	☐	☐	☐	☐	☐
هل تشعرين بالتعب الشديد؟	☐	☐	☐	☐	☐
هل شعرت بالسعادة خلال الفترة أعلاه؟	☐	☐	☐	☐	☐
هل تشعرين بخمول وتعب عام؟	☐	☐	☐	☐	☐

A9- هذه بعض الأسئلة والإجابة عنها بنعم أو لا:

	بالتأكيد نعم	غالباً نعم	غير متأكدة	غالباً لا	بالتأكيد لا
أنه يبدو عليّ من أنني أمرض بسهولة مقارنة بالأخرين	☐	☐	☐	☐	☐
أنه أتمتع بصحة جيدة كما يشعر الأخرين	☐	☐	☐	☐	☐
أتوقع أن تسوء صحتي مع مرور الوقت	☐	☐	☐	☐	☐
صحتي العامة جيدة جدا	☐	☐	☐	☐	☐

<u>الأسئلة المتعلقة بالدورة الشهرية، والتغيرات الهرمونية</u>

B1- كم كان عمرك عند بدء الدورة الشهرية لديك؟ .....

B2- هل كنت بالدورة الشهرية خلال 3 أشهر الأخيرة؟

☐ لا – إذا كانت الإجابة (لا) اذهبي إلى إجابة السؤال B2.1

☐ نعم – إذا كانت الإجابة (نعم) اذهبي إلى إجابة السؤال B2.4

B2.1- ماهي أسباب انقطاع الدورة لديك؟

☐ هل بسبب تعاطيك لعلاجات هرمونية بصورة مستمرة؟

☐ هل كنت حاملا أم مرضعة؟

☐ هل بسبب الوصول إلى سن اليأس وانقطاع الطمث لديك؟

B2.2- تقريبا كم دورة كانت لديك خلال 12 شهر الماضية؟ .....

B2.3- ما هو تاريخ آخر دورة شهرية؟ ...../...../.....

B2.4- هل حصلت الدورة لديك بشكل طبيعي أم بتأثير عقار هرموني (كحبوب منع الحمل، أو إعطائك أي حقن هرمونية)؟

☐ بشكل طبيعي ☐ بتأثير الهرمونات

B2.5- ما هو تاريخ أول يوم لآخر دورة شهرية (LMP)؟

☐ غير متأكدة ☐ آخر دورة شهرية (LMP) .... / .... / .....

B2.6- هل كانت الدورة الشهرية لديك منتظمة خلال الثلاث أشهر الآخرة (هل تأتي بانتظام مثلا كل 28 يوم)؟

☐ منتظمة دائما (بمعدل 1 – 2 يوم قبل أو بعد موعدها المحدد).

☐ منتظمة جدا (بمعدل 3 – 4 أيام قبل أو بعد موعدها المحدد).

☐ منتظمة (بمعدل 5- 7 أيام قبل أو بعد موعده المحدد).

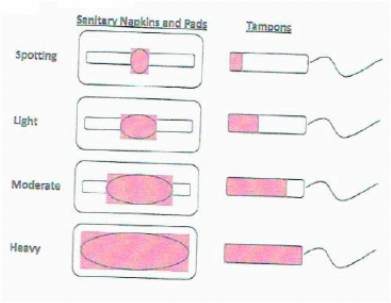
☐ غير منتظمة بعض الأحيان (بمعدل 8 – 20 يوم قبل أو بعد موعدها المحدد).

☐ غير منتظمة دائما (معدل حدوثها لأكثر من 20 يوم قبل أو بعد موعدها المحدد).

B2.7- كم يوم يستمر نزول الدم لديك خلال الدورة الشهرية خلال الأشهر الثلاثة الأخيرة؟

☐ كمية نزول الدم غير منتظمة دائما أو ☐ عدد الأيام (عدد أيام نزول الدم) .....

B2.8- المخطط أدناه يوضح كمية الدم التي تحصل خلال كل 4 ساعات خلال دورتك الشهرية:



- طبقا لشدة نزول الدم

☐ على شكل بقع صغيرة

☐ خفيفة

☐ متوسطة

☐ شديدة

- ضمن المعدلات الطبيعية

☐ على شكل بقع صغيرة

☐ خفيفة

☐ متوسطة

☐ شديدة

B3- يرجى ادراج أسماء العقاقير الهرمونية التي تم تناولها سواء لعلاج حب الشباب، أو عدم انتظام الدورة الشهرية، أو للسيطرة على الإنجاب، أو علاجات العقم الهرمونية؟

اسم العقار الهرموني	العمر عند بداية استخدامها	الهرمونات المستخدمة خلال الثلاثة أشهر الأخيرة	كم من الوقت تم استخدامها؟
	. . . . .	☐ نعم ☐ لا	..... أشهر ..... سنوات
	. . . . .	☐ نعم ☐ لا	..... أشهر ..... سنوات
	. . . . .	☐ نعم ☐ لا	..... أشهر ..... سنوات
	. . . . .	☐ نعم ☐ لا	..... أشهر.... سنوات

B4- هل استخدمت موانع الحمل في حالات طارئة؟

☐ لا

☐ نعم

إذا كانت الإجابة بنعم، هل استخدمتيها خلال الأشهر الثلاثة الأخيرة؟

☐ لا

☐ نعم

B5- ما هي أسباب استخدامك للعقاقير الهرمونية؟

☐ لمنع الحمل

☐ لعدم انتظام الدورة الشهرية

☐ بسبب أن الدورة لديك شديدة

☐ بسبب وجود حب الشباب

☐ بطانة الرحم المهاجرة

☐ تكيس المبايض المتعددة

☐ وجود كيس بويضي

☐ لوجود آلام مصاحبة للدورة الشهرية

B5.1- هل ساعدك استخدام الهرمونات لمعالجة آلام الحوض؟

☐ نعم ☐ لا

B5.2- هل حصل أن غيرت علاج الهرمونات بسبب عدم كفائته أو عدم كسب الفائدة منه لمعالجة الآلام؟

☐ نعم ☐ لا

B6- هل استخدمت موانع الحمل غير الهرمونية (كاللولب مثلاً)

☐ لا ☐ نعم

إذا كانت الإجابة (نعم): B6.1- عند أي عمر استخدمتيها لأول مرة؟ .....

الأسئلة المتعلقة بالحمل والإنجاب

C1- هل حصل أن حملت سابقا؟ (كذلك يجب ذكر حالات الاجهاض أ حالات الحمل خارج الرحم أو الاجهاض لأسباب طبية)؟

☐ لا ☐ نعم

إذا كانت الاجابة (نعم) الرجاء اكمال الجدول أدناه:

	الحمل الأول	الحمل الثاني	الحمل الثالث	الحمل الرابع	الحمل الخامس	الحمل السادس	الحمل السابع	الحمل الثامن
كم كان عمرك عند حصول حملك الأول؟								
يرجى كتابة العمر عند كل حالة حمل	.....	.....	.....	.....	.....	.....	.....	.....
اذكري طرق العلاج المستخدمة للمساعدة على حصول الحمل؟								
هل حصل الحمل بطريقة طبيعية دون عقاقير مساعدة؟	☐	☐	☐	☐	☐	☐	☐	☐
ما هي العقاقير المستخدمة للمساعدة على الحمل (كلوميد، كلوميفين)؟	☐	☐	☐	☐	☐	☐	☐	☐
وجود اللولب	☐	☐	☐	☐	☐	☐	☐	☐
خلال التلقيح الصناعي (IVF)	☐	☐	☐	☐	☐	☐	☐	☐
ماذا كانت نتيجة الحمل؟								
ولادة طفل واحد	☐	☐	☐	☐	☐	☐	☐	☐
ولادة توأم أو أكثر	☐	☐	☐	☐	☐	☐	☐	☐
اجهاض	☐	☐	☐	☐	☐	☐	☐	☐
وفاة الجنين أثناء الحمل	☐	☐	☐	☐	☐	☐	☐	☐
حمل خارج الرحم	☐	☐	☐	☐	☐	☐	☐	☐
حمل كاذب	☐	☐	☐	☐	☐	☐	☐	☐
حصول حمل حديث	☐	☐	☐	☐	☐	☐	☐	☐
كم أسبوع حملك الحالي؟								
أقل من 24 أسبوع	.....	.....	.....	.....	.....	.....	.....	.....
بين 24 – 28 أسبوع	.....	.....	.....	.....	.....	.....	.....	.....
بين 29 – 32 أسبوع	.....	.....	.....	.....	.....	.....	.....	.....
بين 33 – 36 أسبوع	.....	.....	.....	.....	.....	.....	.....	.....
37 أسبوع أو أكثر	.....	.....	.....	.....	.....	.....	.....	.....
إذا كان حملك الحالي قد حصل خارج الرحم أو تعرضت للإجهاض أو إنهاء الحمل لأسباب طبية، كيف تم التعامل معه؟								
هل جراحياً؟	☐	☐	☐	☐	☐	☐	☐	☐
أم سريريا (باستخدام العقاقير الطبية المحفزة للطلق)	☐	☐	☐	☐	☐	☐	☐	☐
أم لم تعد هناك حاجة للتعامل معه	☐	☐	☐	☐	☐	☐	☐	☐
كيف كانت طريقة الولادة لديك؟								
بشكل طبيعي	☐	☐	☐	☐	☐	☐	☐	☐
أم عملية قيصرية	☐	☐	☐	☐	☐	☐	☐	☐
هل حصل لديك طلق طبيعي أو باستخدام محفزات الطلق؟								
لم يحصل طلق	☐	☐	☐	☐	☐	☐	☐	☐
حصل طلق طبيعي	☐	☐	☐	☐	☐	☐	☐	☐
حصل طلق بتأثير محفزات الطلق	☐	☐	☐	☐	☐	☐	☐	☐
هل كنت تعانين من أي مضاعفات مع حملك الحالي؟								
سكر الحمل	☐	☐	☐	☐	☐	☐	☐	☐
ارتفاع ضغط الدم	☐	☐	☐	☐	☐	☐	☐	☐
تسمم الحمل	☐	☐	☐	☐	☐	☐	☐	☐
التهابات الثدي	☐	☐	☐	☐	☐	☐	☐	☐
اعراض	☐	☐	☐	☐	☐	☐	☐	☐
كثرة القئ والاستفراغ المرافق للحمل	☐	☐	☐	☐	☐	☐	☐	☐
ولادة مبكرة	☐	☐	☐	☐	☐	☐	☐	☐

C2- هل سبق أن تعالجت لفترة تزيد على 6 شهور لمتابعة أسباب تأخير الحمل لديك؟

☐ لا ☐ نعم إذا كانت الإجابة (نعم):

C2.1 ماهي أطول فترة من الوقت حاولت الحمل خلالها بغض النظر إذا ما انتهت بحالة حمل من عدمه؟

عدد الشهور .....

C3- هل أنت وزوجك حاولتما القيام بإجراء الفحوصات اللازمة لمعرفة أسباب تأخر الحمل لديكم؟

☐ لا ☐ نعم إذا كانت الإجابة (نعم):

C3.1 يرجى التأشير مقابل كل حالة كأحد أسباب تأخر الحمل لديك

☐ الإصابة ببطانة الرحم المهاجرة

☐ وجود التصاقات داخلية

☐ انسداد الأنابيب الرحمية

☐ التهابات الحوض الداخلية

☐ عدم انتظام أو عدم حصول التبويض

☐ ضعف في مكونات السائل المنوي للزوج

☐ تكيسات المبايض المتعددة

☐ تأليفات الرحم

☐ لم يتم التوصل إلى تحديد الأسباب

☐ أسباب أخرى غير التي ذكرت أعلاه .....

C4- هل سبق أن تعالجت من حالة تأخر الحمل والانجاب لديك في عيادة متخصصة لذلك؟

☐ لا ☐ نعم

إذا كانت الإجابة (نعم):

C4.1 الرجاء ذكر طريقة العلاج كما هو موضح أدناه:

	لم أتناول العقاقير	تناولتها خلال 3 شهور الأخيرة	تناولتها لكن ليس خلال 3 شهور الأخيرة	كم دورة شهرية
عن طريق تحديد أوقات ممارسة العلاقة الزوجية	☐	☐	☐	.....
اتباع جدول محدد لممارسة العلاقة الزوجية	☐	☐	☐	.....
عن طريق استخدام العقاقير الطبية لتحفيز التبويض مثل عقار Clomid أو عقار آخر	☐	☐	☐	.....
استخدام عقاقير تحفيز التبويض على شكل حقن (HCG)	☐	☐	☐	.....
عقار البروجيسترون العضلي أو المهبلي	☐	☐	☐	.....
التلقيح الذاتي بواسطة حقن الحيوانات المنوية (IUI)	☐	☐	☐	.....
عن طريق التلقيح الصناعي (IVF)	☐	☐	☐	.....
عن طريق التلقيح الصناعي بالحقن المجهري (ICSI)	☐	☐	☐	.....

الأسئلة المتعلقة بالشعور بالألم النفسي نتيجة عدم القدرة على الحمل أو تأخيره

D1- الأسئلة التالية متعلقة بالشعور بالألم الداخلي العميق والناتج عن القلق والتوتر المفرط نتيجة لتأخر فرص الحمل لديك وعدم نجاح الطرق العلاجية للمساعدة على الحمل:

	ليس له تأثير	تأثير نفسي بسيط	تأثير لبعض الوقت	تأثير شديد	تأثير طوال الوقت
أنا أشعر بالقلق وأصبحت أفكر إذا كان بالإمكان التغلب على هذا الشعور	☐	☐	☐	☐	☐
أشعر بالإحباط وليس لدي القدرة على الاستمرار بهذا الشعور	☐	☐	☐	☐	☐
إنه شعور مؤلم جدا أحس به، والأعلم إذا كان بالإمكان أن أتحسن قريبا مع هذا الشعور	☐	☐	☐	☐	☐
إنه شعور غير محبب لي وقد بدأ يؤثر عليّ	☐	☐	☐	☐	☐
أشعر أنه ليس لدي القدرة الكافية للسيطرة على هذا الاحساس	☐	☐	☐	☐	☐
أصبحت أشعر بالخوف مع هذا الشعور بالألم العميق أنه قد يصبح أكثر سوءاً مع مرور الوقت	☐	☐	☐	☐	☐
دائما أتذكر جميع المواقف التي تسبب لي هذا الشعور بالألم	☐	☐	☐	☐	☐
كنت أفكر على الدوام كم له تأثير مؤلم علي	☐	☐	☐	☐	☐

كنت أفكر على الدوام كيف أتخلص من الشعور بهذا الألم	☐	☐	☐	☐	☐
ليس بإمكاني عمل شيء للسيطرة على هذا الشعور المؤلم	☐	☐	☐	☐	☐
أنا قلقة على الدوام من أن شيئاً خطيراً قد يحدث لصحتي	☐	☐	☐	☐	☐

الأسئلة أدناه تتعلق بآلام الحوض المرافقة للدورة الشهرية:
وكذلك في الحالات التي تحصل فيها عدم انتظام الدورة الشهرية أو حدوث حالات النزف المرافقة لاستخدام العقاقير الهرمونية (آلام الحوض هنا نعني بها الآلام التي تحصل في منطقة الحوض).

D2- هل سبق وأن شعرت بوجود ألم أثناء الدورة الشهرية؟

☐ ليس هناك ألم ⟵ اذهبي إلى السؤال D12

☐ ألم بسيط في منطقة الحوض وليس بحاجة إلى عقاقير طبية لعلاجه

☐ هناك ألم متوسط الشدة أشعر أنه بحاجة لتناول العقاقير الطبية المسكنة للألم

☐ يحصل ألم شديد في منطقة الحوض وأشعر أنه بحاجة إلى العقاقير المسكنة للألم مع أخذ قسط من الراحة

D2.1- عند أي عمر بدأت تشعرين بالألم المرافق للدورة الشهرية؟ العمر: .....

إذا ماكنت في الدورة الشهرية خلال الأشهر الثلاثة الأخيرة؛ عليك إذن إكمال الأسئلة أدناه:-
وفي خلاف ذلك يرجى الإشارة هنا ..... ثم الاستمرار إلى السؤال D12

D3- كم هي درجة الألم التي كنت تشعرين بها خلال فترة دورتك الشهرية الأخيرة؟

☐ ليس هناك ألم اذهبي ⟵ إلى السؤال D10

☐ أعاني من آلام بسيطة (ليست بحاجة إلى عقاقير لتهدئة الألم)

☐ أعاني من آلام متوسطة الشدة وهي في الغالب بحاجة لعقاقير لتهدئة الألم

☐ أعاني من آلام شديدة وبحاجة إلى مسكنات الألم والراحة

D4- هل كنت تتناولين العقاقير الطبية الخاصة بآلام الدورة الشهرية في خلال آخر دورة شهرية لديك؟

☐ لا

☐ نعم، أتناول بعض العقاقير التي وصفها الطبيب

☐ نعم، أتناول بعض العقاقير التي أطلبها من الصيدلية مباشرة

☐ نعم، أتناول بعض العقاقير الهرمونية، ولكن لازال هناك ألم

☐ نعم، أتناول بعض العقاقير الهرمونية، ولكن الألم تحسن كثيرا

D5- خلال آخر دورة شهرية لك، هل الألم المرافق كان قد منعك من أداء أعمالك اليومية سواء عملك الخاص أو أداء أعمال المنزل اليومية، رغم تناولك مسكنات الألم المعروفة؟

☐ لا ☐ نعم

D6- يرجى تحديد شدة الألم المرافق للدورة الشهرية باستخدام المؤشر أدناه

حيث أن الرقم (صفر) يعني ليس هناك ألم بينما الرقم (10) يعني أنه ألم شديد ولايطاق

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

D7- الأسئلة أدناه تتعلق بحركة الأمعاء – فترات التبرز خلال فترة الدورة الشهرية – خلال 3 أشهر الماضية، وكم هي فترات تكرار هذا الألم؟

	لم يحصل ألم	بعض الأحيان	معظم الأوقات	غالبا	دائما
هل الألم يصبح أقل أو يتوقف بعد حصول التبرز؟	☐	☐	☐	☐	☐
هل يصبح هذا الألم أكثر شدة بعد التبرز؟	☐	☐	☐	☐	☐
هل تعانين من تكرار فترات التبرز عند بدء الألم؟	☐	☐	☐	☐	☐
هل فترات التبرز تصبح أقل عند بداية ألم الدورة؟	☐	☐	☐	☐	☐
هل يصبح البراز أكثر ليونة عندما يبدأ ألم الدورة؟	☐	☐	☐	☐	☐
هل يصبح البراز أكثر صلابة عندما يبدأ ألم الدورة؟	☐	☐	☐	☐	☐

D8- كم كان عمرك عند بدء آلام الحوض لديك أثناء الدورة الشهرية؟ العمر: .....

D9- الرجاء التأشير أدناه لتحديد شدة آلام الحوض المرافقة للدورة الشهرية لديك

حيث أن الرقم (صفر) يعني ليس هناك ألم بينما الرقم (10) يعني أنه ألم شديد ولايطاق

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

الأسئلة التالية (D10-D15) تتعلق بحصول آلام في الحوض أثناء ممارسة العلاقة الزوجية (العلاقة الجنسية بين الزوجين)، وفي البدء نود أن نؤكد بأنه أي معلومات سيتم تثبيتها ستكون ذات سرية عالية، وفي حالة عدم رغبتك في الإجابة على مثل هذه الأسئلة بإمكانك التأشير هنا ..... والذهاب مباشرة إلى السؤال D16 ، وإذا لم تكوني قد مارست العلاقة من قبل الرجاء التأشير هنا ..... والذهاب مباشرة إلى السؤال D16.

D10- هل كنت تعانين من أي آلام أثناء ممارسة العلاقة الزوجية؟

☐ لا، الرجاء الذهاب إلى السؤال D27

☐ نعم، إذا كانت الإجابة (نعم) فعند أي عمر حصل هذا الألم لديك؟ العمر .....

D11- هل كنت تعانين من ألم أثناء ممارسة العلاقة الزوجية؟ وأين كنت تشعرين بهذا الألم؟

☐ عند بداية الممارسة

☐ عند منطقة المهبل

☐ في الحوض أو أسفل البطن

☐ في مكان آخر، يرجى تحديده .....

D12- الرجاء حددي شدة الألم خلال آخر لقاء زوجي باستخدام المؤشر أدناه

حيث أن الرقم (صفر) يعني ليس هناك ألم بينما الرقم (10) يعني أنه ألم شديد ولايطاق

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

D13- حددي كم من المرات كنت تعانين من الآلام أثناء ممارسة العلاقة الزوجية خلال 12 شهراً الأخيرة:

☐ لم أعاني أي ألم على الإطلاق

☐ بعض الأحيان (عدة مرات فقط)

☐ غالبا ما كنت أعني من الألم (العديد من المرات)

☐ دائما كنت أعاني من الألم عند كل ممارسة

D14- خلال ال 12 شهراً الأخيرة، هل كان هناك أي وقت محدد في الشهر كنت تشعرين بالألم أثناء الممارسة أكثر من أي وقت آخر؟ يرجى التأشير أدناه:

☐ لا

☐ نعم

إذا كانت الإجابة (نعم) فيرجى توضيح إذا ما كان الألم في هذا الوقت هو أكثر من أي وقت مضى .....

D15- خلال ال 12 شهراً الأخيرة، هل حصل أن توقفت ممارسة العلاقة الزوجية بسبب حصول آلام متكررة في منطقة الحوض؟

☐ لا ☐ نعم إذا كانت الإجابة (نعم) هل يمكن تحديد وقت حصول ذلك:

☐ عدة أيام قبل بدء الدورة

☐ عدة أيام بعد انتهاء الدورة

☐ عند وسط الدورة

D16- هل سبق وأن عانيت من آلام في الحوض بصورة عامة؟

ملاحظة: أن الألم الناتج والمصاحب للدورة الشهرية والعلاقة الزوجية والحمل والجراحة والولادة لايشمل الإجابة على السؤال أعلاه.

☐ لا ☐ نعم إذا كانت الإجابة (نعم) يرجى توضيح التالي:

D16.1- عند أي عمر كنت قد بدأت تشعرين بآلام في الحوض؟

العمر: .....

D16.2- متى بدأت تشعرين بهذا الألم؟

☐ في خلال الشهر الأخير

☐ خلال 1 – 3 شهور الأخيرة

☐ خلال 4 – 6 شهور الأخيرة

☐ خلال 7 – 12 شهراً الأخيرة

☐ أكثر من 12 شهرا في الفترة الماضية

D17- لأي درجة كانت آلام الحوض تؤثر على انجاز أعمالك اليومية في خلال 3 شهور الماضية؟

	ليس له تأثير	تأثير بسيط	تأثير متوسط	تأثير شديد	أكثر شدة	غير محتمل
تأثيره على العمل	☐	☐	☐	☐	☐	☐
تأثيره على أعمالك اليومية والمنزلية	☐	☐	☐	☐	☐	☐
حصوله أثناء النوم	☐	☐	☐	☐	☐	☐
عند ممارسة العلاقة الزوجية	☐	☐	☐	☐	☐	☐
عند ممارسة التمارين الرياضية	☐	☐	☐	☐	☐	☐
عند ممارسة النشاطات الاجتماعية	☐	☐	☐	☐	☐	☐

D18- تقريبا كم من الوقت كنت تعانين من هذا الألم في خلال الأشهر الثلاثة الأخيرة؟

☐ أقل من يوم واحد

☐ يوم واحد

☐ 2 – 3 يوم

☐ يوم واحد كل أسبوع

☐ أكثر من يوم في الأسبوع

☐ جميع الأيام كنت أعاني من الألم

D19- هل كنت تشعرين بهذا الألم (ألم الحوض) تقريبا في نفس الوقت خلال الدورة الشهرية؟
الرجاء التأشير أدناه؟

☐ لا

☐ نعم أيام قليلة فقط قبل الدورة

☐ نعم أيام قليلة فقط بعد الدورة

☐ نعم عند منتصف الدورة

☐ نعم في أوقات أخرى: .....

D20- هل سبق وأن استخدمت أي من العقاقير الطبية للسيطرة على الألم خلال الأشهر الثلاثة الأخيرة؟ الرجاء التأشير أدناه:

☐ لا، لم استخدم

☐ نعم، استخدمت مسكنات الألم من طبيبي الخاص

☐ نعم، استخدمت مسكنات الألم من الصيدلية مباشرة

☐ نعم، استخدمت عقاقير هرمونية، ولكن لازال الألم نفسه

☐ نعم، استخدمت عقاقير هرمونية، وحصل اختلاف في طبيعة الألم

D21- متى عانيتي من آلام الحوض في الثلاثة أشهر الأخيرة؟ وكيف يمكن أن تصنفي طبيعة هذا الألم؟

	لا يوجد	بسيط	متوسط الشدة	شديد
ألم نابض	☐	☐	☐	☐
ألم حاد	☐	☐	☐	☐
ألم كالطعن	☐	☐	☐	☐
على شكل قوي كالطلق ناري	☐	☐	☐	☐
على شكل مغص	☐	☐	☐	☐
على شكل حرارة	☐	☐	☐	☐
ألم بسيط	☐	☐	☐	☐
شعور بالثقل	☐	☐	☐	☐
عبارة عن شعور بالفتور	☐	☐	☐	☐
عبارة عن شعور بالتعب والإرهاق	☐	☐	☐	☐
الشعور بالمرض	☐	☐	☐	☐
الشعور بالخوف	☐	☐	☐	☐
الشعور بالعقاب القاسي	☐	☐	☐	☐

D22- ما هي أسباب زيادة ألم الحوض لديك؟ يرجى التأشير أدناه.

عند امتلاء المثانة	عند ممارسة العلاقة الزوجية	أثناء الاجهاد	خلال ممارسة الرياضة
عند الجلوس	خلال الوقوف أو المشي	أثناء السعال المتكرر	العوامل النفسية(القلق والتوتر)
أثناء حركة الأمعاء (التبرز)	خلال فترات النهار	بعد وجبة طعام ثقيلة	لا شئ يجعل الألم أكثر شدة
عند وجود امساك	أسباب أخرى.....		

D23- ماهي الحالات التي تساعدك على تقليل الألم والسيطرة عليه؟ يرجى التأشير أدناه.

تناولك للعقاقير المسكنة للألم	أخذ حمام حار
عند الاسترخاء	تناول ملينات الإمساك
عند الاستلقاء	عند تفريغ المثانة
عند سماع الموسيقى	استخدام الكمادات الدافئة
عند عمل المساج الطبي	التأمل العميق
استخدام الكمادات الباردة	لا شئ يساعد
عند حركة الأمعاء (التبرز)	عوامل أخرى يرجى ذكرها.....

الأسئلة أدناه تتعلق بمعرفة وقت حدوث آلام الحوض وآلام أسفل البطن لديك:

D24- كم كان عمرك عندما بدأت تشعرين بآلام الحوض أو آلام أسفل البطن؟

كان عمري .....

D25- الرجاء تحديد شدة الألم (آلام الحوض أو آلام أسفل البطن) باستخدام المؤشر الرقمي

حيث أن الرقم (صفر) يعني ليس هناك ألم بينما الرقم (10) يعني أنه ألم شديد ولايطاق

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

D26- هل تم تشخيص أسباب الألم لديك من قبل طبيبك المعالج؟

☐ لا ☐ نعم

إذا كانت الإجابة (نعم) يرجى التأشير أدناه:

القولون العصبي	التهابات منطقة الحوض
التهابات القولون المزمنة	التهابات المثانة الحادة
بطانة الرحم المهاجرة	الاجهاد
تليفات الرحم	أسباب أخرى .....
أكياس المبايض	

D27- يرجى توضيح إن كنت قد عانيت سابقا من آلام أخرى خلال فترة 12 شهراً الماضية؟

	لا لم أعاني	نعم في الشهر الماضي	نعم لأكثر من شهر مضى
آلام أسفل الظهر	☐	☐	☐
آلام الظهر التي تزول بممارسة الرياضة	☐	☐	☐
آلام الظهر التي لاتزول بممارسة الرياضة	☐	☐	☐
آلام العضلات والمفاصل	☐	☐	☐
الآلام المرافقة للتبويض	☐	☐	☐
آلام الساقين	☐	☐	☐
الآلام المصاحبة للتبول	☐	☐	☐
الآلام المصاحبة للتبرز	☐	☐	☐

D28- هل كنت تعانين من صداع متكرر؟

☐ لا ☐ نعم

D29- هل تعانين من أي آلام مزمنة أخرى استمرت لديك ما يقارب 6 شهور؟

☐ لا ☐ نعم

إذا كانت الإجابة (نعم) يرجى توضيح نوع الألم، وكم فترة يستمر، وهل هو مستمر أم متقطع؟

	أقل من سنة	بين 1-5 سنة	أكثر من 5 سنين	بسيط	متوسط	شديد
آلام الظهر	☐	☐	☐	☐	☐	☐
آلام الرقبة	☐	☐	☐	☐	☐	☐
آلام ما بعد الجراحة	☐	☐	☐	☐	☐	☐
أسباب آلام أخرى:						

<u>الأسئلة المتعلقة بالتاريخ المرضي لديك</u>

E1- هل كنت تعانين من أي مشكلة طبية، وعند أي عمر بدأت؟ وماذا كان التشخيص حينها؟

الحالة المرضية	العمر عند تشخيصها

E2- هل تم اخبارك أنك كنت تعانين من مشاكل خلقية وخاصة في الرحم أو عنق الرحم أو المهبل؟

☐ لا ☐ نعم

إذا كانت الإجابة (نعم)

E2.1- هل أجريت أي عملية جراحية لتصحيح ذلك؟

☐ لا ☐ نعم

إذا كانت الإجابة (نعم)

E2.2- هل تحسنت المشكلة لديك أو تحسنت بعد الجراحة؟

☐ لا ☐ نعم

E3- هل تم تشخيص حالة الإصابة بالسرطان لديك سابقا؟

☐ لا ☐ نعم

إذا كانت الإجابة (نعم)

E3.1- هل بالإمكان معرفة نوع الورم ومتى تم تشخيصه؟

نوع المرض السرطاني	العمر عند التشخيص

E4- هل سبق وأن أجريت أي عملية جراحية منذ الولادة وحتى الآن؟ ولو أجريتي عملية جراحية سابقا؛ كم كان عمرك حينها؟ وهل لديك أي تقرير طبي بذلك؟ وكم عملية جراحية أجريتي؟ مع ذكر أسباب إجراءها.

نوع العمليات الجراحية	العمر عند إجراء العملية الجراحية

E5- هل كنت تعانين من زيادة ظهور الشعر في الوجه أو أي مكان آخر في الجسم، على أن لا يكون ذلك كتأثير جانبي لاستخدام بعض العقاقير الطبية؟

☐ لا ☐ نعم

إذا كانت الإجابة (نعم) يرجى توضيح أماكن ظهور الشعر

	نعم	لا
فوق الشفة العليا	☐	☐
الحنك	☐	☐
أعلى الظهر	☐	☐
أسفل البطن	☐	☐

الساعدين	☐	☐
الفخذين	☐	☐
أعلى البطن	☐	☐
أسفل البطن	☐	☐
الصدر	☐	☐

E6- هل عانيت من الإصابة بحب الشباب عندما كنت بعمر ال 18 سنة؟

☐ لا ☐ نعم

E6.1- هل عانيت من ظهور حب الشباب بعد عمر 25 سنة؟

☐ لا ☐ نعم

E6.1.1- أين ظهر حب الشباب لديك؟

	نعم	لا
الوجه	☐	☐
الصدر والظهر	☐	☐
الأطراف العليا	☐	☐

E7- هل عانيت من تساقط الشعر (لا يشمل ذلك الحاصل بسبب تأثير بعض العقاقير أو المعالجات الأخرى التي قد تسبب تساقط الشعر)؟

☐ لا ☐ نعم

E8- هل تعانين من غمقان في لون البشرة حول الرقبة أو عند الإبط أو المنطقة التناسلية؟

☐ لا ☐ نعم

E9- الأسئلة أدناه تتعلق بحركة الأمعاء – التبرز – خلال 3 شهور الأخيرة

	لم أكن أعاني	بعض الأحيان	معظم الأوقات	غالبا	دائما
هل عانيت من وجود حالات اسهال متكررة؟	☐	☐	☐	☐	☐
هل عانيت من ظهور دم في البراز؟	☐	☐	☐	☐	☐
هل عانيت من حالات امساك متكررة؟	☐	☐	☐	☐	☐

E10- هل سبق وخلال الشهر الماضي عانيت من تغيرات في حالة التبرز لديك؟ يرجى الإشارة إليها أدناه

هل عانيت من وجود دم في البراز (نزيف في الأمعاء)	هل تعانين من صعوبة في السيطرة على التبرز؟
التبرز أقل من ثلاث مرات أسبوعيا	هل لديك شعور بعدم تفريغ الأمعاء عند التبرز؟
التبرز أكثر من ثلاث مرات في اليوم	هل تعانين من آلام في القولون؟
وجود افرازات مخاطية في البراز	هل تعانين من الشعور بالانتفاخ بعد تناولك الطعام؟
هل تعانين من صعوبة في التبرز؟	هل تعانين من الشعور بالغثيان والقيء بعض الأحيان؟

E11- خلال الأشهر الثلاثة الأخيرة هل كنت تعانين مما يلي:

☐ مرور البول أثناء السعال أو العطاس أو خلال نوبة ضحك شديدة

☐ صعوبة في التبول

☐ التهابات المثانة المتكررة

☐ وجود دم في البول

☐ الشعور بامتلاء المثانة رغم التبول

☐ هل لديك شعور بالتبول مجددا خلال دقائق بعد انتهاء التبول لديك

E12- هل تم تشخيص حالة البطانة الرحمية المهاجرة لديك من قبل طبيبك المعالج؟

☐ لا ☐ نعم

إذا كانت الإجابة (نعم)

E12.1- كيف تم تشخيص الحالة؟

☐ عن طريق المنظار

☐ السونار - الأشعة المقطعية

☐ عن طريق الأعراض السريرية

☐ طرق أو أسباب أخرى للتشخيص

E12.2- إذا كنت قد أجريتي عملية جراحية لعلاج بطانة الرحم المهاجرة مؤخرا، هل تمت بواسطة عملية الكي أم إزالتها جراحيا؟

☐ لا ☐ نعم ☐ غير متأكدة ☐ لم أجري عملية جراحية

E12.3- كم كان عمرك عندما كنت تعانين من أعراض الإصابة ببطانة الرحم المهاجرة؟

كان عمري .....

E12.4- ما هي تلك الأعراض؟ وهل راجعت الطبيب المختص لذلك؟

☐ الشعور بآلام في الحوض

☐ صعوبة بالحمل والانجاب

☐ مرافقة الألم مع استمرار صعوبة الحمل والانجاب

☐ ليس هناك أعراض

☐ أعراض أخرى، يرجى تحديدها .....

E12.5- كم كان عمرك عندما تم تشخيص مرض البطانة الرحمية المهاجرة لديك؟

كان عمري .....

E13- هل تعرضت لإجراء جراحي لاشتباه الإصابة بمرض البطانة الرحمية المهاجرة ولكن لم يتم اكتشافها أثناء إجراء العملية؟

☐ لا ☐ نعم

إذا كانت الإجابة (نعم)

E13.1- ما هي الأعراض التي أدت إلى اللجوء للإجراء الجراحي في العلاج؟

☐ آلام متكررة

☐ عدم القدرة على الإنجاب أو تأخره

☐ تكرار آلام الحوض والعقم كأسباب لذلك

☐ أسباب أخرى، يرجى ذكرها .....

E14- هل تم تشخيص أي من الحالات المرضية أدناه لدى أي من أقاربك المقربين؟

	الأم	الأب	الأخت	الأخ	الإبنة	الإبن	الجد،العم،الخال أولاد العم والخال	
							ناحية الأم	ناحية الأب
مرض بطانة الرحم المهاجرة	☐		☐		☐		☐	
آلام الحوض المزمنة	☐		☐		☐		☐	
تكيسات المبايض المتعددة	☐		☐		☐		☐	
تليفات الرحم	☐		☐		☐		☐	
النزف المهبلي المتكرر والشديد	☐		☐		☐		☐	
أمراض الغدة الدرقية	☐	☐	☐	☐	☐	☐	☐	☐
أمراض القلب	☐	☐	☐	☐	☐	☐	☐	☐
مرض السكر	☐	☐	☐	☐	☐	☐	☐	☐
الخرف	☐	☐	☐	☐	☐	☐	☐	☐
السمنة المفرطة	☐	☐	☐	☐	☐	☐	☐	☐
الأورام السرطانية	☐	☐	☐	☐	☐	☐	☐	☐

E15- عند أي عمر وصلت والدتك إلى عمر سن اليأس (انقطاع الدورة الشهرية) وبصورة طبيعية؟

عند عمر ..... أو:

E15.1- ☐ أنها لم تصل بعد إلى سن اليأس (انقطاع الطمث الكلي)

E15.2- ☐ لا أعلم بذلك

الأسئلة المتعلقة بتاريخ تناول العقاقير الطبية

F1- الرجاء اخبارنا إذا ما كنت قد تناولت العقاقير المسكنة للآلام والتي كنت قد استعملتيها ولو لمرة واحدة أسبوعيا خلال 3 شهور أو أكثر من دون وصفة طبية، كما هو موضح أدناه

نوع الدواء	لم استخدمها	نعم لازلت استخدمها	كم عمرك عندما بدأت استخدامها؟	لأي نوع من أنواع الألم تم استخدامها	كم يوم في الأسبوع تم استخدامها	كم عدد الحبوب خلال الأسبوع	بصورة عامة كم من الوقت تم استخدام هذا العلاج
عقار الباراسيتامول (Paracetamol)	☐	☐	.....	☐ آلام الحوض ☐ أنواع ألم أخرى ☐ كل أنواع الألم	☐ 1 ☐ 2 - 3 ☐ 4 - 5 ☐ 6 +	☐ 1 - 2 ☐ 3 - 5 ☐ 6 - 14 ☐ 15 +	..... شهر ..... سنة
عقار الاسبرين (Aspirin)	☐	☐	.....	☐ آلام الحوض ☐ أنواع ألم أخرى ☐ كل أنواع الألم	☐ 1 ☐ 2 - 3 ☐ 4 - 5 ☐ 6 +	☐ 1 - 2 ☐ 3 - 5 ☐ 6 - 14 ☐ 15 +	..... شهر ..... سنة
البروفين (Ibuprofen)	☐	☐	.....	☐ آلام الحوض ☐ أنواع ألم أخرى ☐ كل أنواع الألم	☐ 1 ☐ 2 - 3 ☐ 4 - 5 ☐ 6 +	☐ 1 - 2 ☐ 3 - 5 ☐ 6 - 14 ☐ 15 +	..... شهر ..... سنة
عقار سيليبريكس (Celebrex)	☐	☐	.....	☐ آلام الحوض ☐ أنواع ألم أخرى ☐ كل أنواع الألم	☐ 1 ☐ 2 - 3 ☐ 4 - 5 ☐ 6 +	☐ 1 - 2 ☐ 3 - 5 ☐ 6 - 14 ☐ 15 +	..... شهر ..... سنة
عقاقير أخرى مسكنة للألم (Naproxen)	☐	☐	.....	☐ آلام الحوض ☐ أنواع ألم أخرى ☐ كل أنواع الألم	☐ 1 ☐ 2 - 3 ☐ 4 - 5 ☐ 6 +	☐ 1 - 2 ☐ 3 - 5 ☐ 6 - 14 ☐ 15 +	..... شهر ..... سنة
مسكنات الألم شديدة التسكين مثل الكودايين والمورفين(Narcotic)	☐	☐	.....	☐ آلام الحوض ☐ أنواع ألم أخرى ☐ كل أنواع الألم	☐ 1 ☐ 2 - 3 ☐ 4 - 5 ☐ 6 +	☐ 1 - 2 ☐ 3 - 5 ☐ 6 - 14 ☐ 15 +	..... شهر ..... سنة
عقاقير أخرى مسكنة للألم وتعمل على مراكز الألم والأعصاب في الدماغ	☐	☐	.....	☐ آلام الحوض ☐ أنواع ألم أخرى ☐ كل أنواع الألم	☐ 1 ☐ 2 - 3 ☐ 4 - 5 ☐ 6 +	☐ 1 - 2 ☐ 3 - 5 ☐ 6 - 14 ☐ 15 +	..... شهر ..... سنة
العقاقير المرخية للعضلات مثل عقار الدابزبام (Diazepam)	☐	☐	.....	☐ آلام الحوض ☐ أنواع ألم أخرى ☐ كل أنواع الألم	☐ 1 ☐ 2 - 3 ☐ 4 - 5 ☐ 6 +	☐ 1 - 2 ☐ 3 - 5 ☐ 6 - 14 ☐ 15 +	..... شهر ..... سنة
عقاقير الطب البديل أو ما يعرف بطب الأعشاب (Herbal)	☐	☐	.....	☐ آلام الحوض ☐ أنواع ألم أخرى ☐ كل أنواع الألم	☐ 1 ☐ 2 - 3 ☐ 4 - 5 ☐ 6 +	☐ 1 - 2 ☐ 3 - 5 ☐ 6 - 14 ☐ 15 +	..... شهر ..... سنة

F2- هل سبق وأن تناولت عقاقير دوائية من قبل طبيبك المعالج ولمدة تزيد على 3 شهور، عدا عقاقير الهرمونات ومسكنات الألم؟

☐ لا ☐ نعم

إذا كانت الإجابة (نعم) يرجى ملء الجدول أدناه عن تفاصيل الدواء.

نوع العقاقير التي وصفها لك الطبيب	هل تناولت هذا العقار بشكل يومي لفترة تزيد عن 3 شهور	عند أي عمر بدأت تناول هذا العقار بمعدل يومي لمدة تزيد عن شهر	بنظرة عامة كم عدد السنين التي تناولت فيها ه	هل لازلت تتناولين هذا العقار بمعدل يومي	الرجاء كتابة العقار الذي كنت تتناوليه حديثا
	✓ إذا كانت الإجابة نعم	العمر	عدد السنين	✓ إذا كانت الإجابة نعم	اسم العقار
مدررات البول	☐	.....	.....	☐	.....
عقار معالجة السكر	☐	.....	.....	☐	.....
هرمون الأنسولين	☐	.....	.....	☐	.....
عقاقير الغدة الدرقية	☐	.....	.....	☐	.....
عقاقير الصرع	☐	.....	.....	☐	.....
العقاقير المساعدة على النوم	☐	.....	.....	☐	.....
مضادات الكآبة	☐	.....	.....	☐	.....
عقاقير أخرى لعلاج الاضطرابات النفس	☐	.....	.....	☐	.....
عقاقير خاصة بالعظام	☐	.....	.....	☐	.....
عقاقير أمراض الروماتزم	☐	.....	.....	☐	.....
المضادات الحيوية	☐	.....	.....	☐	.....
مضادات الحموضة	☐	.....	.....	☐	.....
أدوية قرحة المعدة	☐	.....	.....	☐	.....
أدوية الحساسية	☐	.....	.....	☐	.....
أدوية ارتفاع الكوليسترول	☐	.....	.....	☐	.....
عقاقير الكورتيزون	☐	.....	.....	☐	.....
العقاقير المضادة للسرطان	☐	.....	.....	☐	.....
أدوية ارتفاع ضغط الدم	☐	.....	.....	☐	.....
أدوية القلب (موسعات الشرايين)	☐	.....	.....	☐	.....
أدوية أخرى لعلاج القلب	☐	.....	.....	☐	.....
بخاخ لعلاج الربو	☐	.....	.....	☐	.....
مسيلات الدم	☐	.....	.....	☐	.....
عقاقير الصداع النصفي	☐	.....	.....	☐	.....
أدوية أخرى1:	☐	.....	.....	☐	.....

<u>الأسئلة الشخصية المتعلقة بنمط الحياة لديك</u>

G1- ما هو تاريخ ميلادك؟ ..... / ..... / .....

السنة الشهر اليوم

G2- ما هي أصولك؟

☐ عربية ☐ آسيوية ☐ فارسية

☐ خليط ..... ☐ أخرى .....

G3- ما هي أصولك العائلية؟

☐ أفريقية ☐ شرق أوسطية ☐ آسيوية ☐ أوربية ☐ بالوشي ☐ إيران ☐ لا أعلم

☐ أخرى .....

G4- هل والديك هم من الدرجة الأولى أو الثانية من حيث القرابة؟

الجواب: .....

G5- هل أجدادك هم من الدرجة الأولى أو الثانية من حيث القرابة؟

الجواب: .....

G6- ما هي حالتك الاجتماعية؟

☐ عزباء ☐ متزوجة ☐ مطلقة ☐ أرملة

G7- هل لازلت في المراحل الدراسية؟

☐ لا ☐ نعم

G8- ما هي أعلى درجة علمية حصلت عليها؟

☐ الابتدائية ☐ الثانوية العامة ☐ الجامعة ☐ الدراسات العليا ☐ لم تسنح لي الفرصة للتعليم

G9- ما هو طولك بالسنتميتر؟

الطول: .....

G10- ما هو وزنك بالكيلو جرام؟

الوزن: .....

G11- منذ سن 18 عام، كم كان أعلى وزن وصلت إليه؟

الوزن: .....

G11.1- كم كان عمرك حينها عندما كنت في أعلى وزن؟

العمر: .....

G12- منذ سن 18 عام، ما هو أقل وزن كنت قد وصلت إليه؟

الوزن: .....

G12.1- كم كان عمرك حينها عندما كنت في أقل وزن؟

العمر: .....

G13- خلال 12 شهر الأخيرة، كم كنت تمضين من الوقت أسبوعيا في ممارسة النشاطات الرياضية والاجتماعية التالية؟

نوع الرياضة	صفر	1–4 دقائق	5–19 دقيقة	20–25 دقيقة	ساعة واحدة	1–1.5 ساعة	2–3 ساعة	4–6 ساعات	7–10 ساعات	11+ ساعة
المشي لمسافات معينة	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
رياضة الجري (معدل 10دقيقة / ميل 1.5كم)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
رياضة الجري السريع (معدل أقل من 10 دقيقة / ميل 1.5كم)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
استخدام الدراجة الهوائية (جهاز الجهد – الركض)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
تمارين اللياقة (استخدام الأجهزة الرياضية الخاصة باللياقة)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
رياضات أخرى كالتنس والمضرب	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
السباحة	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
غيرها، يرجى ذكرها	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

G14- هل تتعاطين التدخين على شكل ما يعرف بالشيشة هنا؟

☐ لا ☐ نعم

إذا كانت الإجابة (نعم)

G14.1- كم كان عمرك عندما بدأت بتعاطي الشيشة؟

العمر: .....

G14.2- هل تدخنين السجائر حاليا؟

☐ لا

☐ توقفت عن التدخين عند عمر: .....

☐ نعم

☐ كم سيجارة تدخنين أسبوعيا؟ .....

G15- كيف يمكنك توضيح نوع العمل الذي تمارسينه حاليا؟

☐ تعملين بوظيفة بأجر مدفوع

☐ تعملين لنفسك

☐ لا أعمل بأجر مدفوع، يرجى التأشير أدناه:

☐ ربة منزل

☐ لازلت في مراحل الدراسة

☐ أعمال تطوعية

☐ لا أستطيع العمل بسبب ما أعانيه من أعراض وبانتظار العلاج الجراحي

☐ لا أستطيع العمل لأسباب أخرى، يرجى التوضيح: .....

G16- خلال الأسابيع الأربعة الأخيرة، كم أثرت عليك الأعراض المرافقة للمرض لديك على انجاز أعمالك؟

حيث أن الرقم (صفر) يعني ليس هناك ألم بينما الرقم (10) يعني أنه ألم شديد ولايطاق

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

G17- خلال الأسابيع الأربعة الأخيرة، كم أثرت الأعراض على قدرتك على انجاز أعمالك اليومية الخاصة؟

حيث أن الرقم (صفر) يعني ليس هناك ألم بينما الرقم (10) يعني أنه ألم شديد ولايطاق

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

G18- في خلال اربعة أسابيع الماضية، كم بلغ عدد الساعات التي تغيبت فيها عن العمل بسبب مشاكلك الصحية؟ ***قم بتضمين الساعات التي تغيبت فيها بسبب الإجازات المرضية، أو الأوقات التي وصلت فيها متأخرًا أو غادرت فيها مبكرًا، وما إلى ذلك، بسبب مشاكلك الصحية. لا تقم بتضمين الوقت الذي تغيبت فيه للمشاركة في هذه الدراسة.***

.....ساعة/ساعات

G19- في خلال الأيام السبعة الماضية، كم بلغ عدد الساعات التي تغيبت فيها عن العمل لأي سبب آخر، مثال العطلات أو الإجازات أو للمشاركة في هذه الدراسة؟

.....ساعة/ساعات

G20- في خلال الأيام السبعة الماضية، كم بلغ عدد ساعات عملك الفعلية؟

.....ساعة/ساعات *(إن كان عدد الساعات" صفرًا"، انتقل إلى السؤال رقم*

G21- في أي عمر قد زرت لأول مرة طبيب النساء المختص؟

العمر: .....

G22- هل تعرضت للحرب؟ (سحابة الدخان والزيوت، عوامل الحرب الكيميائية بما في ذلك غاز الأعصاب وغاز الخردل ، وارتداء الملابس الواقية الكيميائية ، واليورانيوم المستنفد ، والدخان من البراز المحترق وأبخرة العادم)

☐ لا ☐ نعم

G23- من وين أنت؟.....

نشكركم على تعاونكم وإتاحة الوقت لإجابتكم على الأسئلة،
لو كان لديكم أي تعليق على هذه الأسئلة من فضلكم اكتبوا لنا تعليقكم هن

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