The Cyprus Women's Health Research (COHERE) Initiative: Estimating the prevalence, burden, and associated risk factors of endometriosis in Northern Cyprus

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Abstract

Introduction. There is a lack of research on endometriosis from the Eastern Mediterranean region and a complete absence of data from Northern Cyprus. It is unknown whether regional-specific factors effect endometriosis presentation and if risk factors differ.

Methods. The Cyprus Women's Health (COHERE) Initiative is a cross-sectional study of 7,646 women living in Northern Cyprus. Baseline recruitment involved completing an expanded version of the World Endometriosis Research Foundation Endometriosis and Phenome Biobanking Harmonisation Project (WERF-EPHect) questionnaire, including validated tools. Clinical data was obtained from ultrasound scans attended by 668 women and information on diet was obtained from 513 women who completed a validated Food-Frequency-Questionnaire (FFQ). Associations with endometriosis were compared to a pain symptomatic and a pain asymptomatic control group.

Results. Prevalence of endometriosis was 5.4% (95%Confidence Interval:4.9%-5.9%; n=410), including 15 incident cases identified during the clinical visit. Average age of endometriosis symptom onset was 25.9-years despite average age of first pain occurring at 16.2-years, giving a diagnostic delay of 9.3-years. Compared to asymptomatic controls, endometriosis cases were more likely to report anxiety and migraines (Odds Ratio=1.56; 95%CI:1.03-2.38 and OR=1.39; 95%CI:1.06-1.83, respectively). Physical health-related-quality-of-life was impaired in endometriosis cases compared to

symptomatic controls (p=0.034). There was no significant difference in economic burden between endometriosis cases and symptomatic controls (Int $9,864; 95%CI: $8,812-$10,917 vs Int $10,917; 95%CI: $10,004-$10,855, respectively). Average cost for endometriosis cases peaked between 26-35-years-of-age and decreased after age 36 but remained high across the life-course for symptomatic controls. Participants with endometriosis were more likely to report reproductive, allergic, metabolic/obesity-related and cardiovascular diseases. Women who were iron deficient and vitamin-D deficient were more likely to report to have endometriosis compared to asymptomatic controls (OR:1.70; 95%CI:1.37-2.12 and OR:2.04; 95%CI:1.37-3.02, respectively).

Discussion. For the first time, the epidemiology of endometriosis in Northern Cyprus has been investigated and presented, suggesting that burden of endometriosis is high in this population and the awareness is low. There are multiple opportunities to improve care for endometriosis patients and the findings on iron and vitamin-D deficiency may be unique risk factors for the region, warranting further investigation.

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Publications

Ahillan, T. Emmerson, M. Swift, B. Golamhouse, H. Song, K. Roxas, A. 2023. COVID-19 in the homeless population: a scoping review examining differences in prevalence, presentation, vaccine hesitancy and government response. *BMC Infectious Disease*. doi: 10.1186/s12879-023-08037-x

Swift, B. Imohe, A. Gonzalez, C. Mwirigi, L. 2023**.** An in-depth review of the UNICEF NutriDash Platform: Lessons Learned and Future Perspectives. A mixed-methods study. *BMJ Open.* doi: 10.1136/ bmjopen-2022-062684

Swift, B. Coroners and Covid: Preventable deaths from SARS-CoV-2. *BMJ EBM Spotlight.* March 4th 2022. Available from: https://blogs.bmj.com/bmjebmspotlight/2022/03/04/coroners-and-covid-preventable-deaths-from-sars-cov-2/

Swift, B. Zondervan K.T. Naci, H. Taneri, B. Becker, CT. Rahmioglu, N. 2022. The Cyprus Women's Health Research (COHERE) Initiative: normative data from the SF-36v2 questionnaire for reproductive aged women from the Eastern Mediterranean. *Quality of Life Research*. doi: 10.1007/s11136-022-03100-7*****

Swift, B. Heneghan, C. Aronson, J. Richards, G. 2021. Preventable deaths from SARS-CoV-2 in England and Wales: a systematic case series of coroners' reports during the COVID-19 pandemic *BMJ Evidence-Based Medicine*. doi: 10.1136/bmjebm-2021-111834

Swift, B. Becker, C. Birth control continues to fail women, so why has nothing changed? *The Conversation*, July 14, 2021. Available from: https://theconversation.com/birth-control-continues-to-fail-women-so-why-has-nothing-changed-164195.

Swift, B. Mis, C. Kofali, G. Bahat, PY. Senocak, G. Taneri, B. Hummelshoj, L. Missmer, SA. Becker, CM. Zondervan, KT. Ozgor, BY. Oral, E. Inceboz, U. Hocaoglu, MB. Rahmioglu, N. 2021. Protocol for the cultural translation and adaptation of the World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonisation project endometriosis participant questionnaire (EPHect). *Frontiers in Global Women's Health.* doi: 10.3389/fgwh.2021.644609*****

Conferences

Swift, B. Taneri, B. Becker, C.M. Basarir, H. Naci, H. Missmer, S.A. Zondervan, KT. Rahmioglu, N. 2022. Poster presentation. Endometriosis associations with co-morbidities and iron and vitamin-D deficiencies in an Eastern Mediterranean population. 15th World Congress on Endometriosis. 3rd-6th May 2023*****

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***Relevant to this thesis**

Statement of contribution to work

I drafted the text and produced all figures and tables presented in this thesis. I received the original Turkish dataset and translated (with assistance from Research Assistants at the Eastern Mediterranean University), cleaned and coded it myself. I inputted information from the ultrasound scans and merged this with the dataset. Researchers at the Eastern Mediterranean University cleaned the FFQ data, and I merged this with the baseline data and produced the analysis myself. The base map was sourced and created by Dr Kamil Erguler and I created the subsequent resolution layers. I produced all the analysis plans and conducted all the analysis myself with input from those in the acknowledgements.

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List of abbreviations

ASRM – American Society of Reproductive Medicine
BMI – Body Mass Index
CHD – Coronary Heart Disease
CI – Confidence Interval
CNS – Central Nervous System
COHERE – Cyprus Women's Health Research
CoHERS – Cyprus Women's Health Research Society
DEEP – Deep endometriosis
E3N - The French Etude Epidémiologique auprès de femmes de l'Education Nationale
EMU – Eastern Mediterranean University
EHP-30 - Endometriosis Health Profile 30
EPHect – Endometriosis Phenome and Biobanking Harmonisation Project
ESHRE – European Society of Human Reproduction and Embryology
FFQ – Food Frequency Questionnaire
HR – Hazard Ratio
GnRH – Gonadotrophin Releasing Hormone
GDP – Gross Domestic Product
GSWH – Global Study of Women's Health
GWAS – Genome Wide Association Studies
HPV - Human Papillomavirus Vaccine
HRQoL – Health-Related-Quality-of-Life
IBD – Irritable Bowel Disease
IBS – Irritable Bowel Syndrome
ICD – International Classification for Disease
IHS – International Headache Society
ISCO08 - International Standard Classification of Occupations 2008
IL - Interleukin
Int – International Dollars
IUD – Intra-uterine device
IUS – Intra-uterine systems
SRH – Sexual and Reproductive Health
LARCs – Long-acting Reversible Contraceptives
IUI – Intra-uterine system
IUD – Intra-uterine device
IVF – In Vitro Fertilisation
MCS – Mental Component Summary
MD – Mediterranean Diet
MET – Metabolic Equivalents
MRI – Magnetic Resonance Imaging
NHP – Non-human primate
NHSII – Nurses' Health Study II
NICE – National Institute for Health and Care Excellence
NRS – Numerical Rating Scales
NSAIDs – Non-steroidal anti-inflammatory drugs
OR – Odds Ratio
PCS – Physical Component Summary
PCOS – Polycystic Ovary Syndrome
PCtS – Pain Catastrophising Score
PI – Principal Investigator
PPP – Purchasing Power Parity
QGIS – Quantum Geographic Information System

QoL – Quality of Life
OxTREC – Oxford Tropical Research Ethics Committee
ROC – Reactive Oxygen Species
RCT – Randomised controlled trial
SF-36v2 – Short Form Health Survey Version 2
SF-MPQ – Short Form McGill Pain Questionnaire
SNP – Single Nucleotide Polymorphism
T2D – Type 2 Diabetes
TNF - Tumour Necrosis Factor
TGF – Transforming Growth Factor
TVS – Transvaginal Ultrasound Scan
UCSD – University of California San Diego
UK – United Kingdom
US – United States of America
USS – Ultrasound scan
UTI – Urinary Tract Infection
UV - Ultraviolet
WHR – Waist-to-hip-ratio
WERF – World Endometriosis Research Foundation
WPAI:GH – Work Productivity and Activity Impairment: General Health

Chapter 1 - Introduction

1.1 Definition and classification of endometriosis

Endometriosis is a chronic condition that occurs when tissue similar to the lining of the uterus (endometrium) grows in areas outside of the uterus, such as the ovaries, uterosacral ligaments, peritoneal surface, bowel and bladder[1]. The disease has been surgically classified into three phenotypes: 1) superficial peritoneal and serosal lesions: the most common localisation whereby lesions are located on the peritoneum (membrane that lines the pelvic cavity and organs), 2) endometrioma: fluid-filled cysts, also known as chocolate cysts, in the ovaries and 3) deep endometriosis (DEEP): endometriotic nodular lesions growing >=5mm below the peritoneal surface or on organs near the uterus, such as the bladder and bowel[2].

Endometriosis is an oestrogen-dependent, chronic inflammatory condition. It is the third leading cause of gynaecological hospitalisation in the United States of America (US) as well as a leading cause of hysterectomy[3]. Since the growth of endometriotic tissue is oestrogen-dependent the condition primarily manifests itself between menarche and menopause, but has been also previously described in pre-pubertal girls[4], post-menopausal women[5], and men receiving high dose oestrogen therapy[6]. However, prevalence in these groups is low.

The American Society of Reproductive Medicine's (ASRM) staging system of endometriosis is generally well accepted and is based on a points system that takes into account location, extent and depth of disease in relation to pelvic structures[7]. Organs such as the uterus, ovaries, Fallopian tubes as well as structures such as the rectovaginal septum, pouch of Douglas, uterovesical fold and ovarian fossae are often affected. There are four stages to the classification: Stage I (minimal, 1-5 points) is usually comprised of a few superficial endometriotic spots or adhesions, Stage II (mild, 6-15 points) is usually a few deep peritoneal lesions either in combination with superficial lesions or alone, Stage III (moderate, 16-40 points) will often include an endometrioma either by itself or in combination with deep endometriosis and/or superficial lesions and Stage IV (severe, >40 points) will usually be a combination of all of the above as well as bilateral ovarian endometrioma or dense adhesions[7].

It is important to note that these stages do not correlate with symptoms (location or severity), treatment, response or prognosis[8]. Since this classification does not aid management of endometriosis associated symptoms such as pain and subfertility, there has been much discussion[9] on how relevant the classification is. There have been calls to revise the current system and use empirically derived weights and breakpoints to define disease stages based on outcome data. Furthermore, it has also been argued that since subtle lesions are considered to occur naturally in all women, only moderate-severe endometriosis should be considered as a clinically significant disease[10].

1.2 Pathophysiology of endometriosis

The pathophysiology of endometriosis remains poorly understood despite substantial research efforts. There are three main theories that have been proposed to explain pathogenesis of endometriosis, but each still lacks validity due to the challenges involved in creating clinically valid models of the disease.

1) Retrograde menstruation – Sampson's hypothesis[11] of retrograde menstruation is the most widely accepted origin of endometriosis and is defined as the backwards flow of menstrual fluid and cells into the peritoneal cavity through the Fallopian tubes. Clinical evidence has shown that viable endometrial cells are present in menstrual and peritoneal fluid[12] and it has been shown experimentally that endometrium can grow within the peritoneal cavity[13]. Retrograde menstruation naturally occurs in around 90% of women, so it is likely that there are other factors that contribute to the processes in women with endometriosis. In most women, immune cells including peritoneal macrophages are able to successfully clear refluxed cells, but in women with endometriosis, an impaired immunological response and molecular changes may play an important role in allowing these refluxed cells to persist[14].

2) Coelomic metaplasia – Meyer's theory[15] postulates that endometriosis originates from the metaplasia of specialised cells that are present in the

mesothelial lining of the visceral and abdominal peritoneum. This theory suggests that there may be a metaplastic transformation of peritoneal mesothelial cells into endometrial glandular cells, likely caused by environmental, biochemical or immunological factors[16,1,2,17].

3) Lymphatic and vascular metastasis – This theory suggests that menstrual tissue from the endometrial cavity travels in a metastatic-like manner to various other sites through veins or lymphatic vessels[18]. Rare evidence of endometrial cells in the brain or other pelvically-distant organs (extra-pelvic endometriosis) support this theory[19].

1.2.1 Heritability and genetics

It is widely accepted that endometriosis is a heritable condition. Twin studies have suggested the heritability of endometriosis to be between 47-51%, with common variants contributing to approximately 26% of the risk[20–22]. If sufficiently powered, Genome Wide Association Studies (GWAS) can help uncover and detect common risk variants[22]. To date, there have been nine GWAS studies[1] with the largest published meta-GWAS including 17,045 cases and 191,596 controls, identifying 19 single nucleotide polymorphisms (SNPs) thought to explain approximately 1.75% of risk for endometriosis[23]. A recent meta-GWAS including 58K cases and 733K controls revealed 27 genetic loci associated with endometriosis and of these, 78% had larger effect sizes in stage III/IV compared to stage I/II[24]. As with other complex diseases, there have been no

high penetrance susceptibility genes identified, as of yet[25]. To date, GWAS studies have been limited to European and Japanese ancestries[1,23].

1.2.2 Immune system

Though the theory of retrograde menstruation is the most widely accepted, the fact that it naturally occurs in 76-90% of all women suggests that other processes contribute to the implantation of endometrial cells and formation of lesions in women with endometriosis[26,27]. Studies have shown that the peritoneal fluid of women with endometriosis contains a large number of immune cells which contribute towards the survival and proliferation of ectopic endometrial cells through secreting growth factors and cytokines[28,29]. It has also been reported that inflammatory factors such as interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF- α) and C-reactive protein (CRP) were higher in the peritoneal fluid of women with endometriosis compared to women without. However, although dysfunction of the immune system is evident[30], it is unclear whether inflammation associated with endometriosis is involved in its pathogenesis or whether it is simply an epiphenomenon of the disease process. A nested case-control study using data from the prospective Nurses' Health Study II (NHSII) showed that plasma IL-1 levels were positively associated with an increased risk of laparoscopically confirmed endometriosis but that there was no association between endometriosis risk and IL-6, TNF- α or CRP levels[31]. Difficulties in being able to identify the true time of endometriosis onset at a molecular and cellular level make this type of research hard to conduct.

1.2.3 Hormones

Endometriosis is often referred to as an ‘oestrogen-dependent’ disorder, though there have been suggestions to update this to ‘steroid-dependent’ to encompass the importance of other steroids and their receptors in cell regulation in eutopic and ectopic endometrium[32]. In short, oestrogen and progesterone are produced in the ovaries and cause endometriotic tissue growth by altering oestrogen signalling and expression of aromatase in endometriotic implants[33]. Aromatase activates steroidogenesis and catalyses the biosynthesis of oestrogen[34]. The role of progesterone is to inhibit excessive growth of endometrial tissue and analysis of eutopic endometrium from women with endometriosis has identified steroid responsiveness (progesterone “resistance”)[35]. It is thought that inflammation may induce progesterone resistance by interfering with the progesterone signalling pathway through altering proinflammatory transcriptional factors[36].

1.3 Endometriosis symptoms

1.3.1 Pain

Pain is the most common symptom of endometriosis and often remains even after endometriosis has been treated[26]. The most common types of endometriosis-associated pain are dysmenorrhea (painful periods), dyspareunia

(pain during or after intercourse), pelvic pain (cyclical or non-cyclical), dyschezia (pain on defecation) and dysuria (pain during urination). The severity of pain can range from very mild to debilitating and it is widely accepted that there is no correlation between endometriosis stage and degree of pain symptoms, so women with “minimal” evidence of endometriosis can have extremely severe symptoms and women with “severe” evidence of endometriosis can have very mild symptoms[37]. The prevalence of endometriosis in women hospitalised for pelvic pain is between 5 to 21%[38].

1.3.1.1 Mechanisms

It is believed that development of new blood supply and associated nerves (neuroangiogenesis) can be responsible for endometriotic lesions causing peripheral pain pathway activation[39]. As with other chronic pain conditions, endometriosis is associated with unique alternations in both the central and peripheral nervous system, including changes in the volume of the brain and its biochemistry[40]. Central sensitisation occurs when neural signalling within the central nervous system (CNS) that is responsible for pain hypersensitivity is amplified[41]. Central sensitisation means that around 30% of women with endometriosis will develop chronic pelvic pain that is unresponsive to conventional endometriosis treatments, including surgery[42]. For these women, they will have lower pain thresholds and increased responsiveness to the after effects of noxious stimuli and even feel pain from non-injured tissue[43,44]. Since the CNS is continually activated, removal of endometriotic lesions will usually not have an effect on pain in women suffering from central sensitisation[45,46].

Overall, this means that endometriosis associated pain does not conform to one of the three main classical categories of pain (nociceptive, neuropathic or nociplastic) and has a mixed pain phenotype[47–49]. It has been suggested that some women transition between pain categories, often starting with localised and episodic pain to a phenotype that is chronic, widespread and complex, making it much harder to treat[50].

1.3.1.2 Treatment

As it becomes more widely recognised that the endometriosis pain phenotype is mixed, so it follows that treatment for endometriosis-associated pain should be personalised and interdisciplinary[51]. The most recent guidelines from the European Society of Human Reproduction and Embryology (ESHRE)[51] and National Institute for Health and Care Excellence (NICE) guidelines[52] recommend surgery as one possible treatment for pain, though there are only a limited number of randomised controlled trials (RCTs) that have assessed pain outcomes after surgery. The most recent Cochrane review of surgery for endometriosis pain concluded that they were “uncertain of the effect of laparoscopic surgery on pain and quality of life” as the available studies were of low quality[53]. Hysterectomy is an option for women who do not wish to conceive in the future and who have not responded to more conventional treatment options, but comes with its own risks as it has been associated with long term morbidity[54] including cardiovascular disease[55].

The most recent ESHRE guidelines[51] suggest that hormonal treatments should be the first line of therapy. These include combined contraceptives, progesterone, gonadotropin releasing hormone (GnRH) agonists, GnRH antagonists and aromatase inhibitors. A meta-analysis of these treatments (excluding GnRH antagonists) showed that they all led to a clinically significant reduction in menstrual and non-menstrual pelvic pain compared to a placebo treatment[52]. However, contraceptives are not appropriate if a woman wants to conceive, and symptoms will often return after treatment cessation. Other treatment options may include pelvic physiotherapy, psychology and dietary interventions[56].

1.3.2 Infertility

In addition to pain, infertility is a frequent worry in women with endometriosis. Infertility is significantly more common in women with endometriosis compared to women without, and the risk is approximately double[57]. In women who experience infertility, endometriosis is prevalent in approximately 9-68%[56], and in women who undergo assisted reproductive treatment, endometriosis is discovered in approximately 30-50%[3,58].

1.3.2.1 Mechanisms

There are multiple pathways in which endometriosis could impair fertility and several studies of women undergoing in vitro fertilisation (IVF) have shown that women with endometriosis have a lower oocyte yield or ovarian reserve

compared to women without endometriosis[59,60]. It is believed that women with endometriosis have peritoneal inflammation and endocrine derangements which interfere with the follicular environment and affect ovarian function, ultimately reducing oocyte competence[61]. In addition to this, it is likely that adhesions caused by endometriosis which are particularly common in stage III-IV disease, reduce the chance of natural conception due to distortion of pelvic anatomy, though this remains unproven[56].

1.3.2.2 Treatment

Unlike women whose main symptom is pain, those experiencing infertility should not be treated with postoperative hormone suppression in order to try to enhance future pregnancy rates[56]. Surgery for endometriosis is only recommended in women who are experiencing pain symptoms[51], and it has been suggested that use of the Endometriosis Fertility Index could help guide decision making to choose the best treatment option with the overarching goal of achieving pregnancy after surgery[51,62].

1.4 Endometriosis diagnosis

Endometriosis is difficult to diagnose and there are currently no biomarkers that are able to reliably detect or rule out endometriosis[63]. The diagnostic gold standard[64,65] for endometriosis was until recently laparoscopic identification of endometriotic lesions, whereby endometriotic lesions are visually inspected, and ideally histologically verified. However, laparoscopy is a costly and invasive

procedure that comes with risks of morbidity and/or mortality[66,67]. The most recent ESHRE guidelines[51] state that laparoscopy is no longer gold standard and is only recommended in patients with negative imaging results or for whom treatment was unsuccessful.

There have been significant advances in the quality and availability of non-invasive imaging techniques such as transvaginal ultrasound scan (TVS) and pelvic magnetic resonance imaging (MRI). TVS can be used to identify endometriomas and MRI has an overall high accuracy in detecting deep endometriosis and extra-pelvic endometriosis[68]. However, both techniques have limited ability to detect superficial endometriosis and require specific training in endometriosis diagnostic techniques. Although non-invasive diagnostic modalities such as ultrasound and MRI cannot replace laparoscopies for all subtypes of endometriosis, they are appropriate for advance stage endometriosis. It is important to note that negative imaging results do not necessarily exclude endometriosis.

Confirmation of diagnosis of endometriosis by symptoms alone is not currently advised due to the fact that many women with endometriosis symptoms (dysmenorrhea, dyspareunia, non-cyclic pelvic pain, subfertility) may not have the disease[2], but clinicians should consider the diagnosis of endometriosis in individuals who present with endometriosis symptoms[51]. It has also been suggested[68] that there should not be one gold-standard diagnostic method,

such as laparoscopy, but a multipronged approach based on the individual's circumstances.

1.4.1 Barriers to diagnosis

One of the main barriers to a quick endometriosis diagnosis and treatment plan is diagnostic delay. The delay to diagnosis for women experiencing pelvic pain is longer than that of women experiencing infertility[69,70], and is approximately between 7-12 years[71,72]. Diagnostic delay can not only cause physical and emotional pain but is associated with significant personal and societal costs as well as impairment of the patient-provider relationship[72–74].

Societal barriers that contribute to this delay include stigma associated with menstrual issues and the normalisation of menstrual pain[75], with one study suggesting that women wait 2.3 years from the onset of their endometriosis symptoms to seek help[71]. Topics that are considered to be 'taboo' such as pain during sexual intercourse can often prevent women from discussing symptoms with friends, family and healthcare providers and receiving effective treatment and care[76]. Furthermore, diagnostic delay also occurs because the aetiology of endometriosis is still not fully understood and endometriosis is often misdiagnosed, for example, chronic pelvic pain is common in other diseases such as pelvic inflammatory disease, uterine fibroids, adenomyosis, irritable bowel syndrome, painful bladder syndrome and fibromyalgia[77].

Other barriers to diagnosis include those related to healthcare providers and in current diagnostic tools. Women with endometriosis make on average 7 visits to their primary healthcare provider before being referred to an appropriate specialist[72] and three-quarters of patients will receive a misdiagnosis[71]. A survey of healthcare providers found that around half could not name 3 symptoms of endometriosis and two-thirds admitted to not feeling comfortable diagnosing endometriosis in women presenting with symptoms[78]. Healthcare providers may also feel uncomfortable discussing symptoms of the disease, which may contribute to the long diagnostic delay especially in younger women. The absence of non-invasive diagnostic tools is also an issue, with two-thirds of gynaecologists agreeing that lack of such tools contributed to diagnostic delay[74].

1.5 Epidemiology of endometriosis

1.5.1 Prevalence of endometriosis

It is extremely difficult to accurately measure population-based prevalence and incidence of endometriosis since until recently, surgical visualisation was the gold-standard. There are a multitude of factors that would affect whether someone is able to undergo laparoscopy, varying from availability in the region, symptoms negating referral for surgery and access to surgical expertise, which therefore creates a biased sample among those women who are able to be diagnosed[38]. The estimated overall prevalence of endometriosis is around 10%

in the general population and 2% for undiagnosed symptomatic disease, using prevalence estimates of pelvic pain and subfertility in the general population[79]. However, estimates vary among different populations varying between 2-43%[80,81,82] among asymptomatic women seeking tubal ligation to 5-50%[83,80,84] among infertile women and 5-21%[80,83,84] among women who are hospitalised for pelvic pain. There is currently no robust evidence to confirm that prevalence of endometriosis varies across different ethnic groups because any observed differences may be due to differential access to health care[85].

1.5.2 Quality of life

The painful nature of endometriosis coupled with potential fertility issues and menstrual irregularities means that it can have a negative impact on women's emotional, physical and social wellbeing[86,87], collectively known as health-related-quality-of-life (HRQoL), as well as the work and relationships of women[88,89]. The Global Study of Women's Health (GSWH)[72] is a cross-sectional study that was conducted in 10 countries and included women with symptoms of endometriosis undergoing a first laparoscopy. The study found that women with endometriosis had lower HRQoL, especially physically, across countries. Furthermore, several studies[90,91] have also shown that women with endometriosis are at increased risk of anxiety and depression indicating that clinical care for patients should also include identifying these disorders to prevent any further impact on quality of life. It has also been shown that HRQoL decreases as diagnostic delay increases and persists even after surgical

treatment as women deal with post-operative complications that mean medication is still needed[92,93].

1.5.3 Work productivity and activity impairment

Endometriosis also affects the lives of women during work and activities. Many women report that their endometriosis negatively impacts their education, life opportunities and employment[87]. The GSWH reported that women with endometriosis took more time off work and had reduced productivity compared to a symptomatic control group, losing on average 10.8 hours of work per week[72]. Studies have shown that as pain increases so do productivity losses[94] and chronic pain is one of the biggest contributors to loss of productivity in the workplace[95]. A study of women with endometriosis in Puerto Rico[89] saw substantial losses in work productivity with women losing on average 1 day of work per week, estimated to be higher than among patients with rheumatoid arthritis[96].

1.5.4 Economic burden

The economic burden of endometriosis has been suggested to be similar to that of other chronic conditions such as diabetes and heart disease[72]. The GSWH estimated the annual cost of endometriosis to be €9,579 per person per year, with the majority of costs coming from loss of productivity during work[72]. A study in Australia estimated per person annual costs for women with endometriosis to

be International Dollars (Int) $20,898, with loss of productivity accounting for 83.6%[97]. Reasons for the high cost include long diagnostic delays[98], misdiagnoses[99], high treatment costs including surgery and infertility treatment[51] and severe absence or loss of productivity from work[100].

1.5.5 Risk factors for endometriosis

Epidemiological research has shown that there are some women who are at a higher risk of developing endometriosis compared to their counterparts. Risk factors for endometriosis vary and can be modifiable or non-modifiable. However, due to difficulties with diagnosis, risk factors can vary based on the population which data are collected from[1]. In addition to this, studies often suffer from biases such as reduced statistical power caused by small sample sizes, heterogeneous methodologies and differing definitions of cases and controls. One of the main difficulties in investigating modifiable risk factors is temporality. Prospective cohort studies are most suited to investigating potential associations because they can measure exposures prior to a diagnosis of endometriosis. Case-control and cross-sectional studies are unable to determine if the risk factor being investigated preceded the endometriosis diagnosis or whether the exposure changed over-time as a result of endometriosis symptoms or diagnosis. Therefore, evidence from prospective cohort studies is of higher quality and preferable when examining the literature. In addition, the long diagnostic delay between endometriosis symptoms and

diagnosis and progressive nature of the disease make it uniquely challenging[101].

1.5.5.1 Demographics

It is well established that women with endometriosis are more likely to be of a higher socio-economic status, potentially because they have the financial ability to afford healthcare and seek a diagnosis[102]. Linked to this is education; endometriosis patients are more likely to be higher educated and therefore may have a greater knowledge on common health conditions, including endometriosis[103–105]. A systematic review and meta-analysis found that Black women were less likely to be diagnosed with endometriosis compared to White women, but Asian and Hispanic women were more likely to be diagnosed with endometriosis compared to White women, though the latter association was not significant[106]. It is unclear whether these associations are artefacts of diagnostic biases due to systemic problems relating to race/ethnicity or there is heterogeneity in clinical presentation between racial/ethnic groups. There is evidence that race/ethnicity and gender unconsciously influence referral patterns and clinical care[107] and research has shown that race/ethnicity may influence disease presentation, with Asian women more likely being diagnosed with stage III/IV endometriosis compared to White women[108]. Issues with study design and methodologies means that the current evidence is not strong enough to draw conclusions and future research into race/ethnicity and endometriosis is warranted, but must consider access to care[85].

1.5.5.2 Menstrual characteristics

Shorter menstrual cycles (<26 days)[109], earlier age of menarche (<12 years)[110] and heavy menstrual flow[91,111] have all been associated with endometriosis and support Sampson's theory of retrograde menstruation as the origin of endometriosis because they increase the frequency of exposure to menstruation, menstrual reflux and oestrogen[18]. There is mixed literature surrounding the association between regularity of the menstrual cycle and duration of menstrual phase with endometriosis[91,112].

1.5.5.3 Anthropometric characteristics

Many studies have shown that endometriosis is associated with a lower Body Mass Index (BMI) at adulthood[113], with suggestions that this is also true during childhood[114]. In addition, low waist-to-hip (WHR) has been shown to be related to endometriosis risk both in a case control study[115] and in the prospective NHSII[113]. Genetic studies[116] have further confirmed this association which is explained by the fact that women with a higher ratio of oestrogens to androgens have lower WRHs[117]. The French Étude Épidémiologique auprès de femmes de l'Éducation Nationale (E3N) cohort saw that women with endometriosis were more likely to be taller[114] but since height is reflective of several early life exposures, its association with endometriosis remains unclear.

1.5.5.4 Dietary factors

In addition to the complexities in investigating modifiable risk factors as previously discussed, when considering diet, it must be noted that the nutritional makeup of food items differs across countries, as does pesticide use, frequency of imports and baseline intake of macronutrients e.g. olive oil consumption varies across populations meaning the baseline risk would potentially be different[118]. Since foods are usually consumed as meals, it can be difficult to disentangle the separate effects of particular food items e.g. olive oil is often a dressing on vegetables for salads[119].

Mediterranean diet

Given that Cyprus is in the Mediterranean, it would be right to assume a Mediterranean-style diet is followed. There is no information on current diet practices in Northern Cyprus, but representative data from the Republic of Cyprus suggested that the population has a moderate to low adherence to the Mediterranean diet and that adherence was associated with lower risk of multi-morbidity[120]. The Mediterranean diet is characterised by a diet rich in vegetables, fruits, olive oil, whole grains, fish and low in dairy, red meat and processed foods such as sweets and vegetable oils[121].

Fruit and vegetable intake

Research has shown that dietary factors could have a role in the aetiology of endometriosis through influencing steroid hormones. Several studies[122,123,124] have looked into fruit and vegetable consumption and how this might influence endometriosis risk, however the results have been inconclusive with some suggesting fruits and vegetables to be protective and others suggesting that there is no association. The NHSII saw that increased intake of citrus fruits was associated with a decreased risk of endometriosis whereas there was no association between total vegetable intake and endometriosis but a higher intake of cruciferous vegetables was associated with an increased risk of endometriosis[124]. However, a recent systematic review and meta-analysis saw no association between total fruit or total vegetable intake and endometriosis, but heterogeneity between studies was high[125].

Several studies have investigated the role of specific vitamins and minerals found in fruits and vegetables including folates, carotenoids and vitamins A, E, C in relation to endometriosis risk. Folate was found to be associated with lower endometriosis risk in the prospective NHSII[126], where exposures were assessed prior to endometriosis diagnosis, whereas no associations were found in two case-control studies[127,128]. However, these case-control studies suffer from issues with temporality and in addition, Britton *et al.,* used ovarian endometriotic cysts as the outcome which does not encompass all endometriosis diagnoses. Vitamin A that is preformed is present only in animal products but can be

converted by its precursor, B-carotene, which is found in green leafy and yellow vegetables and orange-coloured fruits[101]. Intake of Vitamin A was found to be significantly lower in endometriosis patients[129] in one study but in general, other studies have not seen an association[127,128,130]. There are also uncertainties surrounding endometriosis risk and intake of vitamins E and C. There were no relationships found in three case-control studies[127,128,130] whereas higher quality evidence from a prospective study saw that vitamin C and E from food sources were inversely related to endometriosis diagnosis, though intake from supplements were not[126]. Vitamins are generally high in antioxidants that can have an effect on lipid peroxidation (LPO) which has been shown to contribute to inflammatory chronic diseases[131] and in addition, markers of oxidative stress have been found to be higher in serum and peritoneal fluid of women with endometriosis[132,133].

Dairy products, calcium, and vitamin D

A systematic review and meta-analysis[125] investigated the relationship between endometriosis and total dairy intake, concluding that there was a slight protective effect on endometriosis with no evidence of significant heterogeneity. There was no relationship between high fat dairy foods, low fat dairy foods, cheese, or milk intake. In addition, the NHSII saw an inverse relationship between dairy intake, calcium and vitamin D from foods and endometriosis risk[134]. It is thought that endometriosis could be related to calcium and vitamin D from dairy foods because these have been shown to be involved in down-

regulation of growth-promoting factors e.g. IL-I and in the up-regulation of negative growth factor modulators, e.g. transforming growth factor (TGF)[127]. It has been previously shown that inflammatory factors such as reactive oxygen species (ROC), IL-6 and TNF-α have been reduced by a higher calcium intake from dairy[135].

Red meat and saturated fat

Results from a systematic review and meta-analysis that included four studies showed that red meat was associated with a significantly higher risk of endometriosis[125]. Red meat is a primary source of saturated fat and in the meta-analysis, saturated fat was also shown to be associated with a higher risk of endometriosis. In the NHSII cohort, both processed and non-processed meat was associated with a higher risk of endometriosis, and this association was strongest amongst women who had not reported infertility[136]. Haem iron intake was also found to be associated with an increased risk of endometriosis, explaining part of the observed observation. The biological mechanism between red meat and endometriosis is not fully understood but has been suggested to be related to circulating steroid hormones[137]. Palmitic acid (a saturated fat found in meat) was found to be associated with increased endometriosis risk[138] and reductions in fat intake have been related to a reduction in endogenous oestrogens[139,140]. Excess oestrogen and inflammation in relation to endometriosis risk has already been discussed. Women with endometriosis who do not have problems with fertility are more likely to have problems with pain;

therefore, the association being stronger in women without fertility problems may reflect the idea that red meat exacerbates pain symptoms[136] and a study has shown that women with endometriosis following a vegetarian diet have reduced pain symptoms[141].

Fish, omega 3, and polyunsaturated fats

Polyunsaturated fats are a key component of the Mediterranean diet and are found in fish, nuts, and leafy greens. A systematic review and meta-analysis investigated the relationship between fish and endometriosis risk and saw no significant relationship between the two[125]. The NHSII saw that women who consumed the highest fifth quintile of omega 3 were less likely to receive an endometriosis diagnosis compared to those in the lowest fifth quintile[142]. Dietary studies examining dietary fat intake and endometriosis are not common but *in vitro* studies examining survival of endometrial cells with and without endometriosis was influenced by fatty acid content of the culture media, with endometrial cells having a decreased survival in cultures with a high proportion of long-chain n-3 fatty acids[143].

Fibre and cereals

Intake of refined carbohydrates has been shown to be associated with a higher concentration of inflammatory markers[144–146] and intake of unrefined carbohydrates has been shown to be associated with a lower

concentration[145,147,148]. In addition to this, fibre intake has been shown to influence metabolism of oestrogen[149,150]. As endometriosis is an oestrogen-dependent inflammatory condition, so it follows that endometriosis risk could be influenced by fibre intake. The NHSII observed a greater risk of endometriosis diagnosis in women who had a higher intake of both total vegetable fibre and cruciferous vegetables but that women who consumed more gluten and fruit fibre had a lower risk of endometriosis, though this was not significant after sensitivity analysis[151]. A study in Iranian women[152] showed that higher intakes of soluble and insoluble fibre were associated with a lower risk of endometriosis, however, dietary data was only collected for one year before endometriosis diagnosis so does not take into account that women may have altered their diets in response to symptoms experienced.

1.5.5.5 Lifestyle factors

Cigarette smoking

Several studies have investigated whether smoking and endometriosis may be related, but the results have been inconclusive. Some research[111] has shown smoking to be protective against endometriosis, since it disrupts oestradiol and progesterone synthesis[153,154,155,156]. However, a systematic review and meta-analysis of 38 studies saw no association between endometriosis and former, ever or current smoking[157]. It has been suggested that though cigarette smoking reduces circulating oestrogens, smoking also exposes the person to

exogenous oestrogens which would then increase endometriosis risk[111]. The prospective NHSII study[103] saw an inverse association in infertile endometriosis cases and a positive association in fertile cases, suggesting that any relationship between endometriosis and smoking is influenced by fertility status.

Alcohol consumption

Alcohol has been shown to be associated with several oestrogen dependent disorders[158,159] as ingesting alcohol increases circulating oestrogen levels and in addition, decreases inflammation and immunity[160]. Several case-control studies[161,162] have investigated the relationship between alcohol intake and endometriosis, concluding drinking alcohol increases risk, which was later confirmed in a systematic review and meta-analysis[163].

Physical activity

Some case-control studies have suggested that physical activity may have a protective effect on endometriosis risk[111,164,165] as exercise is thought to lower oestrogen production[166,167]. However, the evidence is not clear as a systematic review and meta-analysis did not see an association between the two[168] and although the NHSII saw an inverse relationship between endometriosis and increased exercise, the association was not significant[169]. In addition to this, data from the NHSII and French E3N cohorts have suggested a positive relationship between childhood physical activity and endometriosis[170,171].

1.5.5.6 Family history

There is a heritable component to endometriosis[172–174] and women with family members who have endometriosis are at higher risk of developing the disease themselves[175]. Since uterine fibroids and endometriosis have common genetic origins[176], and endometriosis and Polycystic Ovary Syndrome (PCOS) share similar biomarkers[177], so it follows that women with endometriosis may have a family history of other reproductive diseases or suffer from multiple reproductive diseases at once. However, it is possible that co-occurrence of multiple gynaecological diseases is not related to a heritable component, but because of shared risk factors. Additionally, studies have shown that women with endometriosis are more likely to have a positive family history of certain cancers, compared to controls[178,179].

1.5.5.7 Co-morbidities

There is an increasing body of evidence that women with endometriosis are at a higher risk of developing other, chronic co-morbidities[180]. Co-morbidities of endometriosis are difficult to study and rely on large, geographically diverse, prospective studies to truly estimate this increased risk. There is a lack of data on whether associations described below are true for all endometriosis patients, or whether prevalence and risk could vary based on disease stage or severity of

endometriosis[180]. In addition, women with endometriosis are better connected to the medical system and so any observed differences may reflect this.

Migraine

A systematic review and meta-analysis that included a total of 287,174 women from 9 studies showed that women with endometriosis are at an increased risk of migraine[181]. Co-occurrence of endometriosis and migraine gives support to the central sensitisation theory[46], though Miller *et al.,* (2018)[182] found that associations between endometriosis and migraines in adolescents remained after adjustment for pelvic pain. Results from one twin study[183] suggested that there are shared genetic pathways between endometriosis and migraine, going some way to explaining their frequent co-occurrence. It has also been hypothesised that because prostaglandins are involved in the pathogenesis of migraine[184,185] and production of prostaglandins are increased in women with endometriosis[186,187], that the systematic spreading of prostaglandins produced by endometriotic lesions could contribute to the co-occurrence of the two conditions[188].

Bladder pain

A systematic review of 9 prevalence studies has estimated the co-occurrence of endometriosis and bladder pain to be 48%[99] and a more recent population-based study saw that endometriosis patients were over 3 times more likely to

suffer from bladder pain and interstitial cystitis[189]. Studies have shown that bladder pain and endometriosis share common pathomechanisms such as inflammatory changes through mediators such as chemokines or cytokines with IL-6 and TNF being expressed in the interstitium and urothelium of the bladder[190,191]. However, because the clinical presentation of both bladder pain and endometriosis can be similar to other conditions, diagnosis can be challenging and can lead to delays in receiving a diagnosis and potentially an inappropriate treatment regime[99].

Gastrointestinal symptoms and irritable bowel syndrome (IBS)

The findings of a recent systematic review and meta-analysis that included 22 articles revealed that women with endometriosis often have a co-occurrence of gastrointestinal symptoms[192]. The relationship between endometriosis and IBS is difficult to elucidate because there are several confounding factors that need to be taken into consideration. For example, GnRH-analogues are often used in the treatment of endometriosis, but these drugs have also been found to increase the severity of gastrointestinal symptoms[193–196]. In addition, menstrual cycle phase needs to be taken into consideration because abdominal pain related to endometriosis and bowel symptoms can vary across the menstrual cycle[197]. Finally, gastrointestinal symptoms and endometriosis can be exacerbated by stress and other psychological disorders so the existence of gastrointestinal symptoms may actually be a consequence of stress levels[198], rather than the disease itself.

Autoimmune and allergic diseases

Since the aetiology of endometriosis has been proposed to involve abnormalities in the immune system of women[199–202], it follows that women with endometriosis might be at a higher risk of autoimmune and allergy-related diseases. A systematic review and meta-analysis[30] that investigated the potential association between endometriosis and autoimmune disease saw a statistically significant association between endometriosis and at least one autoimmune disease. However, this was based on only four studies due to issues with quality. Women with endometriosis have also been shown to be at a higher risk of having co-occurring allergies such asthma, perennial allergic rhinitis[203] and psoriasis[204]. However, Ferrero *et al.,*[205] did not see an increase in prevalence of asthma in women with endometriosis.

Cardiovascular diseases

Data from the NHSII has suggested that women with endometriosis are at a higher risk of suffering from myocardial infarction, angiographically confirmed angina and coronary artery bypass graft surgery/coronary angioplasty procedure/stent[55]. Although part of this association could be explained by endometriosis treatments that are risk factors for coronary heart disease (CHD),

both conditions are inflammatory conditions, have heightened oxidative stress, atherogenic lipid profiles and potentially shared genetic susceptibilities[206–210].

Metabolism- and obesity-related conditions

There has been evidence that endometriosis could increase the risk of some metabolism-related conditions such as Type 2 Diabetes (T2D). Although the NHSII saw no association between endometriosis and T2D overall, their analysis revealed that women with endometriosis who were obese, had never experienced infertility and never experienced gestational diabetes mellitus were at a greater risk of T2D[211]. This is interesting as these phenotypes are historically not related to a heightened T2D risk, and infertility has been shown to be associated with a higher risk of T2D[212]. Therefore, it is possible that women who are not infertile have a low T2D risk. In addition, obesity is linked to insulin resistance[213], which is the strongest risk factor for developing T2D[214]. There has been a previously demonstrated inverse relationship between obesity and endometriosis[38,113,114].

Thalassemia and iron deficiency

Thalassemia is an inherited blood disorder characterised by an insufficiency to produce haemoglobin at the required level. Due to the fact that malaria was endemic in Cyprus at very high levels[215], the population has a high prevalence of thalassemia thought to have emerged as an adaptive response[216]. Once

malaria had been eradicated, it was estimated that one in ten children under 10 years old were thalassaemic. Thalassaemia is a recessive disease, so for a child to be born with thalassemia, both parents must be carriers. In order to stop this high prevalence, the Thalassaemia Prevention Programme (TPP)[217] was established which is a pre-marriage screening programme that has resulted in no new active cases in Cyprus since 2001. Though no current estimates of prevalence of thalassemia carriers are available for the population of Northern Cyprus, in the Republic of Cyprus, prevalence of thalassemia was estimated at 12.4%[218].

Studies have found that thalassemia carriers are at risk of being iron deficient[218,219] and nonhuman primate (NHP) models have shown that iron deficiency could be a co-existing condition with endometriosis[220]. In addition to this, women with endometriosis may be at risk of heavier menstrual bleeding, which in itself could cause iron deficiency[221,222], making the study of thalassemia, iron deficiency and endometriosis in the Cypriot population an interesting topic to explore.

1.5.5.8 Pigmentary traits

As discussed, many epidemiological studies have used data from Western populations to ascertain potential risk factors for endometriosis. Several pigmentary traits have been found to be associated with endometriosis in such

populations, but the frequency of these traits may vary depending on where the sample population comes from.

The French E3N cohort saw a positive dose-effect relationship between endometriosis risk and skin sensitivity, number of moles and freckling[223] and in addition, the NHSII saw that having more moles on the lower legs to be associated with a higher risk of endometriosis[224]. Other studies have seen associations between the presence of dysplastic naevi and endometriosis risk[225,226]. There is conflicting evidence on whether eye colour is associated with endometriosis risk. Some studies saw that lighter eyes were associated with an increased risk[227–229] whereas others did not see an association[223,224] and similarly, there are mixed results on whether red hair is associated with endometriosis risk[223,224,230,231]. Lighter skin tone has also been shown to be a potential risk factor for endometriosis[223,224,228,232].

Pigmentary traits that have been hypothesised to be risk factors for endometriosis are also known risk factors for melanoma[233,234]. In addition, epidemiological studies have shown family history of melanoma to be associated with endometriosis[224,226] as has personal history[235–237] with a recent GWAS suggested that having an increased genetic risk of melanoma is related to an increase in endometriosis risk, suggesting a shared genetic pathway[238]. However, the GWAS showed no genetic correlation between pigmentary traits and endometriosis, suggesting the correlation between endometriosis and melanoma is not influenced by pigmentary traits.

Sun exposure, sun habits and vitamin D deficiency

Data from the prospective NHSII has suggested a potential link between sun exposure and endometriosis. The study showed that recreational sun exposure was associated with a higher risk of endometriosis whereas residential sun exposure was associated with a reduced risk of endometriosis[239]. The authors found that activities relating to a high ultraviolet (UV) exposure such as use of sunscreen, higher frequency of tanning bed and number of sunbeds increased endometriosis risk whereas activities reflecting a higher level of UV residential exposure i.e., UV in state of residence, were associated with a lower risk of endometriosis. Intense high levels of UV exposure which usually come in the form of UVA are associated with both DNA damage and inflammation[240–242] and endometriosis has been shown to be associated with inflammation[31] and dysfunction of the immune system[1]. On the contrary the authors of this paper suggested that because residential exposure to UV represents shorter UVB wavelengths which causes cutaneous vitamin D production, the decrease in endometriosis risk observed with residential UV exposure may indicate a protective pathway through vitamin D[239]. Vitamin D has been found to both regulate immune function and stop pro-inflammatory processes[135,243]. However, a systematic review of the association between vitamin D and endometriosis did not see any association between the two[244] whereas a meta-analysis concluded that vitamin D levels were lower in women with endometriosis than controls but after removing one of two studies[245,246], the result was null. Evidence from

randomised controlled trials (RCTs) investigating vitamin D supplementation on endometriosis risk have been inconclusive[247,248].

1.6 Methodological considerations

The complex nature and heterogeneity of endometriosis makes it a difficult disease to study. The main issues[38] are:

1) Choosing a valid endometriosis case definition. There are a multitude of ways endometriosis patients can be diagnosed. This may be during an infertility investigation, due to pelvic pain or incidentally during another surgical procedure. Women who seek healthcare due to pelvic pain may differ in pathophysiology, symptomatology and risk factor profiles compared to women who are diagnosed incidentally or women who are using oral contraceptives which manage their symptoms. These differences can introduce selection bias into studies where surgical confirmation of endometriosis is used as the case definition, as access to laparoscopy may vary regionally and the case group is more likely to contain women with more severe symptoms, which does not necessarily correlate with endometriosis staging[249]. Similarly, an endometriosis case definition that includes only incidental cases picked up at fertility investigations or during other procedures may under-sample women with chronic pelvic pain[72] who are not trying to get pregnant and are therefore not experiencing issues[250].

2) Choosing a valid comparison group. In case control studies, the control group must have the same chance of experiencing the exposure as the case group, but the sampling must be independent of the exposure. To ensure no undiagnosed cases are in the control group, sometimes controls will be selected from a group that is undergoing pelvic surgery for another reason. However, selecting a control group like this means that the sample is biased e.g. tubal ligation controls have had children and are therefore not a valid comparison to endometriosis cases who are undergoing fertility investigations[251]. In addition to this, women who are able to seek fertility treatment usually differ from those who are not in demographics such as socioeconomic status, lifestyle and failure to account for these differences introduces bias[252]. This is of particular concern when the exposure of interest is correlated with both infertility and endometriosis e.g., body size or menstrual cycle characteristics.

3) Onset of endometriosis symptoms. To investigate risk factors, epidemiological studies should focus on incident cases as opposed to prevalent cases of disease. However, this is difficult when studying endometriosis because a “threshold” of symptoms must usually be reached before women seek a diagnosis and as a result, most investigations are actually investigating and estimating the incident of endometriosis diagnosis as opposed to onset, which is a problem

when high diagnostic delay is prevalent[72], as it is with endometriosis. Temporality is then an issue here, especially reverse causation. A modifiable risk factor may seem to be associated with higher risk of endometriosis but in fact it changed as a consequence of endometriosis symptoms or diagnosis[38].

1.7 Study setting

Cyprus is an island country located in the Eastern Mediterranean Sea just south of the Anatolian Peninsula. It is the third largest island in the Mediterranean lying east of Greece and south of Turkey. Geographically, Cyprus is located in Asia but is considered to be 'European' in terms of its culture and politics. The island is divided in two parts. The southern part is internationally recognised as the Republic of Cyprus but the northern part of the island, Turkish Republic of Northern Cyprus (TRNC), is only recognised by Turkey. The Republic of Cyprus joined the European Union in 2004 whereas Northern Cyprus has remained under economic sanctions for the past 40 years[253]. There are approximately 700,000 Greek Cypriots and 300,000 Turkish Cypriots living in Cyprus.

1.7.1 Healthcare in Northern Cyprus

There are four potential pathways to accessing healthcare in Northern Cyprus[253]. 1) The public healthcare system – this is a heavily discounted service providing individuals with social security insurance, which is mandatory for everyone in the workforce, their partners and those under 18. Services in accident and emergency departments are free of charge for everyone; 2) The private healthcare system – although the proportions of individuals purchasing voluntary private health insurance has increased in recent years, it is not widespread so there are high out-of-pocket health care costs; 3) Public services in Turkey – the Northern Cyprus government has a formal agreement with Turkey whereby individuals can be sent to Turkey free of charge for specialist

healthcare if the required services are not available within the public sector; 4) Public services in the Republic of Cyprus – since Turkish Cypriots are eligible for citizenship from the Republic of Cyprus, some choose to cross the border and receive healthcare from the public services in the South. It is thought only a small percentage of Turkish Cypriots choose to do this. Similarly, patients can access gynaecology and obstetrics services in public healthcare for free or opt to access private healthcare via their private insurance coverage and at their own expense. Due to the fragmented healthcare seeking behaviours, there is a lack of data on health needs and behaviours of the population of Northern Cyprus.

1.7.2 Rationale

Public health and the management of healthcare is reliant on systematic data collection and effective communication strategies. Current disease prevalence rates in the Turkish Republic of Northern Cyprus are in their infancy (established in 2002) and are not representative of the general population as they are limited to government-run hospitals[253]. Reliable population level data is needed to determine accurate, representative disease frequencies and their risk factors. Successful data collection programs have already been established in this area, for example the TPP, which managed to drastically decrease the rate of babies being born with thalassemia. There is a lack of reliable population-level health data from Northern Cyprus due to unresolved political circumstances[254] and as a result, this region is absent from any health statistics published by the Republic of Cyprus. Women's health cohorts such as the NHSII[255] in the US and the Million

Women Study[256] in the UK have been critical in investigating how different reproductive and lifestyle factors affect women's health. However, risk factors and disease presentation, may vary across different populations making generalisability of clinical guidance and management of these conditions difficult. Current epidemiological data is biased towards countries with comprehensive data collection systems. Furthermore, without understanding the burden of these diseases in each country or region, adequate service planning and policy improvements cannot occur. Given the lack of data in women's health from Northern Cyprus and the Eastern Mediterranean region in general, establishment of a women's health cohort in this region to investigate environmental factors was deemed necessary.

1.8 Thesis aims

The findings presented in this thesis are based on the analyses of data from the cross-sectional Cyprus Women's Health Research (COHERE) Initiative[257]. The COHERE Initiative is the first large-scale cross-sectional study in Northern Cyprus and will provide the first systematically collected population health data for the region. It aims to establish a women's health cohort in Northern Cyprus and to collect information on health, morbidity, resource use as well as investigate factors that affect women's health and their care seeking behaviour. The study will help to understand regional women's health and illness patterns as well as the personal, social, and economic burden of symptomatology and disease. The results produced from this study will form the basis of targeted follow-up studies that are driven by hypotheses based on real evidence. In

addition to this, the Cypriot adaptation of the 'Mediterranean lifestyle' will allow specific environmental and genetic factors to be investigated that are specific to the Eastern Mediterranean region. The results generated from this study have the power to enact real change by informing local health authorities about prevalence and distribution of women's health conditions which is information that can be used to develop evidence-based health strategies in the region. In order to collect these data standardised and previously validated epidemiological questionnaires such as the World Endometriosis Research Foundation's (WERF) Endometriosis Phenome and Biobanking Harmonisation Project (EPHect) were utilised and expanded to include generic instruments such as the Short Form Health Survey Version 2 (SF-36v2) and the Pain Catastrophising Scale (PCtS). Clinical information at clinical visits was obtained for a subset of women and information on diet was collected by utilising a Food Frequency Questionnaire (FFQ). Detailed information on the methods used in this study is described in *Chapter 2*.

This thesis has the following objectives:

- Quantify the prevalence of endometriosis in this population and investigate detailed pain symptomatology and phenotypic profiles of women with endometriosis. The results of these analyses are described in *Chapter 3*.
- Investigate the impact of endometriosis and its associated symptoms on quality of life and prevalence of psychological co-morbidities in this population. The results of these analyses are described in *Chapter 4*.
- Estimate work productivity loss and economic burden of endometriosis in this population. The results of these analyses are described in *Chapter 5*.
- Investigate potential dietary, menstrual, lifestyle, family history, and pigmentary risk factors associated with endometriosis and assess the prevalence of co-morbidities and deficiencies in this population of women. The results of these analyses are described in *Chapter 6*.

Chapter 2 - Methodology

2.1 Introduction

The COHERE initiative[257] is the first study to systematically collect population health data for Northern Cyprus, where public health issues have not yet been explored.

This chapter describes how recruitment of the study population took place, general demographics of the sample and assesses whether the population recruited is representative of the general population of women in Northern Cyprus. This is important to ensure future analyses on prevalence rates and risk factors have external validity. In addition to this, cross-sectional studies can often suffer from selection biases, so whilst women should be recruited into the study at random, certain numerical targets should be met depending on population densities of women in different regions. This chapter also describes baseline characteristics of the participants who took part in the Food Frequency Questionnaire (FFQ) and how normative values for the SF-36v2 were constructed and how they vary with demographic variables[258].

2.2 Methods

2.2.1 Eligibility criteria and baseline recruitment

Women aged 18-55 years, who were residents of Northern Cyprus or had been living there for at least the past 5 years and were able to give informed consent were eligible to take part in the study. Recruitment into the study took place between 31st January 2018 – 31st January 2020 and aimed to recruit 10% of women between the ages of 18-55 in Northern Cyprus (n=8,000). Participants were recruited into the study based on geographical recruitment targets from each of the 6 districts and 12 sub-districts; recruitment targets can be viewed in *Table 1.* These targets were based on 2011 census data.

Baseline assessment was conducted in two ways as detailed below and as depicted in *Figure 1*.

1) Face-to-face recruitment: The research assistants visited both workplaces and households and provided potential participants with an information sheet, remaining on hand to answer any questions potential participants had about the study. Women who were interested in participating were required to provide written consent.

2) Online recruitment: The study was publicised and promoted online, and prospective participants were able to complete an online version of the

questionnaire if they so wished. Online participants were given the same participant information sheet to read with the contact details of the Principal Investigator (PI) and research assistants who were available to be contacted to answer any questions. Women who wished to participate were directed to an online consent form and assigned a unique study ID. Women who chose not to complete the full questionnaire were given two options: i) quit without saving the parts they had already completed and effectively drop-out of the study or ii) submit the parts of the questionnaire they had already completed.

The baseline questionnaire is an expanded version of the World Endometriosis Research Foundation (WERF) Endometriosis Phenome and Biobanking Harmonisation Project (EPHect)-based health minimum questionnaire (*Appendix I & II*). The EPHect questionnaire is a standardised tool used to collect clinical and lifestyle information about endometriosis[259], and includes questions on self-reported medical history as well as associated symptomatology and menstrual patterns, parity, contraception/hormone use, life-style factors, family history, and health care sought including relevant expenses. It contains the following validated tools: Numerical Rating Scale for pain score[260], Pain Catastrophising Scale[261], Short Form McGill Pain Questionnaire[262], Rome IV diagnostic criteria[263], University of California San Diego Migraine Questionnaire[264], the Short-Form-36 Version-2 questionnaire[265], the Work Productivity and Activity Impairment tool[266] and the Nurses' Health Study II Activity Questionnaire[267]. The EPHect questionnaire was expanded for

this study to collect data on other benign women's health conditions relating to chronic pain, such as, bladder pain, bowel pain, migraines, endocrine conditions, uterine fibroids, and PCOS. The questionnaire asked participants about some specific lifestyle factors such as natural skin tone, number of moles, eye colour, hair colour, average sun exposure in both the summer and winter, use of sunscreen and use of solariums. This information is analysed in the risk factor chapter (Chapter 6). Participants were able to complete the questionnaire by tablet or paper-copy, of which the latter was entered into the electronic database by the research assistants on a weekly basis. Each consenting individual was assigned a unique study ID consisting of 6 random letters.

Numerical Rating Scales (NRS)

Numerical Rating Scales (NRS) have been utilised throughout the baseline questionnaire to collect information on pain severity (dysmenorrhea, dyspareunia, pelvic pain). The NRS is an 11-point numerical rating (0-10) scale that subjectively measures an individual's pain. The scale ranges from 0 (no pain at all) to 10 (worst imaginable pain). The NRS has been used extensively in women with menstrual pain and has been shown to have good construct validity[268,269]. Participants who score above 4 on the scale are classified as being 'in moderate to severe pain'[260].

Pain catastrophizing scale (PCtS)

The 13 item Pain Catastrophizing Scale (PCtS)[261] is a 13 item tool that measures the rumination (4 items), magnification (3 items) and helplessness (6 items) of pain. Catastrophizing is characterised by the tendency to magnify the threat of a pain stimulus and to feel helpless in the presence of pain in addition to the inability to prevent pain-related thoughts in anticipation, during or following a painful event[270]. For all four measures, a higher score indicates a high level of pain catastrophizing, with the PCS measure yielding a total score between 0-52. A total score of 30 or above is associated with a clinically relevant level of catastrophizing[261]. A validated, Turkish translated version was utilised for this study[271].

Short-Form McGill Pain Questionnaire (SF-MPQ)

The SF-MPQ is a multidimensional pain questionnaire that was designed to measure the affective and sensory aspects of pain and pain intensity[262,272]. The sensory subscale is comprised of 11 subclasses (throbbing, shooting, stabbing, sharp, cramping, gnawing, hot-burning, aching, heavy, tender, splitting) and the affective subscale 4 subclasses (tiring-exhausting, sickening, fearful, punishing-cruel); for each subclass participants are asked to describe their pain as either ‘none’, ‘mild’, ‘moderate’ or ‘severe’ and their answers are scored ‘0’, ‘1’, ‘2’ or ‘3’, respectively. Scores are summed to produce an affective and sensory score, as well as an overall readout with a higher score on the MPQ indicating

worse pain. Interpretation is in terms of quantity of pain, evidenced by the number of words selected, as well as the score of each subscale.

Rome IV diagnostic criteria for irritable bowel syndrome (IBS)

Establishing a diagnosis of irritable bowel syndrome (IBS) can be difficult as a confirmatory test is not currently available. The Rome diagnostic criteria[263] were first established in 1978 and most recently iterated in 2016, acting as a tool to aid practitioners in making an IBS diagnosis. The criteria can be used to identify IBS related or unrelated to the menstrual cycle. The tool can aid diagnosis of IBS in the last 3 months and relies on the definition of IBS in which recurrent abdominal pain is associated with defecation or a change in bowel habits. The tool is used to describe the frequency of IBS symptoms.

University of California San Diego (UCSD) Migraine Questionnaire

Occurrence of migraine was collected by using the previously validated University of California San Diego Migraine Questionnaire[264], which asks questions relating to occurrence and type of headache. Using the International Headache Society (IHS) criteria[273] for migraine with and without aura as given in the Little Black Book of Neurology[274], cases were recorded as either having migraine with aura or migraine without aura.

Migraine without aura was classified as follows:

- Participant has had at least 5 “attacks”.
- If left untreated, the duration would last between 4-72 hours.
- Participant has at least 2 of the following pain characteristics – a) unilateral, b) pulsating, c) moderate-severe intensity (inhibits or prohibits daily activity), d) increases with generalised physical activity.
- Participant experienced at least one of the following: a) nausea *or* vomiting, b) photophobia *and* phonophobia.

The IHS’s additional criteria is that the headache cannot be accounted for by another International Classification for Disease (ICD) code but, as access to full medical records were not obtained as part of this study, this could not be accounted for.

Short Form-36 Version 2 (SF-36v2) quality of life tool

There are several instruments available to evaluate health-related quality of life (HRQOL) with the best tools seeking to summarise three domains of HRQOL – biological functioning, social functioning, and psychological functioning. The tool used in this study was the SF-36v2 which has been previously validated in the Turkish speaking population[275]. Detailed methods are given in the analyses section of this chapter.

Work Productivity and Activity Impairment General Health (WPAI:GH) questionnaire

The Work Productivity and Activity Impairment General Health (WPAI:GH) questionnaire[266] comprises of 6 questionnaires that ask about the effect of health problems on the ability to work and perform regular activities. Health problems can be either physical or emotional and once scored, the amount of absenteeism (impact of symptoms on absence from work) and presenteeism (reduced productivity whilst working) can be quantified. Information from the WPAI:GH can also be used to calculate the economic burden of disease, the methods for which are detailed in Chapter 5.

Nurses' Health Study (NHS) II Activity questionnaire

The Nurses' Health Study II Activity Questionnaire[267] is a self-reported measure of weekly recreational physical activity estimated for the past year. It collects information on eight moderate and vigorous activates by asking for the average time per week spent on each activity. The intensity of each activity (defined in metabolic equivalents [MET]) is multiplied by the duration of each activity and can be summed to create total METs/week.

Turkish translation and adaptation of the EPHect questionnaire

The full protocol detailing how cross-cultural translation and adaptation of the EPHect questionnaire was carried out is detailed in full elsewhere[276]. It used a sample that consisted of 40 patients who underwent laparoscopic surgery in Turkey and 40 women in Northern Cyprus aged between 18-55. In brief, there were six phases for cross-cultural adaption:

1. Conceptual definition (ensuring concepts were culturally appropriate).
2. Forward translation (two translators translated the questionnaire from English to Turkish to reach a final consensus version).
3. Backward translation (the final Turkish version was back translated into English by a third translator and compared to the original English questionnaire).
4. Expert panel (the expert panel that reviewed the questionnaire was made up of 10 members including gynaecologists, basic scientists and an epidemiologist).
5. Cognitive interviewing (participants were asked to read the instructions, questions and answer options of the questionnaire and to indicate if there was anything unclear to them which was then reviewed by the expert panel).
6. Proofreading (ensured the Turkish EPHect questionnaire did not contain any errors or mistakes).

The questionnaire was found to be comprehensible, informative, and feasible in the two Turkish speaking populations as well as epidemiologically robust.

2.2.2 Anthropometric measurements

After the questionnaire was complete, basic anthropometric measurements were taken from consenting women. These included: height and weight using calibrated digital scaling instruments, waist and hip circumference using the WHO guidelines[277] and blood pressure using a blood pressure monitoring machine. Each measurement was taken twice if possible and averaged into one measurement. If there was a noticeable difference between the two measurements, a third measurement was taken. An average was computed using the collected measurements.

2.2.3 Clinical visit: ultrasound scan (USS)

At the end of the baseline assessment, all participants were invited to make an appointment at a gynaecology clinic with a gynaecologist for either a trans-vaginal or trans-abdominal ultrasound scan (USS). This was to examine the reproductive organs and to provide clinical information about the presence of endometriomas, polycystic ovaries or uterine fibroids. Participants had a choice of three gynaecology clinics that they could visit: two in Nicosia and one in Kyrenia. At the appointment, the gynaecologists completed a standardised form for each patient which included information on reproductive history such as date of last menstrual period and length of period. This form alongside images of the

reproductive organs were provided to the study and the information linked to the baseline questionnaire data using the participants study ID and birth year.

2.2.4 Online follow-up: Food-Frequency Questionnaire (FFQ)

Between July-October 2020, 919 women who had expressed an interest in taking part in future research were contacted to ask if they would like to take part in an online semi-quantitative FFQ. Within this group, endometriosis cases were prioritised, and a random selection of non-endometriosis cases were also contacted. Only a sub-set of the overall cohort were contacted as the FFQ is long and this acted as a pilot to understand the overall level of interest the cohort had in participating in follow-up studies. Those who agreed to take part were required to complete the previously validated Turkish questionnaire[278] which has been used in previous global studies[279,280]. The research assistants contacted participants by phone and if interested, they were provided with a link to the questionnaire which they accessed using their study ID and birth year.

The foods in the questionnaire were grouped into 6 groups representing the highest-frequency consumed foods in the Turkish cuisine – dairy, cereal, sweet, fruit, vegetables and oil and margarine. Local cookbooks were consulted to determine standard recipes from some of the most common dishes and some Turkish Cypriot regional foods were included in the FFQ. Frequency of food consumption was recorded in the following categories: >6/day, 4-5/day, 2-3/day, 1/day, 5-6/week/ 2-4/week, 1/week, 1-3/month, 1-none/month. For each food item, participants were asked to choose the size of their portion using images

(small, medium, large). Daily nutrient intake and daily food-group intake was then calculated using specialised software (EBispro, Stuttgart, Germany; Turkish version: BeBis version 9.2). The data source of this software was 97% Bundeslebensmittelschlüssel (BLS) Version II.3 and 3% United States National Nutrient Database for Standard Reference (USDA SR 19). The same software was used to calculate the daily consumption of each food group (g). Information on the number of meals participants ate per day, including regularity of eating at restaurants or ordering food to be delivered was collected, along with information on whether they took vitamin supplements, and if so, which ones.

Mediterranean diet score (MD score)

A Mediterranean diet (MD) score was created based on previous methods[281–283] and involved assigning a value of 0 or 1 to eight distinct food groups. The median score for each of the eight groups was used to determine cut-offs. For components of the Mediterranean diet that are considered beneficial to health (vegetables, fruits and nuts, legumes, cereal, fish and, olive oil), participants whose consumption was below the median score were assigned a value of 0, and participants whose consumption was at or above the median score were assigned a value of 1. For components that were not considered beneficial to health (meat and dairy), participants whose consumption was below the median were assigned a value of 1 and participants whose consumption was equal to or above the median were assigned a value of 0. The total Mediterranean diet score ranged from 0 (low adherence) to 8 (high adherence) and was

categorised into three groups – low (0-2), medium (3-5) and high (6-8). Though previous studies[281,282,284] have included moderate alcohol intake (5-25 g/day) as a key component of the Mediterranean diet, it was not included in this study due to the large number of participants reporting to not drink alcohol.

2.2.5 Data entry and storage

The data from the questionnaire was entered into an online system by the research team at the Eastern Mediterranean University (EMU) in Cyprus who would reference back to the original questionnaires on a case-by-case basis if requested. The paper-based questionnaires are archived locally until the end of the study (in 20 years) and the data are stored, maintained, and analysed on a secure server space in Cyprus and Oxford, UK.

2.2.6 My fieldwork in Northern Cyprus

Between November-December 2019, I spent 5 weeks undertaking fieldwork in Northern Cyprus. This fieldwork was paramount in helping me to understand the project and the geography of the local area, and I was able to meet the research team who had been recruiting women into the study. I accompanied the research assistants during some of their recruitment days and I was able to observe first-hand how recruitment took place. I spent time in the offices at EMU where I helped with the saliva sample packing and visited the gynaecological clinics where the USS scans took place. The patient records from the USS were all paper copies, which required me to spend some time

creating and entering them into a database, to be able to link participants to their questionnaire data using their unique ID. During my time in Northern Cyprus, I also worked with a local researcher to create a map to represent the area using QGIS. As the questionnaire data was in Turkish, I spent time with the research team to help me translate some of the variables, so I was able to recode and clean the dataset.

I returned to Cyprus for 2 months between May-July 2022. Here, I spent time verifying some of the questionnaire data which involved locating the paper copies of questionnaires and checking whether the data that had been entered was correct. I also conducted data checks for the FFQ and spent time with a faculty member in the Nutrition department at EMU to understand the FFQ dataset in more detail. During my time I also presented the first results from COHERE at EMU's Biotechnology seminar which was attended by faculty staff and students and met with Civic Space, a Technical Assistance Project funded by the European Union (EU), to discuss a funding application related to some analysis that I have carried out on Caesarean section rates in COHERE, which is not discussed in this thesis.

2.2.6 Ethics and funding

Two ethics approvals were obtained for the study: (1) International ethics approval from the Oxford Tropical Research Ethics Committee (OxTREC) of the University of Oxford (OxTREC reference: 37–17), (2) Local ethics approval from the Eastern Mediterranean University Ethics Committee (ETK00-2017-0240).

After the participant was informed about the study and decided to take part, a written consent was obtained.

Mustafa Bahceci (Bahceci Health Group, Istanbul, Turkey) donated funds to the University of Oxford towards the study. Dr Nilüfer Rahmioğlu (PI) crowdfunded for the project which raised a significant proportion of the funding necessary to conduct the study. EMU funded the local data collection. The study received communication funding including telephones, tablets, and call minutes/3G support from Vodafone Mobile Operation Ltd. The project also received local support from Cyprus Women's Health Research Society (CoHERS), which is a registered charity in Northern Cyprus. Through CoHERS, the study received European Union Civic Space support to put together short films to promote the project and inform potential participants.

2.2.7 Analyses

Demographic variables description

Age was described as both a continuous variable and a categorical variable with four levels (18-25, 26-35, 36-45, 46-55), ethnicity was divided into three categories (Turkish Cypriot, Turkish, Other/Mixed) with Other/Mixed comprising of women who identified as any other ethnicity apart from Turkish Cypriot or Turkish. Education was divided into 4 categories (Primary/Middle school, High school/Post-secondary, Undergraduate degree, Postgraduate degree) and employment into two (in paid employment, not in paid employment). Civil status was divided into three (single, married, divorced/separated), residence was divided into six districts (Famagusta, Kyrenia, Lefke, Morphou, Nicosia, Trikomo). BMI was calculated using both self-reported and measured data; measured data was preferred over self-reported data but in the absence of measured height and weight, self-reported values were used. The error in self-reported weight and height was calculated as the difference between self-reported and measured weight and height. Differences were also calculated for BMI and Pearson's correlations were used to assess the correlation between self-reported and measured variables. BMI was calculated as weight in kilograms divided by the square of height in meters and classified in accordance with the World Health Organization guidelines: underweight (≤18.5kg/m^2), healthy weight (>18.5kg/m^2 - ≤24.9kg/m^2), overweight (>24.9kg/m^2 - ≤29.9kg/m^2) and obese (>29.9kg/m^2). Displaced people were defined as those who reported to be born in Republic of Cyprus and this information was

analysed as a dichotomous variable (yes/no). Migrants were defined as those who reported to not be born in Northern Cyprus, or those who were born in Northern Cyprus but whose parents were not and was analysed as a dichotomised variable (migrant/non-migrant).

Smoking and alcohol

Participants were categorised as ever smokers if they answered 'yes' to having smoked over 100 cigarettes over their lifetime. Non-smokers were those who answered 'no' or did not answer the question. Alcohol drinkers were those who answered 'yes' to drinking any alcohol and non-drinkers were those who answered 'no' or did not answer the question. Participants were asked to state the average number of drinks consumed per week from the following list beer/lager/cider (330 mL), whisky (50 mL), wine (125 mL), spirits e.g., vodka (100 mL), raki (85 mL), shots e.g., zivania (15 mL) and cocktails e.g., gin and tonic, mojito (100 mL). Given the non-normal distribution of alcoholic beverages consumed per week, medians and ranges are presented.

Representativeness of the sample

The governmental offices in Northern Cyprus provided their 2019 population estimates as requested, into the following categories: district, sub-district, age, civil status, educational attainment, employment and occupation type (as classified using the International Standard Classification of Occupations 2008 (ISCO08))[285]. This census data was used to compare proportions of the above

demographics using the projected population values with the proportions of the same demographics in COHERE. If a proportion of a demographic in COHERE was within 5% (above or below) of that belonging to the census, then the demographic target was considered to have been met and was therefore representative. Differences between women with and without an USS were compared using t-tests for continuous variables and chi-squared tests for categorical variables. Logistic regressions were used for binary outcomes and to adjust analyses for confounders.

Mapping

Since there was not already a map of Northern Cyprus that was publicly available, the map needed to be created from scratch. The base map (i.e., the outline of the country) was created using Google Maps, which allowed for only the northern part of the island to be selected. Using information from the local authorities as well as local knowledge, certain boundaries and areas located within Northern Cyprus were able to be joined together and numbered. The map was then imported into Quantum Geographical Information System (QGIS), and the numbering acted as an ID for each area, or object. Objects were then merged to create 4 different layers of the map as follows: 1) District - comprises of 6 main areas, 2) Sub-district – each of the 6 main areas are split into towns/villages or cities, giving 12 sub-districts, 3) Municipality – comprised of a further 28 areas and 4) Neighbourhood – comprised of 209 areas. Each of these four layers is known as a shape file, which is a geospatial vector data format used in QGIS. Statistics are usually displayed on the District or

Subdistrict level, to ensure a large enough sample size is used. In this chapter, the map is used to display recruitment statistics. The proportion of women in each District was calculated as described above and these percentages were then imported as a spreadsheet file into QGIS. Once the data was in QGIS, a common variable between the spreadsheet and map (in this case District) was 'joined' so that other variables, i.e., number recruited, could be matched to the map itself. Colour was used to display whether an area was under sampled, over sampled or within an acceptable range. When a difference was seen at the District level, statistics were plotted on the Sub-District level, to see whether the difference existed in both the towns and cities of that District, or whether the under- or over-representation occurred in only one. This method was used to visualise certain other demographics related to recruitment i.e., age, and is used in *Chapter 3* to investigate the prevalence rate of endometriosis.

Key characteristics of the cohort

To effectively interpret information on prevalence rates and burden of endometriosis in future chapters, it is necessary to understand and contextualise the broader healthcare landscape of the region. A description of the care patterns of the whole cohort, including information on gynaecology visits (ever visited and mean age of first visit), medical screenings (ever had a Pap-smear test, regularity of Pap-smear tests, mean age of first Pap-smear test, ever had human papillomavirus vaccine (HPV) (between the ages of 18-35 as the vaccine was not approved until 2006), self-examination of breasts regularly and ever had clinical breast screening (over the age of 30 only) and

regularity of breast screening and hormone use, is presented in this results chapter.

SF-36v2

Within the SF-36, there are 36 items that measure 8 domains. Scores are commonly calculated into separate domains (ranging from 0-100) and are as follows: limitations in physical activity due to health problems (physical functioning, 10 items), limitations in social activities due to physical or emotional problems (social functioning, 2 items), limitations in usual role activities due to physical health problems (role physical, 4 items), limitations in usual role activities due to emotional problems (role emotional, 3 items), well-being and psychological distress (mental health, 5 items), energy and fatigue (vitality, 4 items), bodily pain (bodily pain, 2 items) and perceptions of general health (general health, 5 items). Within the 36 items, there is a singular additional question asking about changes in health over the past year. Using the methods set out by Ware *et al.,*[265] the items within each of the above dimensions were coded, summed, and transformed (calculated by subtracting the lowest possible raw score from the actual raw score, dividing by the possible raw score range, and multiplying this by 10. This gave a scale from 0 (worst possible health state as measured by the questionnaire) to 100 (best possible health state).

SF-36v2 component summary scores

To aid interpretation of the data, the developers recommend that a normative-based scoring method using weights derived from the US population is used to provide a standard with which scores from other populations can be compared. However, there is much discussion[286] surrounding whether it is appropriate to use weights that may not be culturally specific, especially when there are differences in health states. When cultural factors affect how individuals respond to self-reported health status questionnaires, the comparability of the outcomes between different cultural groups may be limited. This constrains the validity of these instruments in determining differences in actual health status between different cultural groups. Therefore, because there are clear differences in healthcare and culture between Northern Cyprus and the US, it was decided that normative values should be produced using the COHERE dataset. In *Chapter 4* of this thesis, HRQOL is investigated in relation to different disease types, and scoring coefficients from the appropriate country are used to make valid comparisons with published literature.

Following the methods set out in the SF-36v2 manual[265], the data was factor analysed to produce scoring coefficients (factor loadings) for the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores. In short, principal components analysis was used to produce factor loadings, and an orthogonal varimax rotation was applied to these loading and subsequent scores obtained. Calculating PCS involved multiplying each SF-36 scale z-score (calculated by subtracting the mean of SF-36 scale and dividing

the difference by the corresponding scale standard deviation) by its respective factor score coefficient and in the case of the MCS, this involved multiplying each SF-36 scale z-score by its respective factor score coefficient.

Z-score calculation:

$$\mathrm{z} = \frac{(X - \bar{X})}{\mathrm{SD}}$$

In this instance where;

- X represents the mean score in the study sample that will be compared with the population norm;

- $\bar{X}$ is the population norm; and

- SD represents the population standard deviation.

Finally, a T-score transformation was used to standardise the scores whereby the mean was set to 50 and the standard deviation to 10. PCS and MCS are two clusters that are produced from each of the eight scales and allow for further interpretation of the results. The statistical formula to calculate these T-scores is as follows:

$$\mathrm{T} = \left(\bar{X}' + \mathrm{SD}'\right) \mathrm{z}$$

In this instance where;

- $\bar{X}'$ represents the new mean (set at 50 for PCS and MCS);

- SD' represents the new standard deviation (set at 10 for PCS and MCS); and

- z represents the original z-score.

Although no previous studies have investigated the SF-36v2 measures in Northern Cyprus, a cross-cultural adaptation of the survey was shown to be successful in Turkey and demonstrated an acceptable level of reliability and validity in its use in Turkish speaking individuals[275,287]. To investigate whether the SF-36v2 questionnaire was valid in Northern Cyprus, reliability and validity was assessed as follows:

Reliability

Cronbach's alpha was used to examine internal consistency reliability; a value of >0.7 was considered satisfactory. To assess whether the summary measures, PCS and MCS were reliable, the reliability of each of the eight subscales, the covariances among them and the factor score coefficients were calculated.

Validity

Principal components analysis, item-subscale correlations (item-rest correlations for the subscales and their respective items) and inter-scale correlations (Spearman correlations) were used to assess construct validity. A value of > 0.4 for item-rest correlations was considered satisfactory. If the correlation between an item and the sum of the other items its respective subscale (item-rest correlation) was shown to be significantly higher than its correlation with other subscales (item-subscale correlations) then the item's inclusion in its subscale was supported. If the correlation between two subscales was less than their reliability coefficients (Cronbach's alpha), then it can be said that there is evidence of reliable variance measured by the respective subscales.

Missing data

As the sample size for the cohort was large (n=7,646) and the intention of this primary analysis was to obtain the factor loadings to construct the summary scores, data substitution algorithms were not used. In addition to this, there has been speculation that substitution of mean values may have either a conservative or attenuated bias[288]. Given these are the first normative scores to be calculated for women in Northern Cyprus between the ages of 18-55, it is also important to report 'actual' scores, so that normative scores here can be used for future analyses and are not differentially attenuated according to the amount of missing data that has been recorded. This approach is consistent with previously published studies[286,289].

Statistical analysis

Descriptive statistics for each of the eight subscales for the included sample and different subsamples according to age, ethnicity, migration status, educational achievement, civil status, city of residence and employment status were calculated. Differences in means of the eight health subscales for each of the subscales were tested using linear regression. Regressions were computed both crudely and after adjustment for age, as age is usually correlated with the covariates examined here. Regressions for ethnicity and migration status were additionally adjusted for educational achievement and employment classification, as these two demographics are often correlated with non-native people.

2.3 Results

2.3.1 Recruitment statistics

The total number of consenting women included in this study is 7,646; a flow-chart depicting how the study population was selected can be seen in *Figure 2.* Dropouts were defined as participants who gave consent to be included in the study but later withdrew their consent, whereas non-starters were women who agreed to take part in the study but did not end up doing so. There were 55 women who initially gave consent but later withdrew, giving an overall drop-out rate of 0.7% compared to 637 non-starters which gave an overall non-starter rate of 8.3%. There was little variation in dropout rates when comparing the number of dropouts in each region with the number of women who were

recruited in each area (0.4-0.9%) and the rate of non-starters ranged from 2.5% in Trikomo and to 8.7% in both Nicosia and Lefke (*Table 2*). Non-governmental workplaces (e.g., markets, banks, shops) were the most common place that dropouts were recruited from (41.9%) and dropout rates for each location varied from 0.0% in households, to 1.2% in non-profit-civil-society-organisations. In agreement with the dropouts, the non-starter rate was highest in those recruited in non-profit organisations (22.9%) and lowest in governmental workplaces (7.8%). The majority of the non-starters (41.4%) were recruited from non-governmental workplaces. The most common reason for participants to dropout from the study that they had 'lost the questionnaire' (32.7%), followed by finding the questionnaire 'too private' (18.2%). Non-starters were more likely to cite the reason for their lack of involvement in the study to be because the questionnaire being 'too long', followed by no reason given (27.6%). The average age of study dropouts was 37.3 (n=55), compared to an average age of 36.9 (n=7,647) in the COHERE cohort ($p<0.001$). The average age of the non-starters was 38.6 (n=363) which was also significantly older when compared to the overall COHERE cohort ($p<0.001$). A total of 7,128 women were recruited face-to-face (93.2%) with the remaining 6.8% (n = 518) being recruited online. Of the 93% who were recruited face-to-face, 84.4% (n=6,555) were recruited in their workplace with the remaining 15.6% (n=1,209) being recruited during the household visits.

2.3.2 Key cohort demographics

Average BMI based on self-reported data was lower than measured BMI (0.71, 95%CI: 0.60-0.81), because of underreporting of weight (0.71, 95%CI: 0.99-1.53) (*Table 3*). There was a negligible difference between self-reported and measured height (-0.01, 95%CI: -0.00-0.00). The Pearson's correlation coefficients between self-reported weight, height and BMI were high at 0.97, 0.92 and 0.96, respectively.

Table 4 shows the demographics of the 7,646 women aged 18-55 included in the study after exclusion of women with missing data. The mean age of the women was 36.9 (SD=9.6), the most common age category was 36-45 (32.0%) and the least common was 18-25 (14.5%). Most women recruited identified as Turkish Cypriot (70.3%), followed by Turkish (19.9%) and 4.5% (n=334) of women were categorised as displaced i.e., they were born in Republic of Cyprus and now reside in Northern Cyprus. One third of women had an undergraduate degree (33.8%), with high school/post-secondary education also being common (33.4%); 13.8% of women recruited were currently still in school. Most women were currently in paid employment (77.5%), and most were married (63.3%). Over two-thirds of women reported to be currently living with a partner (64.8%) and 17.7% of women were not in a relationship. Nearly fifty percent (49.8%) of women fell within the 'healthy weight' category for BMI as defined by the WHO and the most populous district women lived in was Nicosia

(43.2%). Levels of missing data were low and <5% apart from education (6.0%), cohabitation status (5.8%) and BMI (6.7%).

Smoking and alcohol intake

A total of 2,121 (27.7%) women reported to drink any alcohol. Of those who reported to drink each alcoholic beverage in an average week, median number of alcoholic drinks consumed were as follows: beer/larger/cider – 1 (range: 1-30), whisky – 1 (IQR: 1-10), wine – 1 (range: 1-10), spirits – 1 (range: 1-10) raki – 2 (range: 1-20), shots – 2 (range: 1-33) and cocktails – 1 (range: 1-12). Differences in demographics between those who reported to drink any alcohol and those who did not report to drink alcohol are presented in *Table 5.* There were significant differences in all demographics examined between women who reported to drink alcohol and women who reported to not drink alcohol. Compared to those who did not drink alcohol, women who drank were more likely to be younger (18-25: 19.5% vs 12.6%, 26-35: 37.2% vs 28.9%, p<0.001), identify as Turkish Cypriot (78.3% vs 71.9%) and not Turkish (15.0% vs 23.4%) (p<0.001), more likely to have an undergraduate (42.6% vs 33.2%) or graduate (24.2% vs 13.7%) degree (p<0.001), more likely to be single (35.8% vs 19.3%) or divorced/separated (11.9% vs 8.4%) (p<0.001) and live in the cities (51.2% vs 45.5%, p<0.001) such as Nicosia (52.8% vs 39.5%) and Kyrenia (18.9% vs 15.6%) (p<0.001). Women who drank were also more likely to not be displaced (28.3% vs 15.9%) (p<0.001) and not be migrants (30.8% vs 23.6%) (p<0.001).

With regards to smoking, 30.7% (n=2,350) of participants reported to have smoked more than 100 cigarettes in their lifetime and the mean age of starting smoking was 20.3 years (95%CI: 20.1-20.5). The majority (76.6%, n=1,800) of women who had ever smoked still currently smoked and the mean number cigarettes smoked per week was 69.0 (95%CI: 66.3-71.6). There were several significant differences between women who had ever smoked and women who had never smoked (*Table 6*). Compared to never smokers, ever smokers were more likely to between the ages of 36-44 (36.9% vs 29.8%, p<0.001), identify as Turkish (27.3% vs 17.9%) or Other/Mixed (7.0% vs 4.5%) (p<0.001), be employed (83.6% vs 79.9%, p<0.001), divorced/separated (14.1% vs 7.2%, p<0.001) and live in Kyrenia (19.7% vs 15.1%, p<0.001). Women who reported to have ever smoked were more likely to not be displaced (31.0% vs 24.9%) (p<0.001) and more likely to be migrants (42.8% vs 28.5%) (p<0.001). There was no significant difference between the two groups when examining education attainment or residence type.

2.3.3 Recruitment targets

Using the geographical recruitment targets set out in *Table 1, Table 7* shows the original recruitment targets with the addition of the numbers of women recruited who resided in each district and subdistrict. On the district level, recruitment targets were broadly met for Famagusta, Morphou, Trikomo and Lefke, with over-recruitment in Nicosia (aim: 2,716 (34.0%), recruited: 3,301 (43.0%)) and under-recruitment in Kyrenia (aim: 1,912 (24.0%), recruited: 1,263

(16.5%)). On the subdistrict level, there was over-recruitment in the towns and villages of Nicosia (aim: 315 (4.0%), recruited: 1,410 (18.4%)), Famagusta (aim: 516 (6.0%), recruited: 741 (9.7%)) and Kyrenia (aim: 104 (1.0%), recruited: 1,058 (13.8%)) and under-recruitment in the city of Famagusta (aim: 516 (6%), recruited: 741 (9.7%)). Actual recruitment and recruitment targets could not be compared on the subdistrict level for Morphou and Lefke due recruitment target information not being available on the subdistrict level for these regions.

2.3.4 Representativeness of the cohort

During planning of the recruitment for the study, only 2011 census data was available, so recruitment targets were set based on these. However, in 2021, the 2019 census projection became available from the Statistics office in Northern Cyprus, allowing for comparison with these here. On the district level, Nicosia was oversampled (census: 32,503 (32.9%), recruited: 3,301 (43.2%)) and Kyrenia under-sampled (census: 23,848 (24.2%), recruited: 1,263 (16.5%)) (*Figure 3a*). Further breaking this down by subdistrict (*Figure 3b*) shows that within Nicosia, the town/village areas were over-sampled (census: 11,880 (12.0%), recruited: 1,410 (18.4%)) and within Kyrenia, the city was under-sampled (census: 11,966 (12.1%), recruited: 205 (2.7%)), when looking at numbers recruited in COHERE as a proportion of the overall number of women recruited.

When looking at age, the COHERE cohort over-represented women between the ages of 36-45 (census: 25,318 (25.7%), recruited: 2,447 (32.0%)) and underrepresented younger women between the ages of 18-25 (census: 22,355 (22.7%), recruited: 1,108 (14.55%)) (*Table 8*). Delving further into this by exploring recruitment of 18–25-year-olds by district, *Figure 4a* shows that Nicosia, Kyrenia and Lefke were the main areas where under recruitment of this age group occurred (Nicosia: census: 8,396 (25.8%), recruited: 406 (12.3%), Kyrenia: (census: 4,420 (18.5%), recruited: 158 (12.5%) and Lefke: (census: 1,184 (32.1%), recruited: 28 (10.7%)). For the over recruitment of 36-45-year-olds, the most noticeable districts where over recruitment took place was in Nicosia, Morphou and Lefke (Nicosia: census: 8,149 (25.1%), recruited: 1,121 (34.0%), Morphou: (census: 1,445 (23.7%), recruited: 180 (30.8%) and Lefke: (census: 1,940 (52.6%), recruited: 86 (33.0%)) (*Figure 4b*).

Regarding highest level of education attained, COHERE was under-representative of women with primary/middle school education (census: 28,426 (33.4%), recruited: 845 (11.8%) and over-representative of women with university (census: 19,713 (23.2%), recruited: 2,583 (35.9%)) and postgraduate (census: 5,206 (6.1%), recruited: 1,204 (16.8%)) education (*Table 9a*). The under-representation of primary/middle school education was apparent in all areas (*Table 9b*) and when considering high school/post-secondary education (*Table 9c*), there was under-representation in Lefke (census: 1,808 (45.5%), recruited: 75 (28.7%)) and Kyrenia (census: 12,048 (49.1%), recruited: 392

(31.0%)). Both university and post-graduate degrees were over-represented in all areas (*Table 9d and e*).

For employment status (in paid employment, self-employed and not in paid employment), students, homemakers and retirees were excluded from the calculations. When comparing employment status between the census and COHERE, targets were considered met (paid employment: census: 41,689 (88.8%), recruited: 5,436 (88.6%), self-employed: census: 4,440 (9.4%), recruited: 480 (7.8%), not in paid employment: census: 871 (1.9%), recruited: 220 (3.6%) (*Table 10a*). The COHERE study population was found to be representative of retirees (census: 971 (0.9%), recruited: 23 (0.3%)) but under-representative of homemakers (census: 18,551 (18.8%), recruited: 795 (10.4%)) (*Table 10b*). Homemakers were found to be under-represented in Nicosia (census: 4,970 (26.8%), recruited: 121 (15.2%)) and Kyrenia (5,183 (27.9%), recruited: 108 (13.6%)) but under-represented in Morphou (census: 1,291 (7.9%), recruited: 119 (15.0%)) and Trikomo (census: 1,462 (7.9%), recruited: 236 (29.7%)) (*Table 10c*).

For civil status (married, single, divorced/widowed), the COHERE study population was found to be representative for single (census: 24,130 (23.3%), recruited: 1,753 (24.1%)), married (census: 72,311 (70.0%), recruited: 4,839 (66.5%)) and divorced/widowed women (census: 6,917 (6.7%), recruited: 684 (9.4%)) (*Table 11*).

2.3.5 Pelvic ultrasound demographics

Six-hundred-and-sixty-eight women participated in a pelvic ultrasound scan as part of their recruitment into the study (8.7%). Highest clinical visit rate was observed in Nicosia (12%, n=395) and Kyrenia (12.3%, n=155) with rates being lower in other areas (Range: 2.1% (n=13) in Trikomo and 8.8% (n=23) in Lefke) (*Table 12a*). When examining these frequencies as a proportion of the total number of women living in these areas, Nicosia and Kyrenia continued to have the highest attendance at 12%, with Trikomo and Famagusta having the lowest rate (2.1% and 2.6%, respectively). In terms of age frequencies, women between the ages of 36-45 had the highest gynaecological clinic attendance (34.3%, n = 229) however, when examining the rates, the highest rate of attendance was in women between the ages of 46-55 (12.9%) with the lowest rate being found in women between the ages of 18-25 (5.4%). Women identifying as Turkish Cypriot had the highest clinic attendance (72.7%) but women with Mixed/Other ethnicities had the highest relative attendance (12.1%) compared to Turkish Cypriot (8.6%) and Turkish (8.4%) women. Women with an undergraduate degree were the most common group to attend the scan (37.7%) but relative frequency was similar between educational achievements (range = 8.0-9.3%). Most women were married (69.0%) but women who were divorced/separated had the highest relative frequency of attendance (12.1%) compared to women who were single (6.6%) and married (9.1%).

When comparing demographics between women who did and did not have a pelvic scan (*Table 12b*), women attending the scan tended to be older (39.8 vs 36.6, p<0.001) and therefore more likely to belong to the 36-45 and 46-55 age group (34.3% vs 31.8% and 33.1%. vs 21.3%, p<0.001) and less likely to belong to the younger age groups. There was also a statistically significant difference (p<0.001) between residency; frequencies of women attending a pelvic scan were highest in Nicosia (59.1%) and Kyrenia (23.2%) compared to 41.6% and 15.1% for in women without a pelvic scan, respectively, even after adjustment for age. Women in the non-pelvic scan group also had a higher frequency of living in Famagusta (22.5%) compared to 6.3% in the pelvic scan group. Comparing education, women attending the scan were more likely to have an undergraduate (35.8% vs 33.6%) or postgraduate (16.7% vs 17.7%) degree compared to women without a pelvic scan, and this was significant after adjustment for age. There was a significant difference (p<0.001) in employment levels; women attending the scan had higher levels of employment than those not attending (90.7% vs 80.1%). There was no significant difference in civil status between the two groups after adjustment for age.

2.3.6 Food-frequency questionnaire (FFQ)

A flow-chart depicting how the FFQ sample was selected can be seen in *Figure 5*. Nine-hundred-and-nineteen women were contacted and asked if they wanted to complete the FFQ, and a total of 575 women agreed, giving a 62.6% response rate. The most common reason for declining was that they did not

have time to complete the questionnaire (48.5%, n=167), followed by not wanting to complete an online questionnaire (16.6%, n=57) and not answering the phone (15.4%, n=53). Following on from this, a further 12 women were excluded as they were unable to be matched with the baseline questionnaire and 50 women were excluded as their total energy intake was deemed implausible (<800 kcals/day or >4,200 kcals/day).

There were significant differences in demographics between women who completed the FFQ and women who did not after adjustment for age (*Table 13*). Women who completed the questionnaire were more likely to be younger (mean age: 35.3 vs 37.0, p<0.001), more likely to identify as Turkish Cypriot (79.9% vs 73.3%, p=0.017), more likely to have an undergraduate or postgraduate degree (44.4% vs 35.3% and 23.1% vs 16.3%, p<0.001), more likely to be single (31.9% vs 23.5%, p=0.008) and more likely to not be a recent migrant (19.9% vs 25.8%, p=0.006).

In terms of frequency of meals, the majority of FFQ participants reported to eat breakfast (62.9%, n=322), lunch (69.8%, n=358) and dinner (70.0%, n=359) every day, with low numbers of participants reporting to never eat these meals (5.5%, n=28; 2.3%, n=12 and 1.2%, n=6) (*Table 14a*). The large majority (47.0%, n=241) reported to rarely or never eat out or eat takeaway food, with the second most common answer being 2 days/week (32.6%, n=167). One-third (33.1%, n=170) of FFQ participants reported to eat snacks 2 times/day,

followed by 3 times/day (33.1%, n=170), with 14.0% (n=72) of participants reporting to rarely or never eat snacks (*Table 14b)*.

Average energy intake and nutrients consumed through diet per day are listed in *Table 15,* alongside Recommended Daily Intake (RDI) values where available*.* Mean energy intake in those completing the FFQ was 2,408 kcals/day, which is higher than the recommended 2,000 kcals/day. On average, protein, carbohydrate, and fat made up 18.1%, 38.0% and 43.9% of the average diet and compared to the RDIs, fat was higher than the recommended 25-35% and carbohydrate lower than the recommended 45-65%. For minerals, average intakes were above the RDI for all apart from selenium (mean and median intake:11.9 and 9.4 µg vs RDI: 55.0 µg). Consumption of sodium exceeded the recommended intake of 2,300 mg at a mean of 2,614 mg and median of 2,439.1 mg. Average vitamin intake was above the RDIs apart from Vitamin D (average intake: 4.9 µg vs RDI: 20.0 µg). Intake of Vitamin A was much higher in the study at 2,739.7 µg compared to the RDI of 900.0 µg. Levels of cholesterol were much higher than recommended in this study with the average intake being 421.0 mg compared to the RDI at 300.0 mg.

A total of 119 (23.2%) women who completed the FFQ reported to take vitamin supplements. The most common supplement taken was Vitamin D (12.2%, n=64), followed by Vitamin C (10.8%, n=56) and multivitamins (8.3%, n=43). The least common vitamin supplemented was Vitamin A, with only 1.8% (n=9) of FFQ participants reporting to take this.

Mediterranean diet (MD) score

Regarding the MD score, 17.5% (n=90) of FFQ participants scored between 0-2 and were categorised as having a low adherence diet, 63.0% (n=323) scored between 3-5 and had medium adherence and 19.5% (n=100) scored between 6-8 and had a high adherence. The demographics between the three groups are compared in *Table 16.* There were no significant differences between demographics of the three groups but in general, a larger proportion of women in the high MD score group were older, compared to women in the low MD score group (23.0% vs 13.3%) (p=0.608), women who identified as Turkish were more likely to have a high MD score than a low MD score (20.0% vs 6.7%) and Turkish Cypriot women were more likely to have a low MD score (84.4% vs 75.8%) (p=0.228). Women who were employed had a higher proportion of women with a high MD score than a low MD score (86.3% vs 78.9%) as did married women (66.3% vs 52.2%) (p=0.587). There was little difference in MD scores when considering residence type or city of residence.

Table 17 shows the categories of the MD score and intake of dietary variables using the medians as the cut-offs. High MD scores are characterised by high intakes of vegetables, legumes, fruits and nuts, cereals, fish and olive oil, and lower intakes of meat and dairy products. Positive trends are evident for MD score and total energy intake, vegetable oils and fats, butter and margarine, eggs, potatoes, and tea/coffee consumption, whereas for sweets there was a slightly negative trend with MD and for non-alcoholic beverages, this did not

exist. Positive trends between MD score and percentage of energy obtained from carbohydrates, but not protein or fat.

2.3.7 Access to care and hormone use

The mean age women reported to have first visited a gynaecologist was 21.4 (SD=4.7) years. Forty-point-eight percent (n=3,121) of women reported to visit the gynaecologist once a year (*Figure 6*), with 62.3% (n=4,837) reporting to have ever had a pap smear. Only 7.7% (n=425) of women between the ages of 18-35 had ever had the HPV vaccine with 34.1% (n=2,609) of women aged over 30 ever having had a clinical breast screening. Over two-thirds (69.6%, n=5,322) of women reported to regularly examine their breasts. Of those who reported to have ever had a Pap-smear and gave information about their regularity (97.5%, n=4,716), 43.6% (n=2,054) reported to have them once a year with 35.6% (n=1.679) stating they did not have them regularly (*Table 18*). Of those aged over 30 who reported to have ever had a clinical breast screening and provided information on regularity (74.6%, n=1946), 48.0% (n=934) reported to have the screening annually, with 19.4% (n=378) reporting to have it every 5 years. (*Table 18).* The mean age of first breast screening was 34.7 (SD=8.1) and the mean age of first pap-smear was 30.8 (SD=6.9).

Hormone use in COHERE was low; 24.1% (n=1,845) of women stated that they had used hormones and gave information about which they had used. The combined birth control pill was the most common, with 65.6% (n=1,210) of

women who had used hormones reporting to use this, with the average length of use being 2.7 years (SD=3.9). The next most common type of hormones used was oral progestins to regulate the cycle, which was used by 10.8% (n=200) of women who had used hormones in COHERE and had an average length of use of 1.4 years. Frequencies of all hormones is displayed in *Table 19*.

Just under 20% of women reported to have ever used the non-hormonal copper coil (18.6%, n=1,424) and the mean age of first use was 28.3 (5.4). Similarly, 18.9% of women stated that they had ever used emergency contraception at least once, with the mean number of times of use being 2.8 (3.7, range: 1-38).

2.3.8 SF-36v2

Validation of the SF-36v2

Regarding reliability, Cronbach's alpha coefficients were found to be satisfactory (>0.70) for all health domains (*Table 20*), apart from general health (0.69). Reliability of the summary measures was 0.89 for both PCS and MCS[258].

When looking at validity, item-rest correlations were all satisfactory apart from PF10 of the physical functioning perception subscale (0.38). The principal components analysis produced two factors with eigenvalue >1 which indicates a two-factor structure. All items were satisfactory when looking at differences between item-rest correlations and inter-scale correlations i.e., correlations were higher between individual items and their respective subscales, than between

individual items and the other 7 subscales. It was also found that the correlations between subscales were lower than their respective Cronbach's alpha values which suggest that there is unique reliable variance (*Table 20*). Ceiling effects were highest in physical functioning and role physical subscales (39-42%) with the bodily pain subscale having the highest floor effect (1.20%).

Health domain subscales

Women who were younger had better physical health (PF, RP, BP) compared to older women but as age increased, mean scores for the mental health subscales also increased (VT, RE, MH) (*Table 21*). Though GH increased with age, this was not statistically significant. When considering ethnicity, women who self-reported to be Turkish had lower scores across all domains except PF and these scores remained statistically significant after adjustment for age (*Table 22*). Women who were not migrants had higher subscale scores for all the domains compared to women with a migration background (PF, BP, GH, VT, SF, RE, MH (*Table 23*). After adjustment for age, married women generally had the best mental health (MH, RE, SF) but the worst physical health (PF, RP, BP) (*Table 24*). Residency of the women in COHERE did not appear to significantly affect physical or mental health domains (*Table 25*). As educational attainment increased, mean physical health also increased after adjustment for age, (PF, RP, BP, GH) as did mental health domains (VT, RE and MH) (*Table 26*). Generally, women who were employed had better physical subscale scores (PF, RP, BP, GH) with only the VT mental health score remaining significant after adjustment for age (*Table 27*).

SF-36v2 summary measures PCS and MCS

Principal components analysis and orthogonal rotation was used to factor analyse the data and led to a two-factor solution; factor labelled PCS gained an eigenvalue of 4.00, with MCS having an eigenvalue of 1.14. There was better physical health (PCS) in younger women and better mental health in older women (*Table 28*). Higher scores were seen in women with a higher educational achievement and those in paid employment. Single women appeared to have the best physical health and the worst mental health (mean age in single women = 27.03 (SD = 7.20) vs married women = 39.74 (SD = 8.16)). Women residing in Morphou had the lowest PCS scores and those in Famagusta the worst MCS scores, with women in Kyrenia having the highest PCS scores and those in Lefke the highest MCS scores. These associations were not significant once adjusting for age (mean age and SD in each district as follows: Famagusta (mean = 35.5(SD = 9.8)), Kyrenia (mean = 37.2 (SD = 9.4)), Lefke (mean = 38.1(SD = 9.5)), Morphou (mean = 37.6(SD = 10.2)), Nicosia (mean = 37.4(SD = 9.3)) and Trikomo (mean = 36.1(SD = 10.3)) (*Table 28*). Turkish Cypriot women had both the best physical (with other/mixed ethnicities) and mental health scores after adjustment for age as did those women with a non-migration background. After further adjustment for education and occupation classification, associations were especially attenuated for migration status and health scores and although the effect was slightly lessened between ethnicity and the two health scores, associations remained significant for both PCS and MCS.

Comparison of summary scales

Since the transforming of scores to have a mean of 50 and a standard deviation of 10 involves using country-specific algorithms, there are differences when using summary scores from UK and US population in the COHERE dataset (*Table 29*). Compared to the Northern Cyprus scores, using US scores gave a slightly higher PCS score (51.70 vs 50.10) and a much lower MCS score (43.70 vs 50.01), whereas using the UK scores gave both a lower PCS and MCS (48.30 and 46.70). Results from the paired t-test suggested that there were significant differences between the methods of calculating the summary scores ($p<0.001$ for all comparisons), which suggests that country-specific scores may be appropriate. To make valid, international comparisons, endometriosis-specific scores will be presented using Northern Cyprus, US, and UK scores, in subsequent chapters, where appropriate.

2.4. Discussion

2.4.1 Recruitment and demographics

The COHERE Initiative successfully recruited 7,646 women between the ages of 18-55 in Northern Cyprus. There was a low drop-out rate of 0.7% for women who withdrew consent and 8.3% for women who did not start the questionnaire and very little geographical variation in dropout rates in each region, compared to the numbers of women who were recruited into the cohort. There was a significant difference between the mean age of women recruited into the study

and the mean age of both the dropouts and the non-starters – women recruited were more likely to be younger than those who dropped out, though only by 1 or 2 years which is not likely to significantly impact conclusions drawn from these results. As other demographic information was not collected from women who dropped out of the study, we were unable to compare if there were any differences between women in the study and dropouts. Location of recruitment of dropouts and non-starters was highest in non-governmental workplaces which is likely because women working in these positions would only have a short amount of time available to complete the questionnaire so would often end up wanting to take the questionnaire away to complete it at home, but this was often not followed through. The most common reason for participants to drop out from the study was that they had 'lost the questionnaire' but it is likely that participants using this reason did not want to complete it.

During the recruitment process, there was great emphasis on recruiting women in the towns/villages as it was believed that it would be harder to recruit women from these areas in comparison to recruiting women in the city. As a result of this, women living in the city of Kyrenia were under-sampled by around 10%. Recently, Kyrenia city centre has gone through a period of transition and commercialisation so many people moved to the towns/villages. Because the 2019 census data used here is a projection, it may mean that it is wrongly overcounting these people in the cities which can explain some of the discrepancies. In addition to this, there was general over-recruitment in Nicosia, the capital, which may have been for several reasons. As the capital, many

workplaces are located here, which could mean that women who were recruited there may not have necessarily lived there long-term. Many people also reside in Nicosia on weekdays and return to the nearest coastal town (Kyrenia) at the weekends which would also explain the difference in sampling of these two areas.

In terms of age distribution, COHERE under-recruited 18–25-year-olds from Nicosia, Kyrenia and Lefke, and over-recruited 36–45-year-olds in Nicosia, Lefke and Morphou. A large proportion of university aged students (18–25-year-olds) travel to attend university abroad, which may explain why the study under-recruited from this age group. Women between 36-45 years of age are more likely to be in the workplace and so were over-recruited.

For education, women with a primary/middle school education were under-recruited, and women with high educational attainment (bachelors and postgraduate degrees) were over recruitment. In most epidemiological studies, this form of sampling bias is common and people with a higher educational attainment are more likely to want to participate in studies[290–292]. Reasons for this may include lack of engagement in research studies and difficulties in understanding the immediate benefits of taking part. The study sample was well represented in terms of employment status, but under-represented homemakers, particularly in Nicosia and Kyrenia. The majority of women recruited into the study were from workplaces, especially in Nicosia and Kyrenia which can explain why less homemakers were recruited from these regions.

Homemakers were over-recruited in Morphou and Trikomo as in these areas more women were recruited from their houses as there are less workplaces. Recruitment took place between the hours of 8am-6pm, so often when carrying out house-visits no-one was able to be recruited as even if someone was a homemaker, they were not at home.

Regular alcohol consumption in this study was low at 27.7% with one-third (30.7%) of women reporting to ever have smoked. Prevalence of smoking was higher than the prevalence estimated in females by the Global Burden of Disease Study[293] in Central Europe, Eastern Europe, and Central Asia (15.5%), where the prevalence was estimated as 21.3% in Cyprus and 18.4% in Turkey. The low cost of cigarettes in Northern Cyprus may contribute to this high prevalence. Middle-aged women were more likely to drink alcohol and smoke compared to younger and older women, a pattern also seen in a Turkish study[294], presumably related to middle aged women having a relatively higher disposable income than younger women and being more likely to socialise in places that provide alcohol compared to older women. Turkish women were more likely to not drink alcohol, and though information on religion was not collected in this study, it is likely that a high proportion of Turkish women identify as Muslim, and alcohol consumption is forbidden for Muslims. However, a high proportion of Turkish women reported to have ever smoked, which could be attributable to societal norms in Turkey. Consumption of alcohol was higher in those with a higher educational achievement and those who were employed, also seen in previous studies[294,139], but only employment was significant

associated with ever smoking, with higher levels seen in those wo were employed. Education and employment can be used proxies for socio-economic status so akin to age, those with a higher education will most likely have higher paying jobs and would therefore be more likely to be able to afford alcohol and cigarettes and consume it at social events. Married women were more likely to not drink alcohol and not smoke cigarettes, and longitudinal studies have shown that marital termination due to divorce or spousal death, were associated with tobacco and alcohol consumption. It may be that support from a partner through marriage could mitigate things like stress, which could then lead to reductions in the consumption of alcohol and tobacco[295,296]. Alcohol consumption was lower in rural areas, similar to other studies[139]. This finding could be a combination of socioeconomic status, religious norms, and availability of places to socialise and drink alcohol. Though no significant difference was found between ever smoking and whether someone lived in a city or village, ever smoking was higher in Kyrenia, which is a coastal city South of Turkey, and is an area where a large number of Turkish migrants reside. When accounting for multiple testing the correlations described above would remain significant (0.05/6 – p=0.008).

2.4.2 Pelvic ultrasound scan

Women who opted to have an ultrasound scan were on average older, more likely to be employed and more likely to reside in Kyrenia and Nicosia, compared to women who did not have an ultrasound scan. The highest rate of pelvic scans was in these two areas as this is where the gynaecological clinics

were located so it would be easier for women living in these areas to visit for their scan. Women living in Trikomo, and Famagusta are further away so would not wish to travel to the clinics due to distance and cost of travel. Under-representation of 18–25-year-olds can be explained by younger women perhaps not feeling as confident to go to the gynaecologist or perhaps being less likely to notice any symptoms that would warrant an appointment. Over-representation of the oldest age group is likely explained by older women wanting a check-up as they go through menopause or noticing other changes and feeling more confident to visit having probably already been in the past. When accounting for multiple testing the variables found to be significant here would not change ($p=0.05/6 = 0.008$).

2.4.3 Food frequency questionnaire

Overall response rate for the FFQ was high at 62.6%. Refusal to complete the FFQ may reflect the time it took for both the research assistants to contact participants, give them information and direct them to the questionnaire if appropriate, as well as the fact that the FFQ is a long questionnaire, and it is often difficult to encourage people to take part. In addition to this, recruitment took place during the COVID-19 pandemic (July-October 2020) which may have contributed to the low response rate. Significant differences existed between those who took part in the FFQ and those who did not, that will need to be taken into consideration when analysing the data in future chapters. More Turkish Cypriot women completed the questionnaire, most likely because this

group of people were more likely to still be residing in Northern Cyprus at time of recruitment into the FFQ and potentially because they are more likely to be engaged in local research. Women taking part in the FFQ were on average older and more educated, which may reflect the fact that participants with endometriosis were prioritised, and these women were on average older and more educated (*Chapter 3*). In addition to this, studies[297] have shown that people who are well educated are more likely to be able to choose healthier lifestyles and therefore they may be more interested in participating in a diet-related study. The over-recruitment of single women may reflect the fact that the large majority of single women do not have children and therefore would have more time to complete the questionnaire. When accounting for multiple testing, the only significant differences in participation would be age and education ($p=0.05/6 = 0.008$).

Mean daily energy intake was over the recommended[298] 2,000 kcals/day for women at 2,408 kcals/day, however, this recommendation is very general, and optimal calorie intake is based on a number of things such as age, weight, height, basal metabolic rate and activity level, which are not all collected in this study. FFQ participants on average gained a higher proportion of energy from fat and a lower proportion from carbohydrate, than recommended[299] and had a much higher intake of Vitamin A and cholesterol than the minimum requirement, potentially due to the high consumption of meat in this population.

The majority of FFQ participants were found to have a medium adherence to the Mediterranean diet, in line with results from other studies in Greece[282] and 10 countries in Europe[300] using a similar scoring system. There were no significant differences between any demographics examined and MD score, though older age groups, Turkish women, those in paid employment, married women and those living in villages did tend to have a higher proportion of women in the high adherence group, compared to medium or low adherence. A study in Republic of Cyprus[120] suggested that the population was moving away from a traditional Mediterranean diet and the authors saw significant differences between adherence to the Mediterranean diet and urban and rural regions as well as marital status. However, the study used a different scoring system to the one used here so accurate comparisons between studies are unable to be made. Larger quantities of vegetable oil and vegetable fats, butter and margarine, eggs and potatoes consumed was higher in women who had a high adherence to the Mediterranean diet, similar to results from the Greek population[282] as was total energy intake, which most likely relates to the fact that a larger energy intake is correlated with higher general intakes of all food groups, which are not strictly all 'Mediterranean'.

The scoring system used here is robust in that it is based off strong epidemiological evidence concerning individual dietary components and how they relate to the Mediterranean diet. However, the construction of the MD score in this study was different to other studies[282,300] that included alcohol as a ninth component. Due to the low levels of alcohol consumed in this study, it was

omitted from the scoring system as including it would have biased the scoring system to categorising people as having a lower adherence of the Mediterranean diet, resulting in potential misclassification.

Data generated from the FFQ is limited by the small sample size and in that in an ideal scenario, the FFQ would be combined with multiple 24-hour recalls which would increase the precision of estimation of usual dietary intake[301]. The FFQ used here asked participants to recall food they had eaten over the past year which means that although recall bias is likely, bias from seasonal consumption will be limited. In addition, the differences between FFQ participants and non-participants needs to be considered when assessing how 'Mediterranean' the diet consumed by this population is, particularly noting differences in age, ethnicity and education, which could influence the type of diet an individual consumes.

2.4.4 Access to care and hormone use

The overall rate of ever having had a Pap-smear was 62.3% in COHERE, which is a similar percentage as women between the ages of 20-69 attending a cervical screening in the Republic of Cyprus (65%) in 2013[302] and in England (70%) between the ages of 25-49 in 2019/2020. In Northern Cyprus, rate of HPV vaccination was very low at 5.6% between the ages of 18-35, when the vaccine first became available. There is no data on HPV uptake in the Republic of Cyprus, but in the UK, the HPV vaccine is given to girls at the age of 12 years

and in 2020/2021, the uptake was around 76.7%[303] with uptake in Europe varying from 0% to over 70%[304]. In women aged 50 or above in COHERE, 69.6% reported to have ever had clinical breast screenings, the same percentage was reported in the UK for women between the ages of 53-70 years (70%)[305] and this was much higher than for women in Turkey between 50 and 69 years, which had a reported rate of 27%[302].

Hormone use in COHERE is low. A national survey of women living in Sweden[306] between the ages of 16 and 49 years revealed that 72.1% (721/1001) were currently using contraception. In England between 2017 and 2018, data from Sexual and Reproductive Health (SRH) services[307] showed that 41% of women were using long-acting reversible contraceptives (LARCs) (including implants, intra-uterine devices (IUD) intra-uterine systems (IUS) and injectables) and 42% were using oral contraceptives. Prevalence of oral contraceptives and LARCs were lower in COHERE, but use of the copper IUD was higher in COHERE at 18.6% compared to 7% of women in the UK in 2017/2018, suggesting a preference for non-hormonal contraceptives in this population of women. In terms of emergency contraceptive use, 18.9% of women in the COHERE cohort stated that they had used emergency contraception. The COHERE cohort is unique in that it has a low prevalence of hormone use – something that will be important to remember in future chapters when investigating the treatment of endometriosis and the symptoms experienced by women, as hormones are often used for first-line treatment and symptom management in endometriosis patients.

2.4.5 SF-36v2

Reliability and validity

The SF-36v2 was both reliable and valid in women between the ages of 18-55 residing in Northern Cyprus in evaluating HRQOL. Internal consistency reliability of the scales was high (above 0.8) for 5 of the eight scales with the general health scale being the only one to fall somewhat short of the accepted Cronbach's alpha level of 0.7 (0.69). However, this is sufficiently close to argue that this scale too had adequate internal consistency reliability. The highest ceiling value in our sample was 41.8%, for the role physical scale, suggesting that the SF-36v2 was well interpreted and suited to our population of Northern Cyprus.

Physical and mental health domains

This analysis has shown that the highest score of the eight health domains for participants in COHERE was physical functioning and the lowest was vitality. This pattern is consistent with various other studies conducted in several high-income countries such as the United Kingdom[289], Switzerland[308] and the United States[309], as well as countries within the Mediterranean region such as Turkey[275] and Greece[310]. Although the scores presented here vary from those presented by other countries, this does not necessarily mean that there are international health differences; there are a number of reasons normative scores may differ between

countries, such as differences in culture, expectation of health and mode of administration of the questionnaire. As age increased, mean physical health decreased and mean mental health increased, as seen in various other studies[289,308,309]. Education and employment are two demographics that can be used as proxies for the sociodemographic position of people within society. As our results showed higher mean scores in those who had obtained higher educational qualifications as well as in those who were in paid employment, we can be confident that the SF-36v2 was capable of detecting these known differences amongst different socioeconomic positions.

Compared to migrant women, non-migrants had the highest mean scores after adjustment for age only, consistent with previously published studies[308,311]. Once education and occupation type had been adjusted for, the associations were no longer statistically significant, suggesting the observed association may be partly explained by social disadvantages that arose from lower socioeconomic status immigrants in this sample. When examining ethnicity, after adjustment for age, education, and occupation class, the statistically significant association between ethnicity and mental health remained, with Turkish Cypriot women having the highest mean scores. Most studies examining HRQOL in non-natives show that they suffer from higher stressors when compared to their native counterparts, not only due to differences in socioeconomics, but due to other migration-specific difficulties[312,313].

The area most similar to Northern Cyprus both geographically and culturally to have produced normative values for the SF-36v2 is Turkey[275]. Mean health

domain scores in COHERE were lower for all scales, apart from physical functioning (88.28 vs 80.6). The study in Turkey was focussed on an urban region with a small sample size (670 women) which is not representative of the population of Turkey. In addition to this, five of the eight scales had a median ceiling score of 100 (perfect) which is unusually high. This is the first study in Cyprus that has calculated and reported normative values for the SF-36v2[258].

The COHERE Initiative is a women's health cohort in Northern Cyprus that has recruited 7,646 women who are broadly representative of 2019 census projections, adding to the knowledge on women's health conditions in the Eastern Mediterranean region.

The study aimed to investigate the prevalence rate of endometriosis, its associated symptomology and how it effects women's health-related quality of life. In addition to this, the study investigated demographic, menstrual, reproductive, lifestyle and dietary risk factors. The information generated from this study will form the basis of future follow-up studies, which have the potential to improve understanding of women's health in this population and aid policy makers and other stakeholders to develop educational awareness material, as well as ensuring that clinical healthcare professionals are aware the burden this condition has in this population. However, the cross-sectional study design means that there is an inability to assess temporality and a high likelihood of reverse causation. As the data is self-reported, there is also a high likelihood of recall bias.

The next four chapters (3,4,5,6) focus on the investigation of endometriosis prevalence and symptomatology, quality of life, economic burden and risk factors related to endometriosis. Specific methods not described above will be detailed in the subsequent chapters.

Table 1. Recruitment targets for COHERE by district and sub-district

District	Recruitment target *n (%)*	Sub-district	Recruitment target* *n (%)*
Nicosia	2,716 (34.0%)	City Town/village	2,401 (30.0%) 315 (3.9%)
Famagusta	1,981 (24.8%)	City Town/village	1,465 (18.3%) 516 (6.5%)
Kyrenia	1,912 (23.9%)	City Town/village	1,808 (22.6%) 104 (1.3%)
Morphou^	514 (6.4%)	City Town/village	- -
Trikomo	583 (7.3%)	City Town/village	215 (2.7%) 368 (4.6%)
Lefke^	294 (3.7%)	City Town/village	- -

Recruitment targets based on population density from 2011 census
**Calculated as a proportion of the whole target i.e., 8,000*
^There are no recruitment targets for Morphou and Lefke on the sub-district level as these are newer sub-districts that were created by local authorities after these recruitment targets had already been set

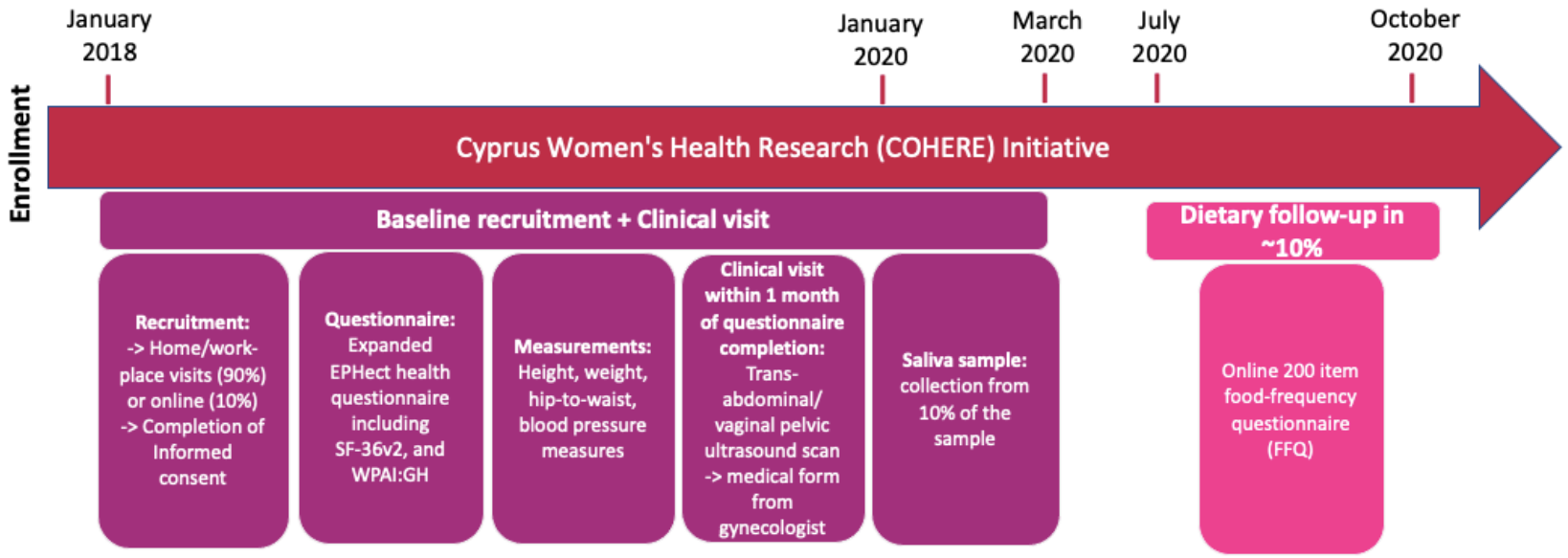


Figure 1. Schematic depicting the recruitment process for the Cyprus Women's Health Research (COHERE) Initiative.

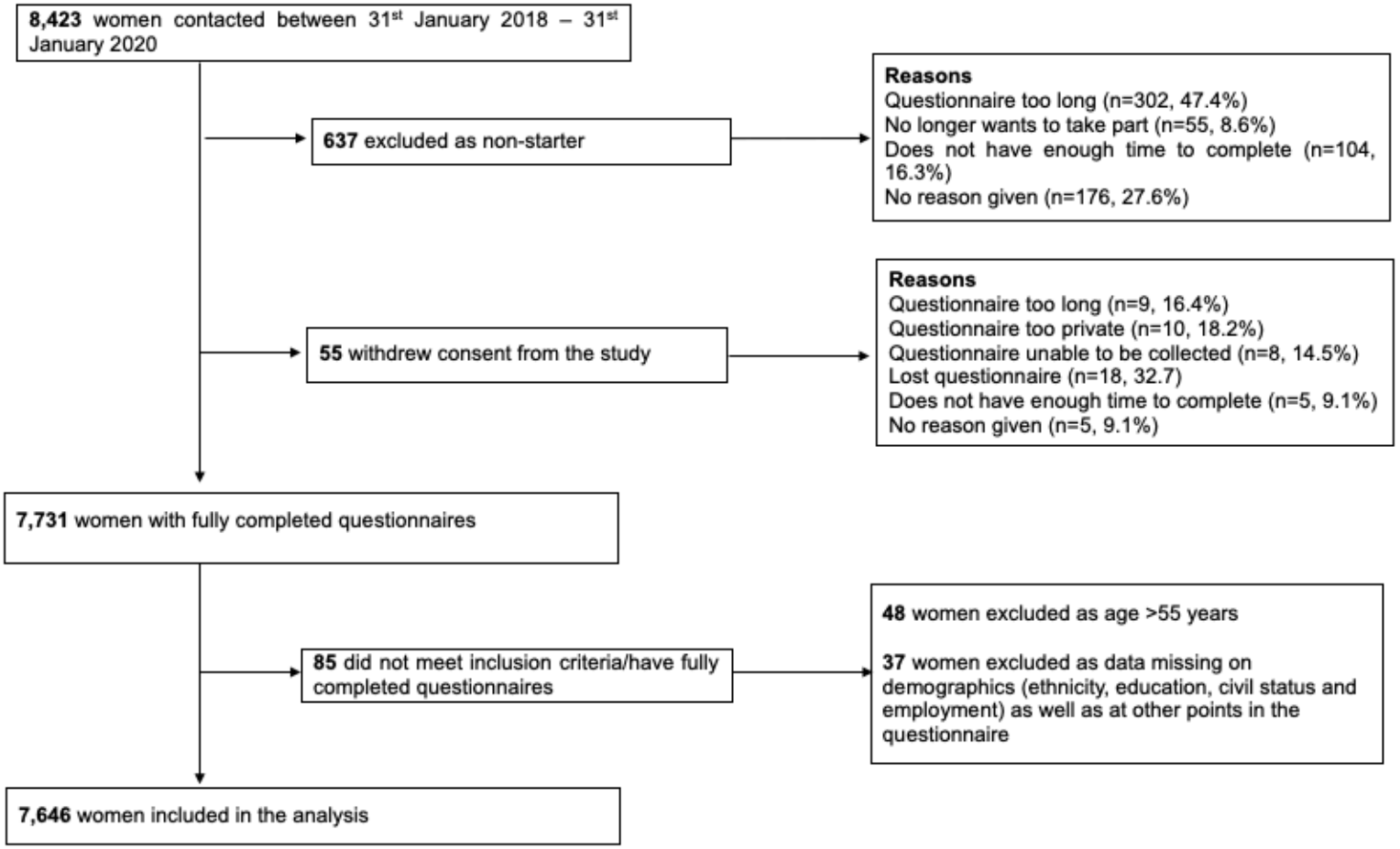


Figure 2. Flow chart of the study population selection including recruitment, exclusions, withdrawals, and dropouts.

Table 2. Frequency, percentage and rate of dropouts and non-starters in relation to various characteristics

	Dropouts (*n* = 55) *n (%)*	Dropout rate %	Non-starters (*n* = 637) *n (%)*	Non-starter rate %
District recruited				
Nicosia	30 (54.5%)	0.9%	316 (49.6%)	8.7%
Famagusta	9 (16.4%)	0.6%	132 (20.7%)	7.6%
Kyrenia	8 (14.5%)	0.6%	119 (18.7%)	8.6%
Morphou	3 (5.5%)	0.5%	29 (4.6%)	4.7%
Trikomo	4 (7.3%)	0.6%	16 (2.5%)	2.5%
Lefke	1 (1.8%)	0.4%	25 (3.9%)	8.7%
Location				
Household	0 (0.0%)	0.0%	12 (1.9%)	1.0%
Non-governmental workplace	27 (49.1%)	1.0%	264 (41.4%)	9.1%
Academic institution	20 (36.4%)	1.1%	217 (34.1%)	10.8%
Governmental workplace	7 (12.7%)	0.5%	120 (18.8%)	7.8%
Non-profit-civil-society-organisations	1 (1.8%)	1.2%	24 (3.8%)	22.9%
Reason for dropping out				
Above recruitment age				
Questionnaire too long	9 (16.4%)	-	302 (47.4%)	-
No longer want to	-	-	55 (8.6%)	-
Too private	10 (18.2%)	-	-	-
Questionnaire unable to be collected	8 (14.5%)	-	-	-
Lost the questionnaire	18 (32.7%)	-	-	-
Does not have enough time	5 (9.1%)	-	104 (16.3%)	-
No reason given	5 (9.1%)	-	176 (27.6%)	-

Table 3. Differences, 95% Confidence Intervals (95%CI) and Pearson's correlation coefficients of differences between measured and self-reported height, weight, and Body Mass Index (BMI).

	Measured	Self-reported	Mean differences	95% CI of mean differences	Pearson's correlation coefficients
Weight	66.89	65.63	0.71	0.99-1.53	0.97
Height	1.61	1.62	-0.01	-0.00-0.00	0.92
BMI	25.67	24.96	0.71	0.60-0.81	0.96

Table 4. Demographics of the Cyprus Women's Health Research (COHERE) Initiative cohort (n=7,646)

Age, mean (SD)	36.9 (9.6%)	**Civil status, n (%)**	
		Single	1,753 (22.9%)
Age categories, n (%)		Divorced / Separated	684 (8.9%)
18-25	1,108 (14.5%)	Married	4,839 (63.3%)
26-35	2,383 (31.2%)	Missing	370 (4.8%)
36-45	2,447 (32.0%)	**Currently living with a partner, n (%)**	
46-55	1,708 (22.3%)	Yes	4,958 (64.8%)
Ethnicity, n (%)		No, but I am in a relationship	891 (11.7%)
Turkish Cypriot*	5,378 (70.3%)	No, I am not in a relationship	1,356 (17.7%)
Turkish**	1,525 (19.9%)	Missing	441 (5.8%)
Other/Mixed	388 (5.1%)	**BMI categories, n (%)**	
Missing	355 (4.6%)	Underweight (≤18.5)	294 (3.9%)
Displaced, n (%)* **		Healthy weight (>18.5 - ≤24.9)	3,810 (49.8%)
Yes	334 (4.4%)	Overweight (>24.9 - ≤29.9)	1,932 (25.3%)
No	7,312 (95.6%)	Obese (>29.9)	1,099 (14.4%)
Education, n (%)		Missing	511 (6.7%)
Primary/Middle school	845 (11.1%)	**District, n (%)**	
High school/Post-secondary	2,557 (33.4%)	Famagusta	1,611 (21.1%)
Undergraduate degree	2,583 (33.8%)	Kyrenia	1,263 (16.5%)
Postgraduate degree	1,204 (15.7%)	Lefke	261 (3.4%)
Missing	457 (6.0%)	Morphou	585 (7.7%)
Currently in school, n (%)		Nicosia	3,301 (43.2%)
Yes	1,053 (13.8%)	Trikomo	625 (8.2%)
No	6,817 (89.2%)		
Missing	348 (4.6%)	**Migrant background, (%)****	
Employment, n (%)		Non migrant	5,436 (71.1%)
In paid employment	5,929 (77.5%)	Migrant	1,854 (24.3%)
Not in paid work	1,374 (18.0%)	Missing	356 (4.7%)
Missing	343 (4.5%)		

**Of the 5,260 Turkish Cypriots who gave further information, 4,931 (91.4%) were born in Northern Cyprus, 365 (7.4%) were born in Republic of Cyprus, 104 (2.1%) reported to be born in Cyprus, 176 (3.3%) were born in Turkey and 4,631 (86.6%) had two parents born in Cyprus.*

***Of 308 Other/Mixed who gave further information, 100 (32.5%) reported to be Turkish Cypriot/Turkish*

****Defined as those reporting to have been born in Republic of Cyprus.*

*****Defined as those who reported not to be born in Northern Cyprus, or those who were born in Northern Cyprus but whose parents were not.*

Table 5. Demographic comparison between women who do and do not drink alcohol regularly.

	All	Does not drink any alcohol (N = 5,525)	Drinks any alcohol (N = 2,121)	
		Number (percent)		p-value
Age category				**<0.001**
18-25		695 (12.6%)	413 (19.5%)	
26-35		1,594 (28.9%)	789 (37.2%)	
36-45		1,830 (33.1%)	617 (29.1%)	
46-55		1,406 (25.5%)	302 (14.2%)	
Ethnicity				**<0.001**
Turkish Cypriot		3,723 (71.9%)	1,655 (78.3%)	
Turkish		1,209 (23.4%)	316 (15.0%)	
Other/Mixed		246 (4.8%)	142 (6.7%)	
Education				**<0.001**
Primary/Middle school		804 (15.8%)	41 (2.0%)	
High school/Post-secondary		1,905 (37.3%)	652 (31.2%)	
Undergraduate degree		1,693 (33.2%)	890 (42.6%)	
Postgraduate degree		700 (13.7%)	504 (24.2%)	
Employment				**<0.001**
Unemployed		1,118 (21.6%)	265 (12.5%)	
In paid employment		4,066 (78.4%)	1,854 (87.5%)	
Civil status				**<0.001**
Single		999 (19.3%)	754 (35.8%)	
Divorced / Separated		434 (8.4%)	250 (11.9%)	
Married		3,734 (72.3%)	1,105 (52.4%)	
City				**<0.001**
Famagusta		1,240 (22.4%)	371 (17.5%)	
Kyrenia		863 (15.6%)	400 (18.9%)	
Lefke		218 (4.0%)	43 (2.0%)	
Morphou		487 (8.8%)	98 (4.6%)	
Nicosia		2,182 (39.5%)	1,119 (52.8%)	
Trikomo		535 (9.7%)	90 (4.2%)	
Residence				**<0.001**
Village		3,016 (54.6%)	1,036 (48.8%)	
City		2,509 (45.5%)	1,085 (51.2%)	
Displaced*				**<0.001**
Yes		281 (84.1%)	53 (15.9%)	
No		5,244 (71.7%)	2,068 (28.3%)	
Migrant**				**<0.001**
Yes		1,417 (76.4%)	437 (23.6%)	
No		3,760 (69.2%)	1,676 (30.8%)	

**Defined as those reporting to have been born in Republic of Cyprus*
***Defined as those who reported to not be born in Northern Cyprus, or those who were born in Northern Cyprus but whose parents were not*

Table 6. Demographic comparison between women who have never and ever smoked.

	All	Never smoked (N = 5,296)	Ever smoked* (N = 2,350)	
		Number (percent)		p-value
Age category				**<0.001**
18-25		840 (15.9%)	268 (11.4%)	
26-35		1,674 (31.6%)	709 (30.2%)	
36-45		1,579 (29.8%)	868 (36.9%)	
46-55		1,203 (22.7%)	505 (21.5%)	
Ethnicity				**<0.001**
Turkish Cypriot		3,841 (77.6%)	1,537 (65.7%)	
Turkish		885 (17.9%)	640 (27.3%)	
Other/Mixed		224 (4.5%)	164 (7.0%)	
Education				0.067
Primary/Middle school		540 (11.1%)	305 (13.2%)	
High school/Post-secondary		1,739 (35.7%)	818 (35.4%)	
Undergraduate degree		1,775 (36.4%)	808 (35.0%)	
Postgraduate degree		824 (16.9%)	380 (16.4%)	
Employment				**<0.001**
Unemployed		998 (20.1%)	385 (16.4%)	
In paid employment		3,957 (79.9%)	1,963 (83.6%)	
Civil status				**<0.001**
Single		1,226 (24.8%)	527 (22.5%)	
Divorced / Separated		355 (7.2%)	329 (14.1%)	
Married		3,357 (68.0%)	1,482 (63.4%)	
City				**<0.001**
Famagusta		1,141 (21.5%)	470 (20.0%)	
Kyrenia		799 (15.1%)	464 (19.7%)	
Lefke		205 (3.9%)	56 (2.4%)	
Morphou		423 (8.0%)	162 (6.9%)	
Nicosia		2,262 (42.7%)	1,039 (44.2%)	
Trikomo		466 (8.8%)	159 (6.8%)	
Residence				0.079
Village		2,842 (53.7%)	1,210 (51.5%)	
City		2,454 (46.3%)	1,140 (48.5%)	
Displaced**				**<0.001**
Yes		251 (75.2%)	83 (24.9%)	
No		5,045 (69.0%)	2,267 (31.0%)	
Migrant***				**<0.001**
Yes		1,061 (57.2%)	793 (42.8%)	
No		3,888 (71.5%)	1,548 (28.5%)	

**Defined as smoking more than 100 cigarettes during lifetime*
***Defined as those reporting to have been born in the Republic of Cyprus*
****Defined as those who reported to not be born in Northern Cyprus, or those who were born in Northern Cyprus but whose parents were not.*

Table 7. Recruitment targets and attained for COHERE by district and subdistrict

District	Recruitment target *n (%)*	Actual recruitment *n (%)*	Subdistrict	Recruitment target* *n (%)*	Actual recruitment** *n (%)*
Nicosia	2,716 (34%)	3,301 (43.2%)	City Town/village	2,401 (30%) 315 (4%)	1,891 (24.7%) 1,410 (18.4%)
Famagusta	1,981 (25%)	1,611 (21.1%)	City Town/village	1,465 (18%) 516 (6%)	870 (11.4%) 741 (9.7%)
Kyrenia	1,912 (24%)	1,263 (16.5%)	City Town/village	1,808 (23%) 104 (1%)	205 (2.7%) 1,058 (13.8%)
Morphou^	514 (6%)	585 (7.7%)	City Town/village	- -	211 (2.8%) 374 (4.9%)
Trikomo	583 (7%)	625 (8.2%)	City Town/village	215 (3%) 368 (5%)	343 (4.5%) 282 (3.7%)
Lefke^	294 (4%)	261 (3.4%)	City Town/village	- -	74 (1.0%) 187 (2.4%)

Recruitment targets based on population density using the 2011 census

**Calculated as a proportion of the whole target i.e., 8,000*
***Calculated as a proportion of the whole cohort i.e., 7,646*
^There are no recruitment targets for Morphou and Lefke on the Sub-district level as these are newer sub-districts that were created by local authorities after these recruitment targets had already been set

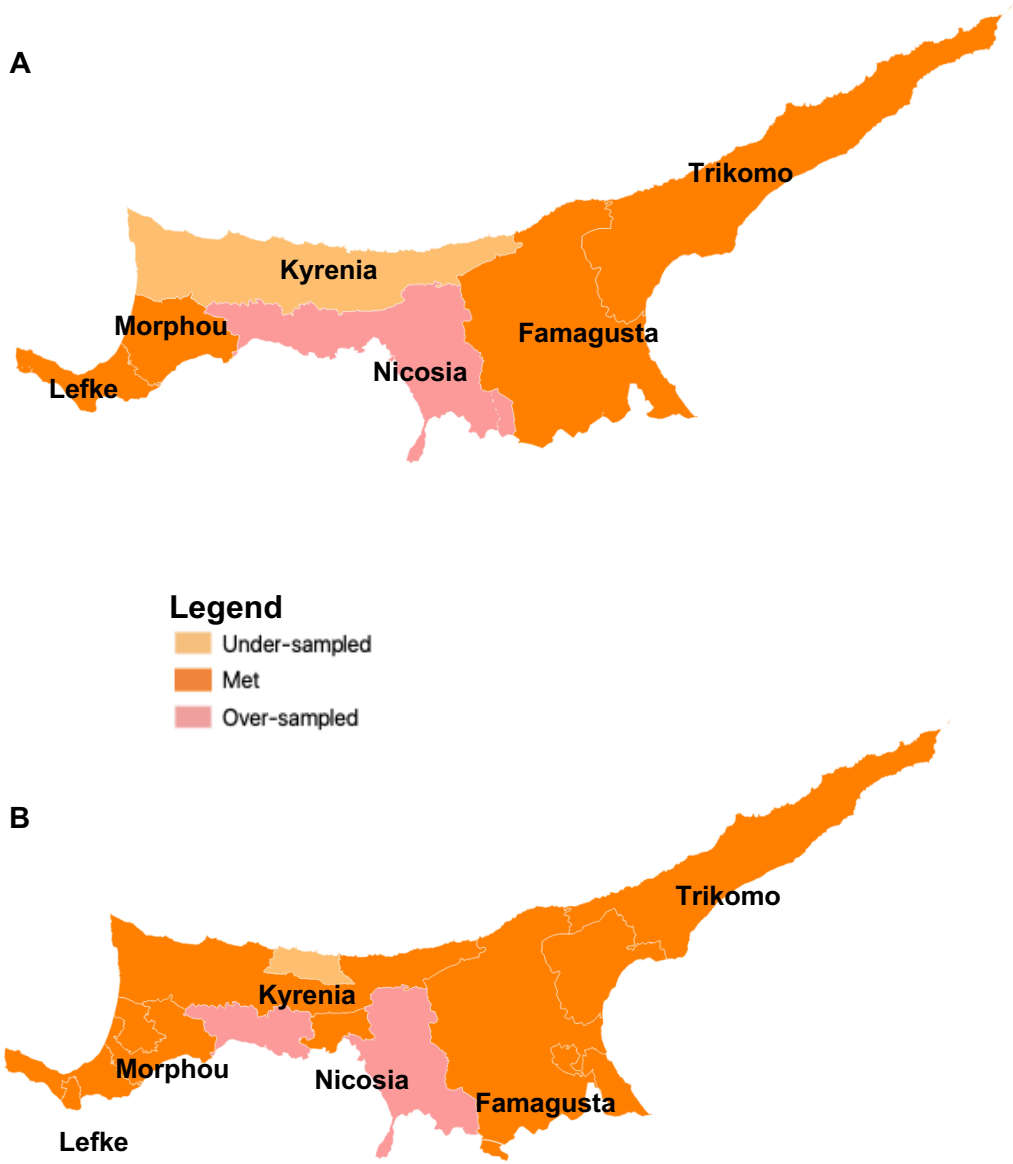


Figure 3. Map of Northern Cyprus created in QGIS depicting census targets for women on the **(A)** District and **(B)** Subdistrict level.

Comparison of population densities from the projected 2019 census to COHERE

District	Census (n = 98,686) *n (%)*	COHERE (n = 7,646) *n (%)*
Nicosia	32,503 (32.9%)	3,301 (43.2%)
Famagusta	25,300 (25.6%)	1,611 (21.1%)
Kyrenia	23,848 (24.2%)	1,263 (16.5%)
Morphou	6,095 (6.2%)	585 (7.7%)
Trikomo	7,249 (7.3%)	625 (8.2%)
Lefke	3,691 (3.7%)	261 (3.4%)

Proportions calculated as the number of women 18-55 living in each district over the total number of women 18-55 projected to be living in Northern Cyprus

Comparison of population densities from the projected 2019 census to COHERE

Subdistrict		Census (n = 98,686)	COHERE (n = 7,646)
n (%)		*n (%)*	*n (%)*
Nicosia	City	20,623 (20.9%)	1,891 (24.7%)
	Town/village	11,880 (12.0%)	1,410 (18.4%)
Famagusta	City	14,544 (14.7%)	870 (11.4%)
	Town/village	10,756 (10.9%)	741 (9.7%)
Kyrenia	City	11,966 (12.1%)	205 (2.7%)
	Town/village	11,882 (12.0%)	1,058 (13.8%)
Morphou	City	2,569 (2.6%)	211 (2.8%)
	Town/village	3,526 (3.6%)	374 (4.9%)
Trikomo	City	2,632 (2.7%)	343 (4.5%)
	Town/village	4,618 (4.7%)	282 (3.7%)
Lefke	City	1,126 (1.1%)	74 (1.0%)
	Town/village	2,566 (2.6%)	187 (2.4%)

Proportions calculated as the number of women 18-55 living in each subdistrict over the total number of women 18-55 projected to be living in Northern Cyprus

Table 8. Comparison of age from the projected 2019 census to COHERE

Age	Census (n=98,686) *n (%)*	COHERE (n=7,646) *n (%)*
18-25	22,355 (22.7%)	1,108 (14.5%)
26-35	31,229 (31.6%)	2,383 (31.2%)
36-45	25,318 (25.7%)	2,447 (32.0%)
46-55	19,784 (20.0%)	1,708 (22.3%)

Proportions calculated as the number of women 18-55 living in each district over the total number of women aged 18-55 projected to be living in Northern Cyprus

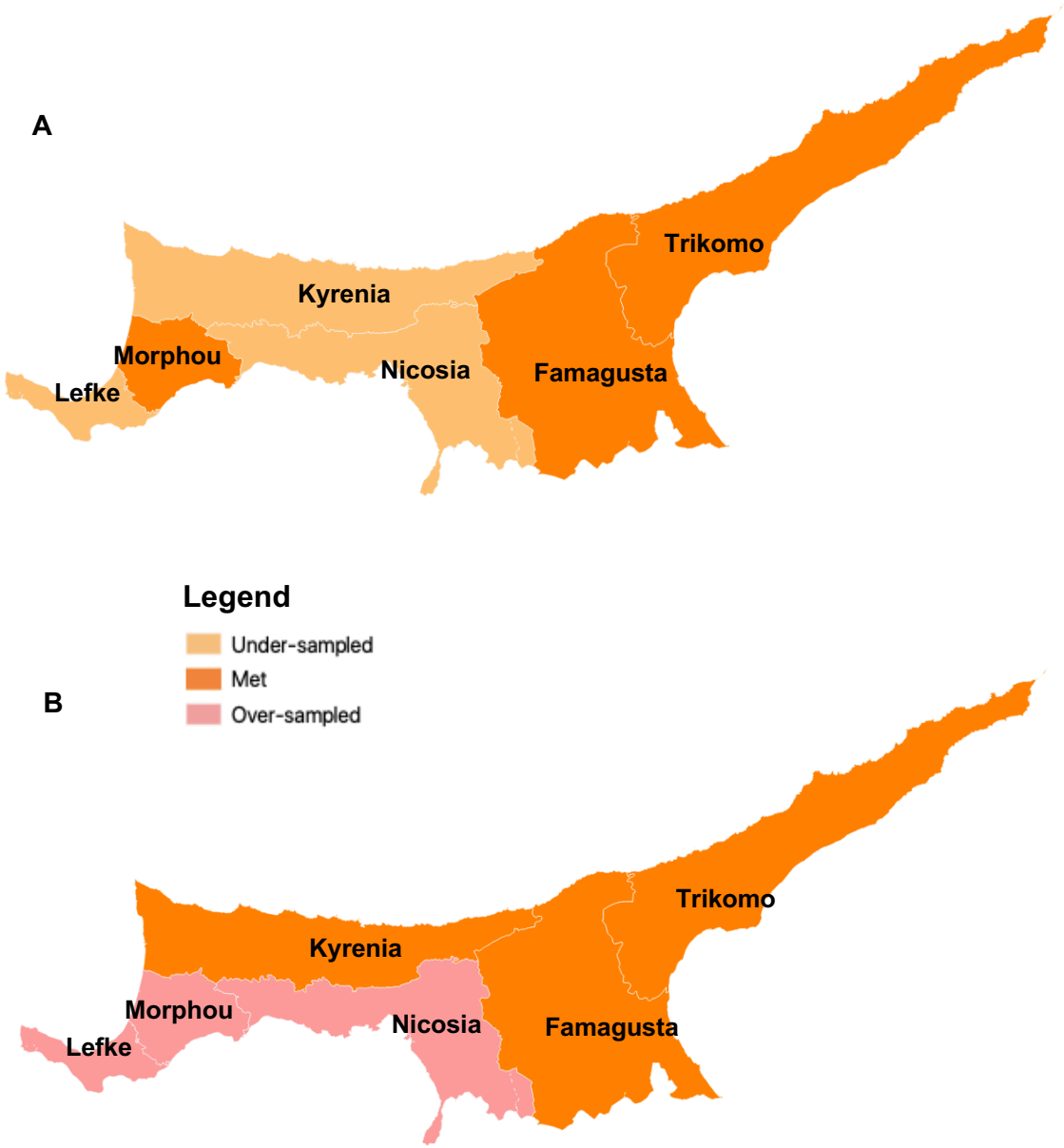


Figure 4. Map of Northern Cyprus created in QGIS depicting census targets for women on the district levels between the ages of **(A)** 18-25 and **(B)** 36-45.

Comparison of 18-25-year-olds from the projected 2019 census to COHERE

District	Census (n = 22,356) *n (%)*	COHERE (n = 1,108) *n (%)*
Nicosia	8,396 (25.8%)	406 (12.3%)
Famagusta	5,925 (23.4%)	309 (19.2%)
Kyrenia	4,420 (18.5%)	158 (12.5%)
Morphou	1,055 (17.3%)	89 (15.2%)
Trikomo	1,376 (19.0%)	118 (18.8%)
Lefke	1,184 (32.1%)	28 (10.7%)

Proportions calculated as the number of women 18-25 living in each district over the total number of women 18-55 projected to be living in each district

Comparison of 36-45-year-olds from the projected 2019 census to COHERE

District	Census (n = 25,471) *n (%)*	COHERE (n = 2,447) *n (%)*
Nicosia	8,149 (25.1%)	1,121 (34.0%)
Famagusta	6,330 (25.0%)	463 (28.7%)
Kyrenia	6,710 (28.1%)	419 (33.2%)
Morphou	1,445 (23.7%)	180 (30.8%)
Trikomo	1,940 (26.8%)	178 (28.5%)
Lefke	897 (24.3%)	86 (33.0%)

Proportions calculated as the number of women 36-45 living in each district over the total number of women 18-55 projected to be living in each district

Table 9a. Comparison of education from the projected 2019 census to COHERE

Highest level of education attained	Census (n = 85,093) *n (%)*	COHERE (n = 7,189) *n (%)*
Primary/Middle school	28,426 (33.4%)	845 (11.8%)
High school/post-secondary	31,748 (37.3%)	2,557 (35.6%)
University	19,713 (23.2%)	2,583 (35.9%)
Postgraduate	5,206 (6.1%)	1,204 (16.8%)

Table 9b. Comparison of primary/middle school education from the projected 2019 census to COHERE

District	Census (n = 28,428) *n (%)*	COHERE (n = 845) *n (%)*
Nicosia	8,471 (24.8%)	216 (6.5%)
Famagusta	7,413 (30.0%)	211 (13.1%)
Kyrenia	6,393 (26.1%)	113 (8.9%)
Morphou	2,143 (34.5%)	91 (15.6%)
Trikomo	3,148 (45.6%)	182 (29.1%)
Lefke	860 (21.6%)	32 (12.3%)

Proportions calculated as the number of women 18-55 in each district with the highest level of educational attainment being primary/middle school education over the total number of women living in that district aged 18-55

Table 9c. Comparison of high-school/post-secondary education from the projected 2019 census to COHERE

District	Census (n = 41,908) *n (%)*	COHERE (n = 2,557) *n (%)*
Nicosia	13,508 (39.6%)	1,063 (32.2%)
Famagusta	9,839 (39.8%)	571 (35.4%)
Kyrenia	12,048 (49.1%)	392 (31.0%)
Morphou	2,360 (38.0%)	233 (39.8%)
Trikomo	2,345 (33.9%)	223 (35.7%)
Lefke	1,808 (45.5%)	75 (28.7%)

Proportions calculated as the number of women 18-55 in each district with the highest level of educational attainment being high-school/post-secondary education over the total number of women living in that district aged 18-55

Table 9d. Comparison of undergraduate education from the projected 2019 census to COHERE

District	Census (n = 24,900) *n (%)*	COHERE (n = 2,583) *n (%)*
Nicosia	9,772 (28.7%)	1,149 (34.8%)
Famagusta	6,365 (25.7%)	516 (32.0%)
Kyrenia	5,110 (20.9%)	506 (40.1%)
Morphou	1,378 (22.2%)	164 (28.0%)
Trikomo	1,298 (18.8%)	150 (24.0%)
Lefke	977 (24.6%)	98 (37.5%)

Proportions calculated as the number of women 18-55 in each district with the highest level of educational attainment being undergraduate education over the total number of women living in that district aged 18-55

Table 9e. Comparison of postgraduate education from the projected 2019 census to COHERE

District	Census (n = 4,057) *n (%)*	COHERE (n = 1,204) *n (%)*
Nicosia	2,343 (6.9%)	654 (19.8%)
Famagusta	1,128 (4.6%)	216 (13.4%)
Kyrenia	945 (3.9%)	197 (15.6%)
Morphou	324 (5.2%)	57 (9.7%)
Trikomo	117 (1.7%)	41 (6.6%)
Lefke	328 (8.3%)	39 (14.9%)

Proportions calculated as the number of women 18-55 in each district with the highest level of educational attainment being postgraduate education over the total number of women living in that district aged 18-55

Table 10a. Comparison of employment status from the projected 2019 census to COHERE

Employment status	Census (n = 46,689) *n (%)*	COHERE (n = 6,136)* *n (%)*
In paid employment	41,689 (88.8%)	5,436 (88.6%)
Self-employed	4,440 (9.4%)	480 (7.8%)
Not in paid employment	871 (1.9%)	220 (3.6%)

**Excludes homemakers, retirees, and students*
Proportions calculated as total number of women aged 18-55 in each occupation group over the sum of women 18-55 in each occupation group

Table 10b. Comparison of homemaker and retirees from the projected 2019 census to COHERE

	Census (n = 98,686) *n (%)*	COHERE (n = 7,646) *n (%)*
Homemaker	18,551 (18.8%)	795 (10.4%)
Retired	971 (0.9%)	23 (0.3%)

Proportions calculated as total number of women aged 18-55 in each category of the total number of women aged 18-55

Table 10c. Comparison of homemakers by district from the projected 2019 census to COHERE

District	Census (n = 18,551) *n (%)*	COHERE (n = 795) *n (%)*
Nicosia	4,970 (26.8%)	121 (15.2%)
Famagusta	4,839 (26.1%)	192 (24.2%)
Kyrenia	5,183 (27.9%)	108 (13.6%)
Morphou	1,291 (7.0%)	119 (15.0%)
Trikomo	1,462 (7.9%)	236 (29.7%)
Lefke	806 (4.4%)	19 (2.4%)

Proportions calculated as the number of homemakers 18-55 living in each district over the total number of homemakers 18-55 projected to be living in Northern Cyprus

Table 11. Comparison of civil status from the projected 2019 census to COHERE

Civil status	Census (n = 46,689) *n (%)*	COHERE (n = 6,136) *n (%)*
Single	24,130 (23.3%)	1,753 (24.1%)
Married	72,311 (70.0%)	4,839 (66.5%)
Divorced/separated	6,917 (6.7%)	684 (9.4%)

Table 12a. Frequency, percentage and rate of women attending the pelvic scan appointment in relation to demographics

	Pelvic scan (n = 668) *n (%)*	Pelvic scan rate* *%*
District		
Nicosia	395 (59.1%)	12.0%
Famagusta	42 (6.3%)	2.6%
Kyrenia	155 (23.2%)	12.3%
Morphou	40 (6.0%)	6.8%
Trikomo	13 (2.0%)	2.1%
Lefke	23 (3.4%)	8.8%
Age		
18-25	60 (9.0%)	5.4%
26-35	158 (23.7%)	6.6%
36-45	229 (34.3%)	9.4%
46-55	221 (33.1%)	12.9%
Ethnicity, n (%)		
Turkish Cypriot	465 (72.7%)	8.6%
Turkish	128 (20.0%)	8.4%
Mixed/Other	47 (7.3%)	12.1%
Education level, n (%)		
Primary/Middle school	68 (10.7%)	8.0%
High school/post-secondary	215 (33.9%)	8.4%
Undergraduate	239 (37.7%)	9.3%
Postgraduate	112 (17.7%)	9.3%
Civil status, n (%)		
Single	115 (18.0%)	6.6%
Married	441 (69.0%)	9.1%
Divorced/separated	83 (13.0%)	12.1%

**Calculated as number of women participating in clinical visit / total number of women recruited in each district*

Table 12b. Comparison between demographics of women who did not and did have a pelvic scan in the COHERE sample

	No pelvic scan (n = 6,978)	**Pelvic scan** (n = 668)	**p-value**	**Age adjusted**
Mean age (years), n (SD)	36.6 (9.6%)	39.8 (9.4%)	**<0.001**	-
Age categories (years), n (%)				
18-25	1,048 (15.0%)	60 (9.0%)		
26-35	2,225 (31.9%)	158 (23.7%)	**<0.001**	-
36-45	2,218 (31.8%)	229 (34.3%)		
46-55	1,487 (21.3%)	221 (33.1%)		
Ethnicity, n (%)			0.145	0.081
Turkish Cypriot	4,913 (73.9%)	465 (72.7%)		
Turkish	1,397 (21.0%)	128 (20.0%)		
Mixed/Other	341 (5.1%)	47 (7.3%)		
Residency, n (%)				
Famagusta	1,569 (22.5%)	42 (6.3%)	**<0.001**	**<0.001**
Kyrenia	1,108 (15.9%)	155 (23.2%)		
Lefke	238 (3.4%)	23 (3.4%)		
Morphou	545 (7.8%)	40 (6.0%)		
Nicosia	2,906 (41.6%)	395 (59.1%)		
Trikomo	612 (8.8%)	13 (2.0%)		

	No pelvic scan (n = 6,978)	**Pelvic scan** (n = 668)	**p-value**	**Age adjusted**
Employment, n (%)			**<0.001**	**<0.001**
Employed	5,346 (80.1%)	583 (90.7%)		
Unemployed	1,315 (19.9%)	59 (9.4%)		
Civil status, n (%)				
Single	1,638 (24.7%)	115 (18.0%)	**0.025**	0.196
Married	4,398 (66.3%)	441 (69.0%)		
Divorced/separated	601 (9.1%)	83 (13.0%)		
Education level, n (%)				
Primary/Middle school	777 (11.9%)	68 (10.7%)	0.176	**0.007**
High school/post-secondary	2,342 (35.7%)	215 (33.9%)		
University	2,344 (35.8%)	239 (37.7%)		
Postgraduate	1,092 (16.7%)	112 (17.7%)		

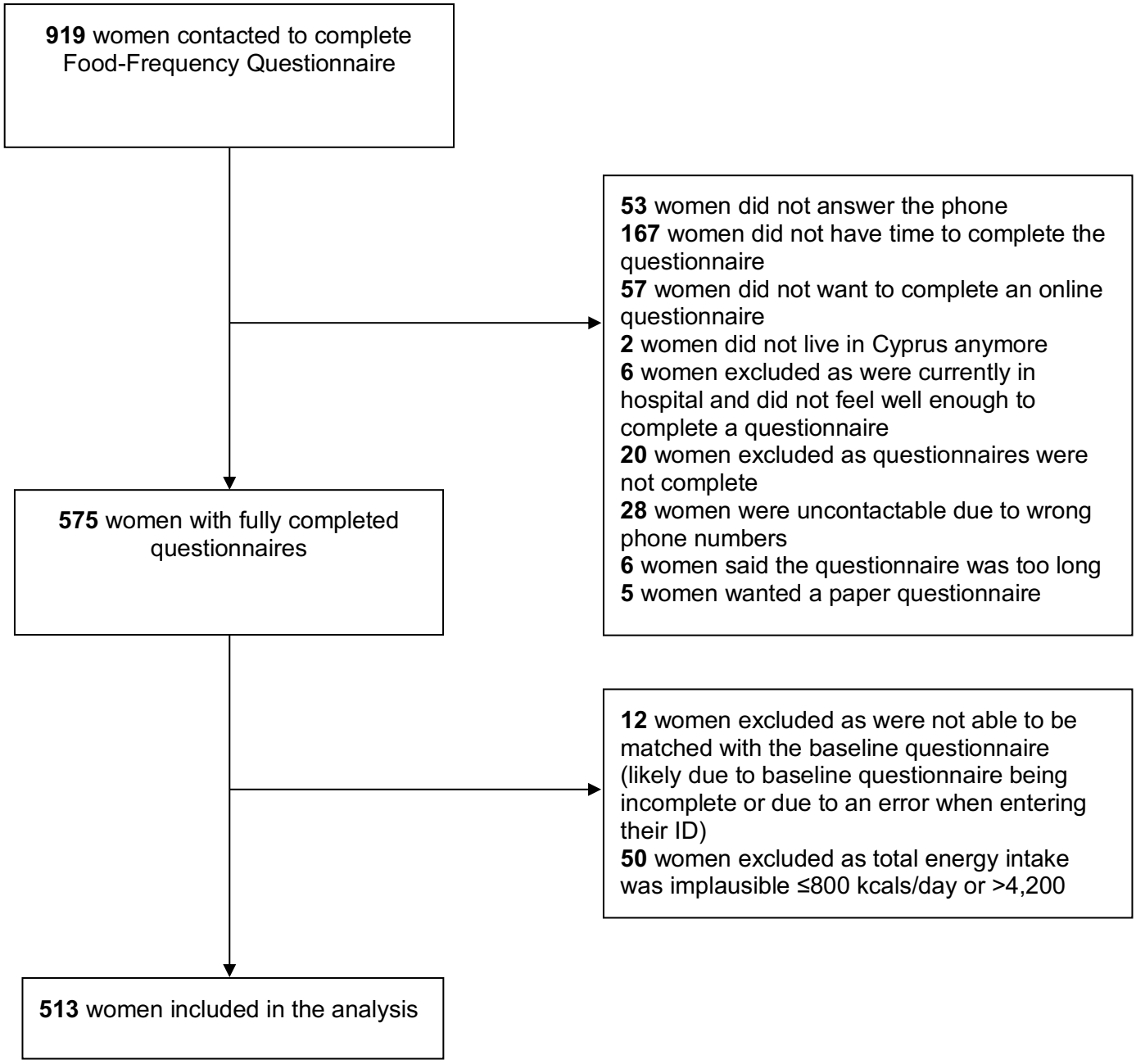


Figure 5. Flow-chart of the Food-frequency questionnaire (FFQ) study population selection including recruitment, refusals/dropouts, and exclusions

Table 13. Comparison of demographics between women with and without Food Frequency Questionnaire (FFQ) data

	No FFQ data (n=7,133)	FFQ data (n=513)	p-value	Adjusted for age
Age, mean (SD)	37.0 (9.6)	35.3 (9.6)	**<0.001**	-
Age categories			**<0.001**	-
18-25	1011 (14.2%)	97 (18.9%)		
26-35	2206 (30.9%)	177 (34.5%)		
36-45	2298 (32.2%)	149 (29.0%)		
46-55	1618 (22.7%)	90 (17.5%)		
Ethnicity			**0.001**	**0.017**
Turkish Cypriot	4980 (73.3%)	398 (79.9%)		
Turkish	1454 (21.4%)	71 (14.3%)		
Other/Mixed	359 (5.3%)	29 (5.8%)		
City			0.193	0.135
Famagusta	1539 (21.6%)	72 (14.0%)		
Kyrenia	1146 (16.1%)	117 (22.8%)		
Lefke	244 (3.4%)	17 (3.3%)		
Morphou	562 (7.9%)	23 (4.5%)		
Nicosia	3045 (42.7%)	256 (49.9%)		
Trikomo	597 (8.4%)	28 (5.5%)		
Residence			0.53	0.595
Village	3787 (53.1%)	265 (51.7%)		
City	3346 (46.9%)	248 (48.3%)		
Education			**<0.001**	**<0.001**
Primary/Middle school	827 (12.4%)	18 (3.7%)		
High school/Post-secondary	2415 (36.1%)	142 (28.8%)		
Undergraduate degree	2364 (35.3%)	219 (44.4%)		
Postgraduate degree	1090 (16.3%)	114 (23.1%)		
Employment			0.859	0.379
Unemployed	1290 (19.0%)	93 (18.6%)		
In paid employment	5514 (81.0%)	406 (81.4%)		
Civil status			**<0.001**	**0.008**
Single	1594 (23.5%)	159 (31.9%)		
Divorced / Separated	633 (9.3%)	51 (10.2%)		
Married	4550 (67.1%)	289 (57.9%)		
Displaced*			**0.013**	0.094
Yes	323 (4.5%)	11 (2.1%)		
No	6,810 (95.5%)	502 (97.9%)		
Migrant**			**0.003**	**0.006**
Yes	1,755 (25.8%)	99 (19.9%)		
No	5,037 (74.2%)	399 (80.1%)		
BMI, mean (SD)	25.1 (5.1)	24.5 (4.7)	**0.007**	0.088

**Defined as those reporting to have been born in Republic of Cyprus*
***Defined as those who reported to not be born in Northern Cyprus, or those who were born in Northern Cyprus but whose parents were not*

Table 14. (A) Frequency of meals and **(B)** snacks per day in women with FFQ data (n=513).

(A)

Frequency of meals	Breakfast, n(%)	Lunch, n(%)	Dinner, n(%)	Eat at restaurants/eat take-away food, n(%)
Everyday	322 (62.8%)	358 (69.8%)	359 (70.0%)	3 (0.6%)
2 days/week	32 (6.2%)	9 (1.8%)	6 (1.2%)	167 (32.6%)
3-4 days/week	44 (8.6%)	41 (8.0%)	34 (6.6%)	51 (9.9%)
5-6 days/week	42 (8.2%)	46 (9.0%)	64 (12.5%)	7 (1.4%)
Rarely/never	28 (5.5%)	12 (2.3%)	6 (1.2%)	241 (47.0%)
Missing	45 (8.8%)	47 (9.2%)	44 (8.6%)	44 (8.9%)

(B)

Frequency of snacks/day	n(%)
2 times/day	170 (33.1%)
3 times/day	99 (19.3%)
4 times/day	36 (7.0%)
5-6 times/day	16 (3.1%)
Once/day	76 (14.8%)
Rarely/never	72 (14.0%)
Missing	44 (8.6%)

Table 15. Mean and median daily energy and nutrient intakes from food overall of the 513 FFQ participants

	RDI*	Mean	SD	Median	5th	95th
Energy (kcal)	2,000[298]	2,408.2	743.9	2,321.1	1,246.5	3,746.7
Protein (g)	-	105.9	40.5	101.2	47.7	177.4
Carbohydrate (g)	-	220.7	83.1	209.4	103.2	372.5
Fat (g)	-	117.3	41.5	111.7	56.7	194.6
Saturated fat (g)	-	39.3	16.1	37.2	17.6	68.5
Monounsaturated fat (g)	-	46.6	17.5	44.1	21.5	79.1
Polyunsaturated fat (g)	-	21.8	9.1	20.3	10.0	38.5
Fibre (g)	-	44.6	20.0	42.5	18.1	81.2
% Total energy from						
Protein	10-30[314]	18.1	3.8	18.0	12.0	25.0
Carbohydrate	45-65[314]	38.0	8.6	38.0	25.0	52.0
Fat	25-35[314]	43.9	7.4	44.0	31.0	56.0
Minerals						
Potassium (mg)	≥4,700[315]	5,150.3	2,051.9	4,778.2	2,241.8	8,978.8
Phosphorus (mg)	≥1,250[315]	1,848.5	658.9	1,791.3	837.0	3,012.8
Calcium (mg)	≥1,300[315]	1,511.7	702.6	1,384.0	593.6	2,775.4
Magnesium (mg)	≥420[315]	537.0	216.8	518.8	249.4	897.7
Iron (mg)	≥18[315]	19.0	8.6	18.0	8.2	34.9
Zinc (mg)	≥11[315]	15.6	6.2	14.7	6.9	27.0
Selenium (ug)	≥55[315]	11.9	10.1	9.4	1.4	30.3
Sodium (mg)	2,400[316]	2,614.5	1,150.1	2,439.1	1,063.5	4,684.2
Vitamins						
Vitamin A (ug)	≥900[315]	2,739.7	1,724.3	2,412.4	857.9	5,627.1
Vitamin B1 (mg)	0.8[298]	1.5	0.6	1.5	0.7	2.6
Vitamin B2 (mg)	1.1[317]	2.2	0.8	2.1	1.0	3.7
Vitamin B6 (mg)	≥1.7[315]	2.7	1.1	2.5	1.2	4.6
Vitamin B12 (ug)	≥2.4[312]	6.8	4.7	5.7	2.0	14.3
Vitamin D (ug)	≥20[312]	4.9	4.5	4.1	1.4	9.9
Vitamin E (mg)	≥15[312]	26.6	10.9	25.6	12.3	44.7
B-Carotene (mg)		13.6	8.5	12.1	3.9	28.1
Retinol (ug)	600[312]	755.8	951.1	458.8	188.8	2,352.2
Niacin (mg)	≥16[315]	22.9	10.2	21.4	9.4	41.8
Folate (ug)	≥400[315]	562.9	250.1	518.9	231.9	1,011.2
Lutein (ug)	-	571.0	1,676.8	3.0	0.4	2,238.2
Lycopene (ug)	-	2.2	2.5	1.7	-	5.5
Antioxidants (nmol)	-	10.1	10.2	7.8	2.8	24.0
Fatty acids						
Palmitic acid (g)	-	21.0	8.0	19.9	9.8	36.1
Oleic acid (g)	-	43.4	16.3	40.7	19.7	74.5
Cholesterol (mg)	<300^[318]	421.0	225.9	386.1	121.9	864.8
Omega 3 (g)	>1.1[319]	2.6	1.1	2.4	1.2	4.6
Omega 6 (g)	>12[319]	19.0	8.3	17.5	8.3	33.8

RDI, recommended daily intake; SD, standard deviation

**Reference daily intake is the daily intake level of a nutrient that is likely to meet the needs of almost all healthy people in a population. Does not include pregnant or lactating women. RDIs were not available for all items.*

^Denotes an upper limit which should not be exceeded

Table 16. Comparison of demographics between the three Mediterranean diet score groups.

	All	Diet score of 0-2 (N = 90)	Diet score of 3-5 (N = 323)	Diet score of 6-8 (N = 100)	p-value
			Number (percent)		
Age category					0.608
18-25		23 (25.6)	59 (18.3)	15 (15.0)	
26-35		29 (32.2)	115 (35.6)	33 (33.0)	
36-45		26 (28.9)	94 (29.1)	29 (29.0)	
46-55		12 (13.3)	55 (17.0)	23 (23.0)	
Ethnicity					0.228
Turkish Cypriot		76 (84.4)	250 (79.9)	72 (75.8)	
Turkish		6 (6.7)	46 (14.7)	19 (20.0)	
Other/Mixed		8 (8.9)	17 (5.4)	4 (4.2)	
Education					0.629
Primary/Middle school		2 (2.3)	11 (3.6)	5 (5.3)	
High school/Post-secondary		26 (29.2)	91 (29.5)	25 (26.3)	
Undergraduate degree		34 (38.2)	145 (46.9)	40 (42.1)	
Postgraduate degree		27 (30.3)	62 (20.1)	25 (26.3)	
Employment					0.587
Unemployed		19 (21.1)	61 (19.4)	13 (13.7)	
In paid employment		71 (78.9)	253 (80.6)	82 (86.3)	
Civil status					0.502
Single		29 (32.2)	104 (33.1)	26 (27.4)	
Divorced / Separated		14 (15.6)	31 (9.9)	6 (6.3)	
Married		47 (52.2)	179 (57.0)	63 (66.3)	
City					0.109
Famagusta		8 (8.9)	53 (16.4)	11 (11.0)	
Kyrenia		15 (16.7)	79 (24.5)	23 (23.0)	
Lefke		4 (4.4)	8 (2.5)	5 (5.0)	
Morphou		6 (6.7)	10 (3.1)	7 (7.0)	
Nicosia		51 (56.7)	153 (47.4)	52 (52.0)	
Trikomo		6 (6.7)	20 (6.2)	2 (2.0)	
Residence					0.862
Village		44 (48.9)	166 (51.4)	55 (55.0)	
City		46 (51.1)	157 (48.6)	45 (45.0)	
Displaced*					0.288
Yes		0 (0.0)	8 (2.4)	3 (3.0)	
No		90 (100.0)	315 (97.5)	97 (97.0)	
Migrant**					0.055
Yes		12 (13.3)	61 (19.5)	26 (27.4)	
No		78 (86.7)	252 (80.5)	69 (72.6)	

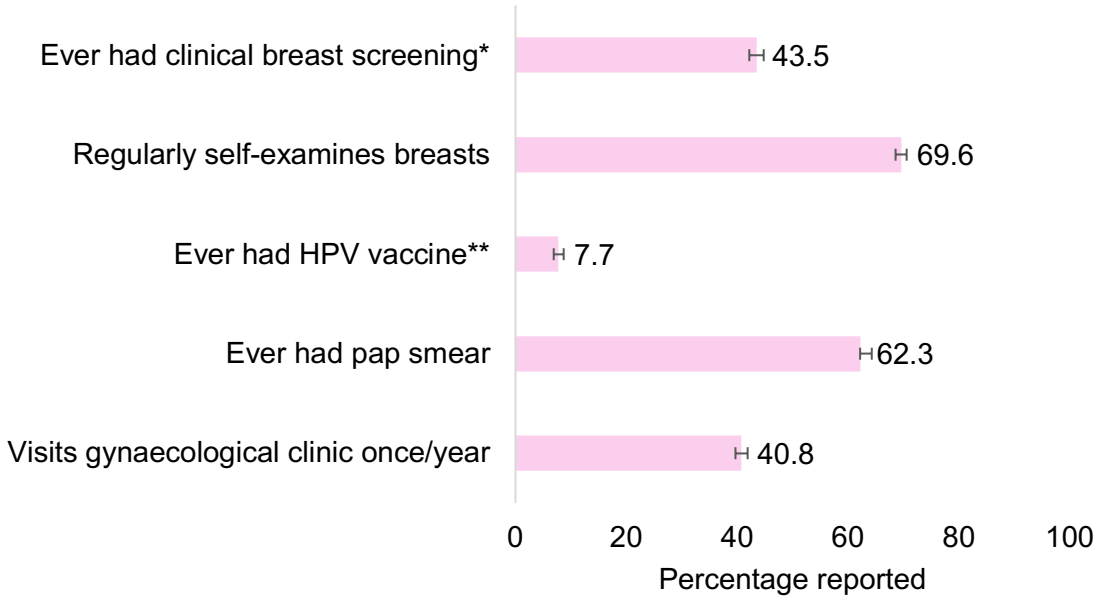
**Defined as those reporting to have been born in Republic of Cyprus*
***Defined as those who reported to not be born in Northern Cyprus, or those who were born in Northern Cyprus but whose parents were not*

Table 17. Daily dietary intake of several food groups in relation to the Mediterranean diet score

Dietary variable	All	Diet score of 0-2 (N = 90)	Diet score of 3-5 (N = 323)	Diet score of 6-8 (N = 100)
				Number (percent)
Vegetables				
Median (g/day)	567.0			
≥Median		10 (11.1)	157 (48.6)	90 (90.0)
<Median		80 (88.9)	166 (51.4)	10 (10.0)
Legumes				
Median (g/day)	39.0			
≥Median		7 (7.8)	165 (51.1)	87 (87.0)
<Median		83 (92.2)	158 (48.9)	13 (13.0)
Fruits and nuts				
Median (g/day)	850.0			
≥Median		17 (18.9)	156 (48.3)	84 (84.0)
<Median		73 (81.1)	167 (51.7)	16 (16.0)
Dairy products				
Median (g/day)	243.0			
≥Median		37 (41.1)	157 (48.6)	62 (62.0)
<Median		53 (58.9)	166 (51.4)	38 (38.0)
Cereals				
Median (g/day)	70.0			
≥Median		18 (20.0)	161 (49.9)	83 (83.0)
<Median		72 (80.0)	162 (50.2)	17 (17.0)
Meat				
Median (g/day)	124.0			
≥Median		59 (65.6)	156 (48.3)	43 (43.0)
<Median		31 (34.4)	167 (51.7)	57 (57.0)
Fish				
Median (g/day)	8.0			
≥Median		12 (13.3)	168 (52.0)	80 (80.0)
<Median		78 (88.7)	155 (48.0)	20 (20.0)
Olive oil				
Median (g/day)	19.0			
≥Median		13 (14.4)	176 (54.5)	86 (86.0)
<Median		77 (85.6)	147 (45.5)	14 (14.0)
Vegetable oil and fats				
Median (g/day)				
≥Median	10.0	39 (43.3)	174 (53.9)	63 (63.0)
<Median		51 (56.7)	149 (46.1)	37 (37.0)
Butter and margarine				
Median (g/day)	1.0			
≥Median		59 (65.6)	226 (70.0)	76 (76.0)
<Median		31 (34.4)	97 (30.0)	24 (24.0)
Eggs				
Median (g/day)	34.0			
≥Median		34 (37.8)	154 (47.7)	55 (55.0)
<Median		56 (62.2)	169 (52.3)	45 (45.0)
Potatoes				
Median (g/day)	33.0			
≥Median		32 (35.6)	158 (48.9)	62 (62.0)
<Median		58 (64.4)	165 (51.1)	38 (38.0)

Sweets				
Median (g/day)	17.0			
≥Median		50 (55.6)	164 (50.8)	48 (48.0)
<Median		40 (44.4)	159 (49.2)	52 (52.0)
Non-alcoholic beverages				
Median (g/day)	14.0			
≥Median		57 (63.3)	181 (56.0)	57 (57.0)
<Median		33 (36.7)	142 (44.0)	43 (43.0)
Tea/coffee				
Median (g/day)	234.8			
≥Median		30 (33.3)	117 (36.2)	45 (45.0)
<Median		60 (66.7)	206 (63.8)	55 (55.0)
Energy				
Median (kcals/day)	2,321.0			
≥Median		22 (24.4)	162 (50.2)	73 (73.0)
<Median		68 (75.6)	161 (49.9)	27 (27.0)
Percentage energy from carbohydrate				
≥Median	38.0			
≥Median		27 (30.0)	161 (49.9)	70 (70.0)
<Median		63 (70.0)	162 (50.2)	30 (30.0)
Percentage energy from protein				
≥Median	18.0			
≥Median		62 (68.9)	180 (55.7)	47 (47.0)
<Median		28 (31.1)	143 (44.3)	53 (53.0)
Percentage energy from fat				
≥Median	44.0	63 (70.0)	172 (53.3)	41 (41.0)
<Median		27 (30.0)	151 (46.8)	59 (59.0)

The Mediterranean Diet (MD) score ranges from 0-8 with a higher score indicating a higher level of adherence to the Mediterranean diet. More details are presented in the Methods section.



**Includes only women >30 years*
***Includes only women between the ages of 18-35 as HPV vaccine was not approved until 2006*
Error bars are 95% confidence intervals

Figure 6. Bar chart showing frequencies of various health-related behaviours

Table 18. Regularity of pap-smear test and clinical breast screenings in COHERE

Regularity	Pap-smear test (n=4,716)	Clinical breast screening* (n=2,142)
Once a year	2,054 (43.6%)	934 (48.0%)
Every other year	617 (32.1%)	436 (22.4%)
Every three years	245 (5.2%)	198 (10.2%)
Every five years	121 (2.6%)	378 (19.4%)
Not regularly	1,679 (35.6%)	-

**Includes only women >30 years*

Table 19. Frequencies, mean years of use and percentage using of overall hormone use in COHERE

Hormone	Mean years of use	n	Proportion (%) In those who report use of hormones (n=1,845)	COHERE (n=7,646)
Combined birth control	2.7	1210	65.6%	15.8%
Oral progestins to regulate cycle	1.4	200	10.8%	2.6%
Don't know what type of hormone	1.8	136	7.4%	1.8%
Other	3.2	130	7.0%	1.7%
Progesterone coil	3.6	86	4.7%	1.1%
Progestin only birth control	1.6	68	3.7%	0.9%
Unsure which type of oral birth control	1.4	57	3.1%	0.7%
Hormone replacement therapy	3.2	57	3.1%	0.7%
Norethindrone acetate	0.5	54	2.9%	0.7%
Progestin injection/shot	1.7	39	2.1%	0.5%
GnRH agonist	2.1	11	0.6%	0.1%
Transdermals: patches, dots	1.2	6	0.3%	0.1%
Hormonal implant	1.3	4	0.2%	0.1%
Vaginal ring	6.3	3	0.2%	0.0%
Danazol	2.5	2	0.1%	0.0%

Table 20. SF-36v2 health domain subscales: mean 0-100 scores with 95% confidence intervals, standard deviation, percentage floor, percentage ceiling, rotated factor loadings, Cronbach's alpha

Scale	N	Mean 0-100 score	95% CI	SD	Percentage floor (%)	Percentage ceiling (%)	Factor score coefficients		Cronbach's alpha
							PCS	MCS	
Physical functioning (PF)	7,607	88.28	(87.92, 88.63)	15.84	0.17	39.49	0.49	-0.21	0.87
Role Physical (RP)	7,558	80.67	(80.15, 81.18)	22.81	0.48	41.81	0.41	-0.11	0.92
Bodily pain (BP)	7,596	68.22	(67.67, 68.77)	24.38	1.20	22.63	0.35	-0.08	0.87
General health (GH)	7,548	63.79	(63.35, 64.24)	19.82	0.21	1.50	0.17	0.08	0.69
Vitality (VT)	7,426	57.50	(57.03, 57.97)	20.71	0.83	1.25	-0.15	0.37	0.74
Social functioning (SF)	7,577	77.40	(76.87, 77.92)	23.27	0.73	35.87	0.03	0.22	0.74
Role emotional (RE)	7,457	77.10	(76.56, 77.64)	23.88	0.62	37.29	-0.06	0.28	0.88
Mental health (MH)	7,455	64.05	(63.60, 64.50)	19.81	0.31	1.99	-0.20	0.41	0.83

CI confidence interval, *SD* standard deviation, *PCS* physical component summary, *MCS* mental component summary

Table 21. SF-36v2 health domain subscales: mean 0-100 scores with 95% confidence intervals, standard deviation, p values from linear regression (global test) according to age (18-25, 26-35, 36-45, 46-55)

	18-25 years				26-35 years				36-45 years			
Scale	**N**	**Mean 0-100 score**	**95% CI**	**SD**	**N**	**Mean 0-100 score**	**95% CI**	**SD**	**N**	**Mean 0-100 score**	**95% CI**	**SD**
Physical functioning (PF)	1,107	93.23	(92.50, 93.97)	12.46	2,374	90.97	(90.42, 91.53)	13.77	2,431	87.90	(87.28, 88.52)	15.61
Role Physical (RP)	1,103	85.17	(83.94, 86.41)	20.93	2,361	82.09	(81.19, 82.99)	22.30	2,407	79.50	(78.58, 80.41)	22.84
Bodily pain (BP)	1,100	72.07	(70.64, 73.49)	24.08	2,370	69.93	(68.98, 70.89)	23.71	2,426	67.28	(66.31, 68.25)	24.39
General health (GH)	1,098	63.41	(62.22, 64.60)	20.07	2,361	64.35	(63.57, 65.13)	19.32	2,413	62.87	(62.07, 63.68)	20.18
Vitality (VT)	1,086	56.19	(54.95, 57.43)	20.84	2,315	57.35	(56.54, 58.17)	20.08	2,372	57.18	(56.34, 58.02)	20.86
Social functioning (SF)	1,100	77.32	(75.95, 78.68)	23.07	2,363	76.78	(75.82, 77.73)	23.74	2,420	77.71	(76.80, 78.61)	22.75
Role emotional (RE)	1,093	73.73	(72.22, 75.23)	25.33	2,333	76.79	(75.82, 77.75)	23.85	2,379	77.78	(76.83, 78.72)	23.50
Mental health (MH)	1,085	62.09	(60.87, 63.32)	20.57	2,339	63.91	(63.13, 64.69)	19.30	2,370	63.73	(62.94, 64.53)	19.71

Scale	**46-55 years**				
	N	**Mean 0-100 score**	**95% CI**	**SD**	**p value**
Physical functioning (PF)	1,695	81.81	(80.92, 82.69)	18.5	**<0.001**
Role Physical (RP)	1,687	77.39	(76.25, 78.54)	23.98	**<0.001**
Bodily pain (BP)	1,700	64.68	(63.50, 65.87)	24.92	**<0.001**
General health (GH)	1,676	64.58	(63.63, 65.53)	19.76	0.665
Vitality (VT)	1,653	59.03	(58.01, 60.05)	21.21	**0.001**
Social functioning (SF)	1,694	77.88	(76.76, 79.00)	23.47	0.146
Role emotional (RE)	1,652	78.80	(77.68, 79.93)	23.25	**<0.001**
Mental health (MH)	1,661	65.99	(65.03, 66.95)	19.98	**<0.001**

N total number CI confidence interval, SD standard deviation

P values from linear regression (crude)

P values <0.05 are bold

Table 22. SF-36v2 health domain subscales: mean 0-100 scores with 95% confidence intervals, standard deviation, p values from linear regression (global test) without and with adjustment for age according to ethnicity (Turkish Cypriot, Turkish, Other/Mixed).

	Turkish Cypriot				Turkish			
Scale	**N**	**Mean 0-100 score**	**95% CI**	**SD**	**N**	**Mean 0-100 score**	**95% CI**	**SD**
Physical functioning (PF)	5,359	88.71	(88.30, 89.13)	15.52	1,516	87.30	(86.45, 88.15)	16.91
Role Physical (RP)	5,323	81.26	(80.67, 81.86)	22.23	1,507	79.69	(78.46, 80.93)	24.40
Bodily pain (BP)	5,346	69.40	(68.76, 70.04)	23.79	1,516	64.72	(63.40, 66.03)	26.09
General health (GH)	5,317	64.61	(64.08, 65.13)	19.60	1,501	61.54	(60.49, 62.59)	20.75
Vitality (VT)	5,238	58.53	(57.99, 59.08)	20.21	1,472	54.38	(53.26, 55.51)	22.04
Social functioning (SF)	5,335	78.13	(77.53, 78.74)	22.58	1,512	76.58	(75.33, 77.83)	24.77
Role emotional (RE)	5,260	77.94	(77.32, 78.57)	23.22	1,480	75.72	(74.42, 77.02)	25.45
Mental health (MH)	5,261	64.86	(64.34, 65.38)	19.22	1,481	62.29	(61.22, 63.37)	21.14

	Other/Mixed				p value	
Scale	**N**	**Mean 0-100 score**	**95% CI**	**SD**	**Crude**	**Adjusted for age**
Physical functioning (PF)	383	89.92	(88.66, 91.19)	12.63	0.362	0.116
Role Physical (RP)	384	80.32	(78.03, 82.62)	22.96	**0.042**	**0.020**
Bodily pain (BP)	384	67.21	(64.72, 69.69)	24.85	**<0.001**	**<0.001**
General health (GH)	386	63.85	(61.95, 65.75)	19.04	**<0.001**	**<0.001**
Vitality (VT)	381	55.61	(53.40, 57.82)	22.01	**<0.001**	**<0.001**
Social functioning (SF)	386	73.45	(70.87, 76.02)	25.83	**<0.001**	**<0.001**
Role emotional (RE)	379	74.85	(72.38,77.31)	24.51	**<0.001**	**<0.001**
Mental health (MH)	379	61.46	(59.24, 63.69)	22.13	**<0.001**	**<0.001**

N total number CI confidence interval, SD standard deviation

P values from linear regression (crude) and with adjustment for age (adjusted for age)

P values <0.05 are bold

Table 23. SF-36v2 health domain subscales: mean 0-100 scores with 95% confidence intervals, standard deviation, p values from linear regression (global test) without and with adjustment for age according to migration background (non-migration background, migration background)

	Non-migration background				Migration background				p value	
Scale	**N**	**Mean 0-100 score**	**95% CI**	**SD**	**N**	**Mean 0-100 score**	**95% CI**	**SD**	**Crude**	**Adjusted for age**
Physical functioning (PF)	5,415	88.90	(88.49, 89.31)	15.42	1,842	87.27	(86.52, 88.02)	16.42	**<0.001**	**0.004**
Role Physical (RP)	5,384	81.42	(80.83, 82.02)	22.17	1,829	79.31	(78.20, 80.42)	24.29	**0.001**	**0.003**
Bodily pain (BP)	5,406	69.33	(68.70, 69.97)	23.87	1,839	65.30	(64.13, 66.48)	25.74	**<0.001**	**<0.001**
General health (GH)	5,376	64.50	(63.98, 65.03)	19.55	1,827	62.24	(61.29, 63.18)	20.60	**<0.001**	**<0.001**
Vitality (VT)	5,300	58.47	(57.93, 59.02)	20.31	1,790	54.69	(53.67, 55.70)	21.86	**<0.001**	**<0.001**
Social functioning (SF)	5,395	78.08	(77.47, 78.68)	22.67	1,837	76.04	(74.90, 77.18)	24.87	**0.001**	**0.001**
Role emotional (RE)	5,322	77.83	(77.21, 78.46)	23.34	1,796	75.77	(74.62, 76.93)	25.01	**0.002**	**0.001**
Mental health (MH)	5,326	64.70	(64.18, 65.22)	19.34	1,794	62.48	(61.50, 63.46)	21.15	**<0.001**	**<0.001**

N total number CI confidence interval, SD standard deviation

P values from linear regression (crude) and with adjustment for age (adjusted for age)

P values <0.05 are bold

Table 24. SF-36v2 health domain subscales: mean 0-100 scores with 95% confidence intervals, standard deviation, p values from linear regression (global test) without and with adjustment for age according to civil status (Single, Married, Divorced/Separated or Widowed).

	Single				Married			
Scale	**N**	**Mean 0-100 score**	**95% CI**	**SD**	**N**	**Mean 0-100 score**	**95% CI**	**SD**
Physical functioning (PF)	1,751	92.46	(91.82, 93.09)	13.55	4,815	87.00	(86.54, 87.46)	16.17
Role Physical (RP)	1,747	84.19	(83.18, 85.19)	21.40	4,779	79.53	(78.87, 80.18)	23.11
Bodily pain (BP)	1,744	71.36	(70.24, 72.47)	23.78	4,807	67.07	(66.38, 67.76)	24.51
General health (GH)	1,738	64.30	(63.36, 65.25)	20.06	4,777	63.55	(62.99, 64.10)	19.69
Vitality (VT)	1,724	57.37	(56.38, 58.35)	20.89	4,693	57.43	(56.83, 58.01)	20.59
Social functioning (SF)	1,738	76.95	(75.84, 78.06)	23.64	4,802	77.86	(77.22, 78.52)	23.04
Role emotional (RE)	1,738	75.08	(73.93, 76.23)	24.52	4,699	78.23	(77.56, 78.90)	23.40
Mental health (MH)	1,724	62.52	(61.57, 63.48)	20.17	4,714	64.97	(64.41, 65.52)	19.40

Scale	**Divorced/Separated or Widowed**				**p value**	
	N	**Mean 0-100 score**	**95% CI**	**SD**	**Crude**	**Adjusted for age**
Physical functioning (PF)	679	88.73	(87.54, 89.91)	15.80	**<0.001**	0.061
Role Physical (RP)	676	82.22	(80.53, 83.92)	22.47	**<0.001**	**0.003**
Bodily pain (BP)	681	69.55	(67.69, 71.40)	24.69	**<0.001**	**0.007**
General health (GH)	677	65.95	(64.43, 67.48)	20.28	**0.040**	**0.007**
Vitality (VT)	665	58.83	(57.17, 60.50)	21.85	0.724	**0.024**
Social functioning (SF)	679	77.39	(75.61, 79.18)	23.74	0.156	0.488
Role emotional (RE)	668	77.06	(75.23, 78.88)	24.06	**<0.001**	**0.028**
Mental health (MH)	670	62.78	(61.15, 64.42)	21.56	**<0.001**	**0.005**

N total number CI confidence interval, SD standard deviation

P values from linear regression (crude) and with adjustment for age (adjusted for age)

P values <0.05 are bold

Table 25. SF-36v2 health domain subscales: mean 0-100 scores with 95% confidence intervals, standard deviation, p values from linear regression (global test) without and with adjustment for age according to residency (Famagusta, Kyrenia, Lefke, Morphou, Nicosia, Trikomo).

	Famagusta				Kyrenia				Lefke			
Scale	N	Mean 0-100 score	95% CI	SD	N	Mean 0-100 score	95% CI	SD	N	Mean 0-100 score	95% CI	SD
Physical functioning (PF)	1,601	88.17	(87.36, 88.98)	16.50	1,257	88.87	(88.05, 89.69)	14.82	260	87.71	(85.86, 89.56)	15.21
Role Physical (RP)	1,594	81.26	(80.15, 82.37)	22.64	1,251	81.24	(80.01, 82.47)	22.15	257	81.61	(78.93, 84.30)	21.99
Bodily pain (BP)	1,603	68.73	(67.54, 69.93)	24.44	1,257	69.30	(67.96, 70.63)	24.12	261	67.67	(64.61, 70.74)	25.26
General health (GH)	1,586	62.68	(61.70, 63.66)	19.90	1,248	64.93	(63.83, 66.03)	19.86	257	64.02	(61.80, 66.24)	18.13
Vitality (VT)	1,560	56.41	(55.37, 57.46)	21.11	1,223	57.72	(56.58, 58.86)	20.33	253	58.37	(55.93, 60.81)	19.80
Social functioning (SF)	1,596	77.13	(75.96, 78.30)	23.82	1,254	77.70	(76.45, 78.96)	22.68	259	81.71	(79.06, 84.36)	21.77
Role emotional (RE)	1,566	77.28	(76.06, 78.51)	24.76	1,227	77.23	(75.93, 78.54)	23.35	254	80.77	(77.95, 83.60)	22.98
Mental health (MH)	1,568	63.28	(62.29, 64.28)	20.05	1,237	63.86	(62.75, 64.98)	20.03	254	65.59	(63.24, 67.94)	19.11

Scale	Morphou				Nicosia				Trikomo				p value	
	N	Mean 0-100 score	95% CI	SD	N	Mean 0-100 score	95% CI	SD	N	Mean 0-100 score	95% CI	SD	Crude	Adjusted for age
Physical functioning (PF)	584	87.34	(85.89, 88.79)	17.86	3,283	88.43	(85.89, 88.96)	15.26	622	87.64	(86.29, 89.00)	17.28	0.658	0.495
Role Physical (RP)	581	79.88	(77.91, 81.86)	24.33	3,257	80.43	(79.66, 81.20)	22.50	618	79.57	(77.61, 81.54)	24.92	0.061	0.167
Bodily pain (BP)	581	65.85	(63.74, 67.95)	25.89	3,272	68.06	(67.25, 68.87)	23.61	622	68.00	(65.90, 70.09)	26.68	0.125	0.275
General health (GH)	580	63.17	(61.45, 64.90)	21.17	3,259	64.41	(63.74, 65.08)	19.42	618	61.60	(59.97, 63.23)	20.69	0.576	0.590
Vitality (VT)	572	56.27	(54.38, 58.16)	23.05	3,208	58.37	(57.68, 59.06)	20.06	610	56.06	(54.34, 57.78)	21.67	0.093	0.132
Social functioning (SF)	582	78.95	(77.02, 80.88)	23.74	3,269	76.65	(75.86, 77.44)	23.05	617	78.16	(76.26, 80.06)	24.08	0.563	0.513
Role emotional (RE)	577	76.56	(74.53, 78.59)	24.91	3,223	76.56	(75.75, 77.38)	23.49	610	78.18	(76.28, 80.09)	23.97	0.493	0.326
Mental health (MH)	575	64.98	(63.26, 66.71)	21.10	3,213	64.04	(63.38, 64.71)	19.34	608	64.93	(63.33, 66.54)	20.16	0.121	0.193

N total number CI confidence interval, SD standard deviation
P values from linear regression (crude) and with adjustment for age (adjusted for age)
P values <0.05 are bold

Table 26 SF-36v2 health domain subscales: mean 0-100 scores with 95% confidence intervals, standard deviation, p values from linear regression (global test) without and with adjustment for age according to educational attainment (Primary or middle school, high school or post-secondary, undergraduate degree, postgraduate degree).

	Primary or middle school				High school or post-secondary			
Scale	**N**	**Mean 0-100 score**	**95% CI**	**SD**	**N**	**Mean 0-100 score**	**95% CI**	**SD**
Physical functioning (PF)	838	84.18	(82.87, 85.48)	19.29	2,538	87.23	(86.59, 87.87)	16.53
Role Physical (RP)	834	77.63	(75.80, 79.46)	26.97	2,516	80.00	(79.09, 80.91)	23.34
Bodily pain (BP)	843	61.37	(59.47, 63.28)	28.24	2,537	67.43	(66.46, 68.40)	24.87
General health (GH)	831	58.42	(56.96, 59.88)	21.44	2,516	63.45	(62.65, 64.26)	20.67
Vitality (VT)	820	51.27	(49.69, 52.84)	23.01	2,467	57.14	(56.27, 58.01)	22.03
Social functioning (SF)	842	76.68	(74.92, 78.44)	26.03	2,526	77.39	(76.47, 78.31)	23.55
Role emotional (RE)	816	77.15	(75.37, 78.94)	26.00	2,478	76.70	(75.75, 77.65)	24.14
Mental health (MH)	821	61.19	(59.64, 62.73)	22.58	2,486	63.44	(62.62, 64.25)	20.70

	Undergraduate degree				Postgraduate degree				p value	
Scale	**N**	**Mean 0-100 score**	**95% CI**	**SD**	**N**	**Mean 0-100 score**	**95% CI**	**SD**	**Crude**	**Adjusted for age**
Physical functioning (PF)	2,579	90.27	(89.75, 90.79)	13.56	1,203	90.54	(89.74, 91.34)	14.12	**<0.001**	**<0.001**
Role Physical (RP)	2,570	81.96	(81.15, 82.77)	20.99	1,197	82.84	(81.63, 84.05)	21.36	**<0.001**	**<0.001**
Bodily pain (BP)	2,570	69.94	(69.06, 70.83)	22.95	1,196	71.55	(70.27, 72.82)	22.44	**<0.001**	**<0.001**
General health (GH)	2,566	64.86	(64.14, 65.58)	18.63	1,193	66.79	(65.72, 67.85)	18.76	**<0.001**	**<0.001**
Vitality (VT)	2,525	58.85	(58.09, 59.60)	19.32	1,183	59.95	(58.89, 61.00)	18.49	**<0.001**	**<0.001**
Social functioning (SF)	2,566	77.84	(76.97, 78.71)	22.38	1,198	78.01	(76.74, 79.27)	22.37	0.162	0.094
Role emotional (RE)	2,540	77.54	(76.65, 78.44)	23.07	1,189	78.30	(77.02, 79.58)	22.58	0.095	**0.012**
Mental health (MH)	2,535	65.02	(64.30, 65.74)	18.46	1,182	65.79	(64.75, 66.83)	18.22	**<0.001**	**<0.001**

N total number CI confidence interval, SD standard deviation
P values from linear regression (crude) and with adjustment for age (adjusted for age)

Table 27. SF-36v2 health domain subscales: mean 0-100 scores with 95% confidence intervals, standard deviation, p values from linear regression (global test) without and with adjustment for age according to employment status* (In paid employment, not in paid employment).

	In paid employment				Not in paid employment				p value	
Scale	**N**	**Mean 0-100 score**	**95% CI**	**SD**	**N**	**Mean 0-100 score**	**95% CI**	**SD**	**Crude**	**Adjusted for age**
Physical functioning (PF)	5,901	88.49	(88.10, 88.88)	15.26	1,370	88.28	(87.36, 89.21)	17.50	0.659	**<0.001**
Role Physical (RP)	5,865	80.97	(80.40, 81.53)	21.98	1,362	80.51	(79.15, 81.87)	25.67	0.506	**0.029**
Bodily pain (BP)	5,890	68.56	(67.96, 69.17)	23.62	1,368	67.33	(65.87, 68.80)	27.58	0.093	**0.003**
General health (GH)	5,860	64.58	(64.09, 65.08)	19.34	1,357	61.12	(59.97, 62.28)	21.63	**<0.001**	**<0.001**
Vitality (VT)	5,762	58.19	(57.67, 58.72)	20.21	1,343	54.79	(53.57, 56.01)	22.81	**<0.001**	**<0.001**
Social functioning (SF)	5,878	77.33	(76.74, 77.92)	23.05	1,367	78.45	(77.17, 79.72)	24.09	0.11	0.066
Role emotional (RE)	5,780	77.64	(77.04, 78.24)	23.25	1,351	75.98	(74.60, 77.36)	25.84	0.021	0.127
Mental health (MH)	5,781	64.32	(63.82, 64.82)	19.40	1,352	63.44	(62.29, 64.59)	21.54	0.143	0.430

N total number CI confidence interval, SD standard deviation

P values from linear regression (crude) and with adjustment for age (adjusted for age)

P values <0.05 are bold

**In paid employment includes both employees, self-employed. Not in paid work includes students, homemakers, retirees, those without employment*

Table 28 PCS, MCS: mean (T scores) with 95% CI, SD and p values from linear regression (global test) without and with adjustment for age for the overall sample (n = 7,089) and subsamples according to age, ethnicity, educational achievement, civil status, city of residence, employment status*.

	PCS			p value		MCS			p value	
Characteristics	**Mean T score**	**95% CI**	**SD**	**Crude**	**Adjusted for age**	**Mean T score**	**95% CI**	**SD**	**Crude**	**Adjusted for age**
Overall sample	50.1	(49.87, 50.34)	9.97	-	-	50.01	(49.78, 50.25)	10.01	**-**	**-**
Age										
18-25	53.32	(52.82, 53.83)	8.34	**<0.001**	-	47.95	(47.31, 48.59)	10.50	**<0.001**	-
26-35	51.50	(51.12, 51.87)	9.10			49.43	(49.02, 49.84)	9.97		
36-45	49.58	(48.17, 50.00)	10.01			50.13	(49.72, 50.53)	9.86		
46-55	46.72	(46.18, 47.26)	10.96			52.07	(51.59, 52.54)	9.56		
Ethnicity										
Turkish Cypriot	50.42	(50.15, 50.69)	9.76	0.072	**0.014**	50.43	(50.16, 50.70)	9.760	**<0.001**	**<0.001**
Turkish	49.30	(48.74, 49.86)	10.71			49.10	(48.55, 49.66)	10.59		
Other/Mixed	50.82	(49.88, 51.76)	9.05			48.40	(47.26, 49.55)	11.06		
Educational achievement				**<0.001**	**<0.001**				**<0.001**	**<0.001**
Primary or middle school	47.55	(46.70, 48.40)	12.17			48.88	(48.14, 49.63)	10.64		
High school or post-secondary	49.60	(49.18, 50.01)	10.26			49.95	(49.53, 50.37)	10.42		
University	51.04	(50.69, 51.39)	8.84			50.24	(49.86, 50.63)	9.57		
Postgraduate	51.58	(51.05, 52.11)	9.13			50.59	(50.03, 51.14)	9.59		
Civil status				**<0.001**	**<0.001**				**<0.001**	**0.047**
Single	52.70	(52.28, 53.12)	8.77			48.61	(48.10, 49.11)	10.53		
Married	49.21	(48.91, 49.51)	10.10			50.64	(50.35, 50.92)	9.69		
Divorced / Separated or Widowed	50.68	(49.87, 51.48)	10.41			49.8	(48.97, 50.62)	10.65		
Migration status				**<0.001**	**0.002**				**<0.001**	**<0.001**
Non migration status	50.48	(50.22, 50.75)	9.7			50.33	(50.06, 50.61)	9.87		
Migration status	49.39	(48.89, 49.90)	10.56			49.18	(48.68, 49.68)	10.47		
City of residence				0.019	0.182				0.243	0.578
Famagusta	50.43	(49.93, 50.94)	9.90			49.6	(49.08, 50.11)	10.11		
Kyrenia	50.62	(50.07, 51.16)	9.59			50.04	(49.46, 50.62)	10.12		
Lefke	49.86	(48.63, 51.08)	9.68			51.37	(50.20, 52.53)	9.190		
Morphou	49.14	(48.24, 50.04)	10.83			50.2	(49.33, 51.07)	10.48		
Nicosia	50.08	(49.74, 50.42)	9.68			50.03	(49.68, 50.38)	9.870		
Trikomo	49.38	(48.45, 50.31)	11.45			50.2	(49.38, 51.02)	10.05		
Employment status*				0.317	**<0.001**				**0.001**	0.083
In paid employment	50.25	(50.00, 50.50)	9.50			50.25	(49.99, 50.51)	9.87		
Not in paid work	49.95	(49.32, 50.58)	11.59			49.24	(48.66, 49.82)	10.65		

PCS Physical Component Summary MCS Mental Component Summary, CI confidence interval SD standard deviation

P values from linear regression (crude) and with adjustment for age (adjusted for age)

P values <0.05 are bold

**In paid employment includes both employees, self-employed. Not in paid work includes students, homemakers, retirees, those without employment*

Table 29. Frequency statistics and component summary scores in Northern Cyprus, and using US and UK scoring coefficients

	Northern Cyprus		US		UK	
	PCS	**MCS**	**PCS**	**MCS**	**PCS**	**MCS**
Time period of data collection	2018-2020		1998		1996	
Mean	50.10	50.01	51.70	43.70	48.30	46.70
Standard deviation	10.00	10.00	7.70	11.90	8.80	11.00
Percentiles						
25	44.95	43.74	47.55	36.41	43.54	40.01
50	52.33	51.63	53.06	46.05	49.93	48.74
75	57.32	57.49	57.14	52.81	54.66	54.95

PCS, physical component summary score; MCS, mental health component summary score

Chapter 3 - Prevalence of endometriosis and related symptoms

3.1 Introduction

Endometriosis is a common, chronic gynaecological condition characterised by the presence of endometrial-like tissue growing in other locations other than uterus, such as the ovaries, bladder and bowel[1]. The true prevalence of the disease is unknown, as estimates can be affected by population samples and diagnostic methods[320], but has been estimated to be around 10%[321]. Estimates vary among different populations from anywhere between 2-43%[80,81,82] among asymptomatic women seeking tubal ligation to 5-50%[83,80,84] among infertile women and 5-21%[80,83,84] among women who are hospitalised for pelvic pain. In addition, observed differences in prevalence rates across populations may be caused by differential access to health care[38]. Endometriosis is difficult to diagnose because definitive diagnosis can only be made through direct visualisation during laparoscopy in combination with histological verification, which is a costly and invasive procedure[66,67]. Significant advancements in quality and availability of non-invasive imaging techniques mean that laparoscopy is no longer recommended as gold standard[51]. However, imaging techniques such as ultrasound and magnetic resonance imaging (MRI) have limited ability to detect superficial endometriosis so cannot replace laparoscopy for detection of all endometriosis subtypes.

Symptom heterogeneity of endometriosis is high; the most common symptoms are dysmenorrhea, dyspareunia, non-cyclic pelvic pain, and infertility, though a large proportion of women are asymptomatic. One difficulty with diagnosing endometriosis is that symptoms can also be attributed to other conditions such as those relating to the bladder or bowel[322]. These difficulties with diagnosis mean that on average, women see a total of seven clinicians before receiving a diagnosis of endometriosis[72,323]. The cross-sectional GSWH[72] included women from ten countries who were undergoing a first laparoscopy for symptoms suggestive of endometriosis. In these women, diagnostic delay ranged from 3-10 years. Women with endometriosis are also at a higher risk for other pain conditions such as migraines, with one study[183] containing the largest known collection of families containing multiple women with surgically confirmed endometriosis, seeing a significantly increased risk of migraine in women with endometriosis compared to those without endometriosis (OR: 1.57, 95%CI: 1.12-2.21).

Studies investigating prevalence rates and symptoms of endometriosis have been limited to Western populations, and moreover, there a lack of data on endometriosis in Northern Cyprus and the broader Eastern Mediterranean region. The endometriosis profile of women from undescribed populations may differ from those already described, and differences in healthcare and health systems may affect diagnoses, symptoms and accessibility of care. Data on endometriosis cases in this study is primarily self-reported, though research has

shown that women self-report endometriosis with reasonable accuracy (>70%)[324].

Therefore, this chapter had the following aims:

1) Estimate the self-reported prevalence rate of endometriosis in this population of women
2) Describe the pain symptomologies of women with endometriosis and compare this to symptomatic pain and asymptomatic pain controls
3) Ascertain the prevalence of co-occurring conditions such as bladder pain and irritable bowel syndrome as well as investigate the odds of migraine as a co-morbidity of endometriosis.
4) Estimate the prevalence of infertility in women with and without endometriosis

3.2 Methods

3.2.1 Prevalence

Definition of prevalence

The prevalence of a disease in a population is defined as the proportion of the population that has the disease at some point in a time period (period prevalence) or at a specific point in time (point prevalence). Prevalence of endometriosis in this sample was calculated as the (number of endometriosis

cases/total number of women recruited)*100. This chapter also looks at prevalence rates of endometriosis based on geographical area; relative prevalence was calculated as the (number of endometriosis cases reporting to live in an area/the total number of women reporting to live in that area)*100.

3.2.2 Case and control ascertainment

Self-reported endometriosis cases were defined as those participants who answered 'yes' to the following question: *'Has a doctor or health care provider ever diagnosed you with endometriosis?'* or when asked the reason for using hormones the answer was 'endometriosis' or 'chocolate cyst'. Additional endometriosis cases were women who were found to have evidence of an endometrioma at their clinical visit where they had an USS (*Chapter 2*). Further information on cases was also ascertained from the medical history table and from the infertility-related question: *'Have you or your partner ever had any test/investigations to find out why you were not getting pregnant?'*. The control group was the remainder of the cohort who had not self-reported to have endometriosis and had no evidence of an endometrioma on their ultrasound scan, if they had a clinical visit.

3.2.3 Sociodemographic characteristics

Differences in demographics were examined between cases and controls. Age was analysed as a continuous variable. Educational attainment was examined as a categorical variable with four categories (primary and middle school, high

school and post-secondary, undergraduate degree, and postgraduate degree). Employment status is presented as a categorical variable with two categories (employed and unemployed). Ethnicity had three categories (Turkish Cypriot, Turkish and Mixed/Other). Marital status was analysed as a categorical variable with three categories (married, divorced/widowed and single). Displaced women were defined as those who reported their birthplace to be in the Republic of Cyprus and were analysed as a dichotomous variable (displaced, not displaced). Migrant status was analysed as a dichotomised variable (migrant/non-migrant) with migrants being defined as those who were either not born in Northern Cyprus or were those who were born in Northern Cyprus but did not have at least one parent who was also born in Northern Cyprus. Residence type was also analysed as a dichotomous variable (city or town/village) and was based on the Sub-District women reported to live in. District of residence was categorised into 6 distinct groups: Famagusta, Kyrenia, Lefke, Morphou, Nicosia or Trikomo (*Chapter 2*).

3.2.4 Diagnosis

Data on diagnostic method, symptoms that prompted a medical appointment that led to diagnosis of endometriosis, age at symptom onset and age of diagnosis was obtained from the questionnaire for women who self-reported their endometriosis diagnosis. Diagnostic delay was calculated by subtracting age of symptom onset from age of diagnosis. Hypothesising that symptom awareness of endometriosis was low in this population, an alternate age of symptom onset variable was created by examining the earliest age women self-reported to have experienced either dysmenorrhea, non-cyclical pelvic pain, or dyspareunia. For

women who did not self-report an endometriosis diagnosis but had evidence of an endometrioma at their pelvic ultrasound scan, age of diagnosis was taken as age at recruitment and diagnostic delay was described as above. An alternative diagnostic delay variable was created by subtracting the alternate age of symptom onset variable from age of endometriosis diagnosis.

Differences in mean diagnostic delay were examined against symptoms that participants reported prompted their healthcare appointment (pain, infertility, other symptoms, no symptoms) as well as the following demographics: age, education, employment, ethnicity, civil status, residence type and district of residence, analysed as stated above.

3.2.5 Pain symptomology

Endometriosis is a complex condition with a lot of symptom heterogeneity[2]. Pain is one of the most common symptoms. To investigate the pain symptomology of women in this population, women were defined as suffering from severe pain if they scored above 4[260] on the 11-point NRS (0-10)[268] for one of the following questions:

- Dysmenorrhea – *severity of period pain at its worst in the last 12 months.*
- Dyspareunia – *severity of pain at its worst during the last time you had vaginal intercourse/penetration* or *in the 24 hours after the last time you had vaginal intercourse/penetration.*

- Non-cyclic pelvic pain – *severity of pelvic pain at its worst in the last 3 months*.

The NRS has been used extensively in women with menstrual pain and has been shown to have good construct validity, allowing the intensity and severity of pain experienced to be investigated[268,269]. An average pain severity rating was also deduced from the above. The SF-MPQ[272] was utilised to explore subcategorization of pain symptoms based on two separate domains: sensory and affective, the PCtS[261] was used to investigate the rumination, magnification and helpless of the presence of pain in endometriosis cases and controls. The Rome IV[263] criteria allowed assessment of the percentage of women who suffered from IBS symptoms during the menstrual cycle and during an episode of pelvic pain. The UCSD[264] was used to assess the presence of migraine with aura and migraine without aura and to see if migraine was more common in endometriosis cases.

Similar to the NRS above, participants were asked to rate their bladder pain at its worst over the last 7 days and how often their bladder pain affected them in various situations, using a 5-point Likert scale ranging from ‘Never’ to ‘Always’. As these questions were designed to assess bladder pain in the last 7 days only, bladder pain is described as a co-morbidity of endometriosis, rather than a separate pain category, given many short-term conditions can cause bladder pain, such as urinary tract infections (UTIs) and other bacterial conditions.

3.2.6 Infertility

It is well established that infertility can be symptom of endometriosis. According to the WHO[325], infertility is defined as *'the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse'.* Infertility was not a criterion for symptom grouping of cases and controls in this study, because the questionnaire only asked about difficulties in trying to get pregnant for 6 months and did not ask about regularity of intercourse or whether timed intercourse during the fertile period was attempted. Nevertheless, frequency of 'infertility' in this population is described here. Furthermore, the questionnaire design meant that primary infertility (where someone who has never conceived a child in the past has difficulty conceiving) could not be distinguished from secondary infertility (where someone has had one or more pregnancies in the past but is having difficulty conceiving again).

3.2.7 Symptomatic and asymptomatic control group

Theoretically, a control group should be comprised of disease-free women sampled from the same source population as cases. However, as explained in *Chapter 1*, the complexity and heterogeneity of endometriosis means that choosing a valid comparison group is complex and it is more appropriate to select multiple control groups to investigate the sensitivity of results to control selection. Here two control groups were created to explore whether certain symptoms or characteristics were due to endometriosis *per se*, or due to the pain that endometriosis cases were experiencing:

1. Symptomatic pain controls – defined as women who did not report to have endometriosis or have evidence of an endometrioma on their ultrasound scan but reported to have dysmenorrhea, dyspareunia or pelvic pain and reported the severity as >4 on the relevant NRS, as described above.
2. Asymptomatic pain controls - the remainder of the cohort i.e., those women who did not self-report an endometriosis diagnosis, did not have evidence of an endometrioma on their ultrasound scan and did not report the severity of dysmenorrhea, dyspareunia or pelvic pain as >4 on the relevant NRS.

3.2.8 Missing values

Missing values were dealt with in Stata using listwise deletion, i.e., observations that were missing any values for a specific variable were dropped in the analysis for that variable. In general, if there were missing values, then the values were scored as none.

3.2.9 Statistical methods

Prevalence was calculated as the proportion of endometriosis cases in the study population. Confidence intervals (95% CI) for observed prevalence were calculated using the standard error of the estimates in the population. For each characteristic, frequencies were described. Differences in characteristics

between cases and controls were examined using the appropriate statistical methods; for univariate associations, Chi-squared tests for equality of proportions was used for categorical variables or Fisher's exact where the expected value of a variable in any cell of a 2x2 contingency table was <5. For differences in means, continuous variables were examined using student's t-test of equality of means, for non-parametric variables that did not follow a normal distribution, the appropriate non-parametric test equivalent was used. To adjust for variables, unconditional multivariate logistic regression modelling was used. Confounding variables were either chosen based on an *a priori* assumption or were shown to be significantly associated with both the exposure and outcome during univariate analyses. Variables were deemed significant if $p<0.05$ and for each model, the confounders are listed in the respective table.

3.3 Results

3.3.1 Endometriosis prevalence and demographic comparison

The self-reported prevalence of endometriosis was 5.2% (95%CI; 4.7%-5.7%, n=395/7,646). Nearly 50% (47.5%, n=192) of cases reported their diagnosis solely in the endometriosis-specific part of the questionnaire (*Figure 1*), with 41.2% (n=168) reporting it in both the endometriosis-specific part of the questionnaire and in the medical history table. A total of 7.8% (n=32) of women also reported their diagnosis in the infertility section and 3.7% (n=15) of the cases showed endometriomas on their USS and did not report to have

endometriosis in any other part of the questionnaire. Overall prevalence of endometrioma was 2.7% (95%CI; 1.7%-4.3%, 18/663). Therefore, the overall prevalence of endometriosis in this study was 5.4% (95%CI; 4.9%-5.9%, n=410/7,646).

There was a significant difference in prevalence of endometriosis across the island (p=0.001) (*Figure 2*). Relative prevalence of endometriosis across Northern Cyprus varied from 3.0% (95%CI: 2.0%-4.7%, mean age=37.3) in Trikomo to 6.5% (95%CI:4.1%-10.2%, mean age=37.1) in Lefke. When examining the relative prevalence rates at the sub-district level there was a significant difference in endometriosis prevalence (p=0.009). The towns/villages of Trikomo had the lowest relative prevalence at 2.1% (95%CI: 1.0%-4.6%, mean age=34.3) and the city of Kyrenia had the highest prevalence at 7.8% (95%CI: 4.9%-1.2%, mean age=35.2). Relative prevalence in the cities of Trikomo was 3.8% (95%CI: 2.2%-6.4%, mean age=38.7) and 4.9% (95%CI: 3.8%-6.4%, mean age=39.2) in the towns/villages of Kyrenia.

There was no significant difference in any demographics between the incident endometrioma (n=15) cases diagnosed at the pelvic USS and the self-reported endometriosis (n=395) cases before or after adjustment for age (*Table 1*). Mean age was slightly higher in endometriosis cases compared to incident endometrioma cases (37.9 (8.2) vs 34.7 (8.8)) and the endometrioma cases were less likely to be Turkish Cypriot (60.0% (n=9) vs 78.4% (n=301)) and more likely to be Turkish (26.7% (n=4) vs 16.9% (n=65)) or Mixed/Other (13.3% (n=2)

vs 4.7% (n=18)). They were also more likely to have a postgraduate degree (26.7% (n=4) vs 22.8 (n=85)). The endometrioma cases were less likely to be employed (80.0% (n=12) vs 89.6% (n=344)) and less likely to be single (13.3% (n=2) vs 19.7% (n=75)). They were also more likely to be a healthy weight compared to the self-reported endometriosis cases (66.7% (n=10) vs 57.7% (n=214)).

Table 2 shows the comparison of demographics between women with and without endometriosis. Women in the endometriosis group had a mean age of 37.8 (SD=8.3) compared to a mean age of 36.9 (9.7) for women in the control group (p=0.05), there was no significant difference between the endometriosis and non-endometriosis group in terms of ethnicity (p=0.141 after adjustment for age), type of residence (City/Village, p=0.43) or district currently residing in (p=0.09). Women with endometriosis were more likely to have a higher education compared to those without endometriosis (undergraduate degree: 39.2% (n=152) vs 35.7% (n=2,431)) and postgraduate degree (endometriosis 22.9% (n=89) vs controls 16.4% (n=1,115), p<0.001 after adjustment for age) and were also significantly more likely to be in paid employment (89.2% (n=356) vs 80.6% (n=5,564), p<0.001 after adjustment for age). Women with endometriosis appeared to be more likely to be married compared to those without endometriosis (68.9% (n=272) vs 66.4% (n=4,567)), but this difference was not significant after adjustment for age (p=0.59). There was no significant difference between the two groups in terms of displaced women.

Ten percent (n=41) of endometriosis cases reported that they were born with a structural problem/birth defect of their uterus, cervix, or vagina, compared to 4.0% (n=286) of controls (p<0.001). Of the 40 endometriosis cases, 36.6 (n=15) reported to have had surgery for this issue, compared to 28.0% (n=80) of controls (p=0.482), 60.0% (n=9) of the endometriosis cases reported that the problem was improved or corrected after surgery compared to 81.3% (n=65) of controls, p=0.085.

3.3.2 Diagnosis

Of the 395 (93.4%) self-reported cases of endometriosis who gave information about their endometriosis diagnosis, 83.8% (n=331) were diagnosed via ultrasound/MRI, 11.6% (n=46) via laparoscopy, 15.2% (n=60) based on symptoms and 4.3% (n=17) via another method e.g., during delivery, surgery, or a general check-up (*Table 3*). The overlap of diagnostic method can be viewed in *Figure 3.* In terms of symptoms that prompted the women to see their healthcare provider before receiving a diagnosis, the most common was pain, with 51.9% (n=205) of women reporting this symptom (*Table 3*). The overlap of symptoms prompting a healthcare appointment can be viewed in *Figure 4.* Only 5.8% (n=23) of women reported infertility as the reason for seeking healthcare, 20.5% (n=81) reported another reason e.g., changes in menstruation and 15.9% (n=63) did not report any symptoms.

Table 4 compares the demographics of women who were reported to be diagnosed with endometriosis surgically with women who were not diagnosed surgically; there were no significant differences between demographics and diagnosis method before or after adjustment for age. On average, women diagnosed by laparoscopy tended to be slightly older than those not diagnosed by laparoscopy (39.4 (SD=7.3) vs 37.7 (SD=8.3), p=0.200) and a higher percentage identified as being Turkish (21.7% vs 16.3%) or Mixed/Other (8.7% vs 4.1%) rather than Turkish Cypriot (69.6% vs 79.6%), p=0.083. Women who were diagnosed surgically were more likely to reside in the city (58.7% vs 46.7%, p=0.136), more likely to be in paid employment (91.3% vs 89.3%, p=0.641), have a postgraduate degree (27.3% vs 22.2%, p=0.463) and be married (75.6% vs 68.1%, p=0.646). There were no differences in frequencies of displaced persons (4.3% vs 4.3%, p=0.690). For the women who were diagnosed via laparoscopy, they were more likely to cite pain (67.4% vs 49.9%, p=0.025) and infertility (19.6% vs 4.0%, p<0.001) as reasons for seeking healthcare and opposed to other (21.74% vs 20.3%, p=0.826) and no symptoms (6.5% vs 17.2%, p=0.063).

The mean age of symptom onset was reported to be 25.9 (SD=8.0) and the mean age of diagnosis was 27.5 (7.8), giving a diagnostic delay of 1.6 years. Nearly three-quarters (71.2%, n=80) of women reported 0 years between symptom onset and receiving their diagnosis. Given the relatively high age at symptom onset compared to the age of diagnosis, it can be hypothesised that women in this population have low awareness of endometriosis symptoms,

specifically pain. Examining the pain-related variables confirmed this; for dysmenorrhea, the earliest mean age of pain was 16.2 years (5.4), for non-cyclic pelvic pain, the earliest mean age of pain was 26.1 years (6.5) and for dyspareunia, the earliest mean age of pain was 23.1 years (9.5). Recalculating diagnostic delay using this information for 76.5% (n=199) of the endometriosis cases gave a mean of 11.9 (7.9) years. Combining this new information with older information on diagnostic delay gave an overall mean diagnostic delay of 9.3 years (n=292). There was a significant difference between diagnostic delay and current age at time of survey after adjustment for education, employment, ethnicity, residence, civil status and BMI, with younger women between the ages of 18-25 having the lowest diagnostic delay at 4.4 years, compared to women between the ages of 46-55, who had a diagnostic delay of 17.1 years (*Figure 5*). There were no significant differences between diagnostic delay and other demographic factors, including education, employment, ethnicity, residence, and civil status.

Examining the symptoms women experienced that prompted their healthcare appointment, women who reported no symptoms had the highest mean diagnostic delay at 10.9 years (SD=9.3), with women reporting pain having the lowest diagnostic delay at 8.8 years (SD=8.1) (*Figure 6*). There were no significant differences in mean diagnostic delay when examining reason that prompted healthcare appointment and subsequent endometriosis diagnosis.

3.3.3 Characteristics of women who did not report pain as a symptom to seeking healthcare

To understand whether the women who did not report pain as a reason to seek healthcare were, in fact pain-free, self-reported pain profiles were examined. For these 190 women, 88.4% (n=168) reported to have ever had dysmenorrhea, 21.1% (n=40) ever experienced non-cyclic pelvic pain and 20.5% (n=39) reported ever having pain during or after intercourse. NRS scales were examined to investigate this further – of the 138 women who had periods in the last 12 months, 50% (n=69) rated their pain as above 4 in relation to dysmenorrhea at its worst in the last 12 months. Of the 31 women who had experienced pelvic pain in the last 3 months, 54.8% (n=17) rated their pelvic pain as above 4 at its worst in the last 3 months. Of the 16 women who had experienced pain during intercourse in the last 12 months, 37.5% (n=6) rated it above 4 at its worst, and of the 15 women who experienced pain in the 24 hours after intercourse, 20.0% (n=3) rated it above 4 on the NRS.
However, women who reported pain as a symptom that prompted them to seek healthcare advice did have higher mean NRS scores on average compared to women who did not report pain as a symptom. Mean scores for dysmenorrhea at its worst in the last 12 months were 8.2 vs 7.1 ($p<0.001$), for pelvic pain at its worst in the last 3 months scores on average were 7.0 vs 4.9 ($p=0.001$), for pain at its worst during last intercourse average scores were 5.6 vs 4.4 ($p=0.09$) and pain at its worst after last intercourse scores were 4.7 vs 3.0 ($p=0.07$) (*Figure 7*).

Examining the pain characteristics of the 15 incident endometrioma cases showed that 100% (n=15) had ever had dysmenorrhea, 26.7% (n=4) report to have ever suffered with non-cyclic pelvic pain, one reported to experience pain during last intercourse and two (66.7%) reported to experience pain in the 24 hours after last intercourse. Nearly all women (93%, n=14) reported the severity of their dysmenorrhea at its worst was above 4 in the last 12 months, 50% (n=2) reported their pelvic pain to be above 4 on the NRS at its worst in the last 3 months, and 25% (n=1) stated the severity of pain during and after intercourse at its worst was above 4 (*Table 5*).

Of the 40 women who said pain was not a symptom that prompted them to seek healthcare but had reported to suffer from pelvic pain, 50% (n=20) reported to have received a diagnosis for their pelvic pain from a doctor, compared to 61.3% (68/111) of women who said pain was a symptom ($p<0.001$) (*Table 6*). Just under 70% (69.1%, n=47) of those who had pain as a symptom had been told their pelvic pain was a symptom of endometriosis compared to 25% (n=5) of women who did not state pain was a symptom prompting their appointment, $p<0.001$. Women in both groups were given a range of different reasons for their pain, ranging from fibroids (21%, n=14 in pain as a symptom group vs 10%, n=2 in pain not a symptom group, $p=0.28$), ovarian cysts (32%, n=22 in pain as a symptom group vs 40%, n=8 in pain not a symptom group, $p=0.526$) and stress (12%, n=8 in pain as a symptom group vs 10%, n=2 in pain not a symptom group, $p=0.827$).

Of the four incident endometrioma cases who experienced pelvic pain, two (50.0%) women stated that they had received a diagnosis for their pelvic pain: one individual stated the reasons were uterine fibroids and ovarian cysts and the other stated they had received the following diagnoses: irritable bowel syndrome, inflammatory bowel disease, ovarian cysts, pelvic inflammatory disease, painful bladder/interstitial cystitis. Only one woman (6.7%) stated that she had tried to get pregnant for 6 months in a row without succeeding and the results of the tests were poor sperm count/quality.

3.3.4 Treatment of endometriosis

Regarding surgical treatment of endometriosis, 26.3% (n=104) of self-reported cases had not had surgery for endometriosis, 20.5% (n=81) of cases reported that their endometriosis was treated during their last surgery, 30.1% (n=119) of cases said that their endometriosis was not treated during their last surgery, and 3.8% (n=15) were not sure if it was treated. As shown in the previous chapter (*Chapter 2*), use of hormones in this study overall was low, and women with endometriosis were significantly more likely to use hormones compared to women without endometriosis (48.1% vs 21.7%, $p<0.001$), with 14.2% (n=28) of women with endometriosis reporting the reason for using hormones was because of their endometriosis. Compared to the control group, endometriosis cases were less likely to use hormones for birth control (24.9% vs 42.6%, $p<0.001$), heavy bleeding (27.9% vs 30.8%, $p<0.001$) and irregular periods (27.9% vs 30.8% $p<0.002$) but more likely to use hormones for pelvic pain (18.3% vs 6.8%, $p<0.001$) (*Figure 7)*.

3.3.5 Pain characteristics

The flowchart depicted in *Figure 8* shows the different groups of participants. In the endometriosis group, 52.9% (n=217) were characterised as being symptomatic for pain as detailed in the methods section of this chapter. Overall, endometriosis cases were significantly more likely to suffer from pain compared to the control group (52.9% vs 40.5%, p<0.001) for the following pains: dysmenorrhea (48.1% vs 40.0%, p<0.001), dyspareunia (6.1% vs 3.8%, p=0.018) and non-cyclic pelvic pain (12.9% vs 6.1%, p<0.001). In total, 47.1% (n=193) of endometriosis cases were categorised as not suffering from pain; 25.4% (n=49) reported that their endometriosis was treated at their last surgery. Fifteen percent of the asymptomatic pain endometriosis cases (n=29) had tried to get pregnant for more than six months in a row without succeeding but only one (3.5%) of these women failed to get pregnant. Of the symptomatic control group, only six (0.2%) reported to have had surgery to look for endometriosis and none was found; all women who answered the question about the symptoms that prompted the surgery reported pain (n=3). Hormone use in the symptomatic control group was significantly lower compared to endometriosis cases (23.6% vs 48.1%, p<0.001).

Table 7 shows the comparison of demographics between endometriosis cases, symptomatic and asymptomatic pain controls. Average age of women with endometriosis was 37.8 (8.3) years compared to 32.7 (8.7) years in symptomatic controls, p<0.001 and 39.6 (9.3) years in asymptomatic controls,

p<0.001. There was no significant difference in ethnicity between endometriosis cases and asymptomatic controls (p=0.216) but compared to symptomatic controls, there was a higher proportion of women identifying as Turkish Cypriot (75.6%, n=310; 70.35%, n=2,035) and a lower proportion identifying as Turkish (16.8%, n=69; 21.5%, n=632, p=0.041). There was no difference in residence type between endometriosis cases and symptomatic controls (City: 48.2% vs 48.8%, p=0.745) or asymptomatic controls (46.0%, p=0.327). There was no difference in district of residence between endometriosis cases and symptomatic controls but some differences between asymptomatic controls (p=0.047). The proportion of women in paid employment was highest in endometriosis cases (86.8%, n=356) compared to symptomatic and asymptomatic controls (76.1%, n=2,204; 77.6%, n=3,369) and this difference was significant after adjustment for age (p=0.001; p<0.001). Higher educational achievement was significant between endometriosis cases and symptomatic controls (p<0.001) and endometriosis cases and asymptomatic controls (<0.001) after adjustment for age. There was no significant difference in civil status between endometriosis cases and symptomatic controls or asymptomatic controls (p=0.195; p=0.247). After adjustment for age, there was no significant difference in numbers of women displaced between endometriosis cases and symptomatic controls (4.1% vs 2.0%, p=0.446) or asymptomatic controls (6.0%, p=0.622).

3.3.6 Co-existing pain symptoms

3.3.6.1 Dysuria (painful urination)

There was no significant difference in the prevalence of bladder pain between endometriosis cases and symptomatic pain controls (6.3% (n=26) vs 6.4% (n=187), p=0.94), but endometriosis cases had a significantly higher frequency of this pain compared to the asymptomatic control group (1.0%, n=42, p<0.001). Almost all (96.2%, n=26) of women with bladder pain in the endometriosis group were classified as being in the symptomatic endometriosis group i.e., they suffered from dysmenorrhea, dyspareunia, or pelvic pain by scoring above 4 on the relevant NRS.

Figure 9 panels A-G display the frequency of responses to questions regarding bladder pain in the last 7 days. There were no significant differences between frequency of responses between endometriosis cases and symptomatic controls for most questions apart from when answering ‘how bothered were you by frequent urination during the daytime?’ (p=0.035) in which the endometriosis group was more likely to report ‘most of the time’ (7.5% vs 2.4%) and ‘always’ (4.1% vs 0.8%). There was a significant difference in the frequency of responses between endometriosis cases and asymptomatic controls when asked ‘how often did you have a feeling of pressure in your bladder?’ (p=0.002) where endometriosis cases were more likely to report ‘often’ (26.8% vs 11.9%) and less likely to report ‘never’ (33.1% vs 43.8%) and ‘how often did you have

pain in your bladder' (p=0.014) where endometriosis cases were more likely to report 'often' (11.5% vs 9.9%) or 'most of the time' (3.6% vs 1.3%).

3.3.6.2 Irritable bowel syndrome (IBS)

Women with endometriosis had a higher prevalence (4.6%, n=19) of IBS symptoms (filled the Rome IV diagnostic criteria) related to pelvic pain, compared to both symptomatic (2.6%, n=75; p=0.018) and asymptomatic (0.3%, n=13, p<0.001) controls. However, there was no significant difference in prevalence of IBS symptoms that were related to the menstrual cycle between endometriosis cases (4.6%, n=19) and symptomatic controls (5.4%, n=157, p=0.531) but there was a significant difference when comparing endometriosis cases to the asymptomatic control group (1.2%, n=50; p<0.001).

3.3.7 Pain catastrophizing scale (PCtS)

Overall PCtS scores were similar between endometriosis cases and symptomatic controls (27.6 (12.1) vs 27.5 (12.1), p=0.94) as were scores for rumination (9.6 (4.7) vs 9.6 (4.7), p=0.39), magnification (6.0 (2.8) vs 6.0 (2.8), p=0.62) and helplessness (13.0 (6.0) vs 12.8 (6.0), p=0.76) (*Figure 10*). After adjustment for relevant demographics (age, ethnicity, location of residence, employment, education) endometriosis cases had significantly (p<0.001) higher scores for all four components, compared to asymptomatic controls (PCtS: 23.2 (10.6), rumination: 8.0 (4.2), magnification: 5.2 (2.5), helplessness: 10.7 (5.2)) (*Figure 10*).

Although the overall PCtS mean score did not reach 30 (cut-off for clinical significance, *Chapter 2*), 48.3% (n=198) of endometriosis cases scored equal or over 30, compared to 47.3% (n=1,382) of the symptomatic control group. Splitting the endometriosis cases into symptomatic and asymptomatic for pain and adjusting for demographics, women in the symptomatic endometriosis group scored significantly higher overall compared to the asymptomatic endometriosis group (29.5 (12.2) vs 25.2 (11.5), p=0.021) and compared to the symptomatic control group (p=0.035). Though the symptomatic pain endometriosis group scored consistently higher than the asymptomatic pain endometriosis group, these differences were not significant after adjustment for demographics: rumination (symptomatic endometriosis: 10.1 (4.6) vs asymptomatic endometriosis 8.9 (4.7), p=0.0.76), magnification (6.4 (2.8) vs 5.6 (2.8), p=0.051) and helplessness (13.7 (5.9) vs 12.1 (6.0), p=0.081) with the associations also being significant between symptomatic endometriosis and symptomatic controls for helplessness (p=0.016) but not magnification (p=0.056) or rumination (p=0.115) after adjustment for demographics.

3.3.8 Short-Form McGill Pain Questionnaire (SF-MPQ)

Mean affective pain scores were slightly higher in endometriosis cases (9.0 (4.5)) compared to symptomatic controls (8.5 (4.0)), though this was not significant (p=0.37), but scores were significantly lower in asymptomatic controls (4.9 (1.9)), compared to endometriosis cases, (p<0.001) (*Table 8*). Sensory pain scores were similar in endometriosis cases and symptomatic

controls (24.6 (9.4) vs 23.6 (8.1), p=0.46), with endometriosis scores being significantly higher compared to the asymptomatic control group (15.0 (4.0), p<0.001). Endometriosis cases had the highest overall scores (33.1 (13.8)), with symptomatic controls have slightly lower overall scores (31.9 (11.4), p=0.55) and asymptomatic controls having significantly lower scores compared to the endometriosis cases (19.8 (5.3), p<0.001).

3.3.9 Migraine

Compared to symptomatic controls, women with endometriosis had a higher prevalence of recurrent headaches (52.1%, n=209 vs 48.7%, n=1,392, p=0.198) and a significantly higher prevalence compared to asymptomatic controls (38.4%, n=1,544, p<0.001). In the endometriosis group, 11.2% (n=46) women were classified as having migraine with aura, compared to 10.7% (n=312) in the symptomatic control group (p=0.740) and 5.8% (n=251) of women in the asymptomatic control group (p<0.001). Migraine without aura affected 19.8% (n=81) of the endometriosis group compared to 16.4% (n=479) of the symptomatic control group (p=0.088) and 11.1% (n=477) of the asymptomatic controls (p<0.001). Since there were only 109 women across all groups who experienced migraine with aura independently of migraine without aura, the two types of migraine are not distinguished between going forwards.

Crude odds of migraine in women with endometriosis compared to women without endometriosis was 1.62 (95%CI 1.24, 2.11, p<0.001) (*Table 9*). After adjustment for age and ever use of hormones, the odds of migraine in women

with endometriosis compared to women without endometriosis was attenuated slightly to 1.49 (95%CI 1.13, 1.95, p=0.003). The odds further decreased to 1.39 (95%CI 1.06, 1.83, p=0.013) after further adjustment for pain during last period and having pelvic pain in the last 3 months.

3.3.10 Infertility

Women with endometriosis were significantly more likely to report to have tried to get pregnant for more than 6 months in a row without succeeding compared to symptomatic pain controls, with 15.6% (n=64) of cases and 7.1% (n=206) of symptomatic controls reporting this (p<0.001) (*Table 10*). Frequency of infertility in the asymptomatic pain control group was like that of the symptomatic controls and significantly lower than endometriosis cases (7.3%. n=315, p<0.001). However, for women who struggled to get pregnant, there was no significant difference in the longest amount of time they struggled to get pregnant with endometriosis cases reporting an average of 21.6 (29.0) months, symptomatic controls reporting an average of 22.0 (31.8) months, p=0.948 and asymptomatic controls reporting an average of 23.3 (37.8) months, p=0.838. Women with endometriosis and/or their partners were significantly more likely to have tests or investigations into why they were not getting pregnant with 87.3% (n=55) of endometriosis cases and 73.0% (n=149) of symptomatic controls reporting to have done so, (p=0.020) and 77.1% (n=235) of asymptomatic controls, (p=0.070). This difference between endometriosis cases and symptomatic controls remained strong even after adjustment for demographics. Over half (63.6%, n=35) of endometriosis cases were told the reason for their difficulty

conceiving was due to endometriosis compared to 0.7% (n=1) of the symptomatic, (p<0.001) and 0.4% (n=1) of the asymptomatic control groups (p<0.001) (*Table 10*). Other reasons reported by women to explain their difficulties in getting pregnant for endometriosis cases included PCOS (10.9%, n=15.4), no/irregular ovulation (5.5%, n=3) and poor sperm count/quality (10.9%, n=6). Of the 64 endometriosis cases reporting to have difficulties with getting pregnant, 90.6% (n=58) reported to have ever been pregnant compared to 74.3% (n=153) of symptomatic controls, p=0.006 and 89.2% (n=281) of asymptomatic controls, p=0.736.

Women with endometriosis were 2.49 (95%CI: 1.83-3.39) times more likely to have tried to get pregnant for 6 months or more compared to symptomatic controls and after adjustment for demographics the odds slightly attenuated to 1.94 (95%CI: 1.40-2.68) (*Table 11*). Compared to the asymptomatic control groups, odds of trying to get pregnant for 6 months were 2.39 (95%CI: 1.77-3.22) times higher in the endometriosis group and after adjustment for demographics, odds increased to 2.55 (95%CI: 1.87-3.46).

3.4 Discussion

In this chapter, I have described for the first time the prevalence rate and pain symptomology of endometriosis in Northern Cyprus, using a nationally representative[258] sample, contributing to the wider literature on endometriosis and helping to fill a prominent gap in women's health research in non-Western populations.

These data suggests that self-reported prevalence of endometriosis was 5.2% (95%CI; 4.7%-5.7%, n=395/7,646) in reproductive-aged women. Based on extrapolation of these findings, this represents approximately 7,500 women living in Northern Cyprus. This is akin to other published studies which have used similar sampling methods, such as an Australian cohort, which estimated prevalence to be 3.4%[104] and 3.7%[326], Puerto Rico, which estimated prevalence to be 4.0%[81] and the Global Burden of Disease Study[327], which estimated prevalence of endometriosis to be 4.8% between 2006 and 2013. Though self-reported data may not be seen as reliable, research from four international prospective cohort studies, including the NHSII and the E3N, has shown that women self-report endometriosis with reasonable accuracy (>70%) and if their diagnosis was made by a clinician laparoscopically, the accuracy rises to >94%[324].

The prevalence of endometrioma was 2.7% (95%CI; 1.7%-4.3%). There are few studies that report incident endometrioma using ultrasound methods, but, a population cohort study in the USA[82], used MRI to visualise endometriosis and saw a prevalence of 11%. The low incidence in the present study may reflect an issue surrounding a lack of specialised healthcare providers in Northern Cyprus who are able to accurately and confidently detect endometriomas using ultrasound scans. Ultrasounds that are performed by sonographers/clinicians who are not experienced are more likely to be falsely negative[328,329]. In addition, accurate diagnosis of pelvic endometriosis by ultrasound may rely strongly on

the extent of the disease, in terms of location and amount. Holland *et al.,* (2013)[330] saw that accuracy of ultrasound increased with an increasing number of lesions and sensitivity decreased with more extensive disease. In addition, it is important to remember that a negative imaging result does not rule out endometriosis so this estimate of prevalence of endometriosis and endometriomas in COHERE is likely an underestimate in that though endometriomas can theoretically be detected with high sensitivity using ultrasound methods, deep endometriosis with moderate and superficial peritoneal (the most common macro phenotype) will be missed, which also biases detection to older women. If, alongside ultrasound scans, there were opportunities for other methods of detection as part of the clinical visit, e.g., surgical visualisation, it is likely that the incidence of new endometriosis cases would be higher. When comparing demographics between the new incident cases diagnosed via ultrasound as part of this study with the self-reported endometriosis cases, there were no significant differences in demographics, but due to the small sample size of incident endometrioma (n=15) there may have not been enough power to detect a true difference between these groups[331].

Compared to the control group, women with endometriosis were on average slightly older, more likely to be employed, and more likely to have a higher educational attainment. Older women are more likely to have visited a gynaecologist and have had more health check-ups, which may have led to their diagnosis of endometriosis, compared to younger women. The observed higher frequencies in cases in terms of higher educational achievement in

endometriosis cases compared to controls may reflect biases such as being more health-aware and therefore more knowledgeable on endometriosis symptoms and signs. Endometriosis cases were more likely to be employed and this may be a subsequent follow-on from them more likely to be educated. These differences may be relevant for interpreting other results i.e., if women with endometriosis are older then they may have less severe symptoms or may have higher parity as they are more likely to have had a pregnancy due to their age. In addition to this, when interpreting the HRQOL results in the following Chapter (Chapter 3) it will be important to adjust for these demographics as it was shown in Chapter 2, that women who were more educated and in employment, had better HRQOL compared to women with lower educational attainment and who were unemployed.

Only a small number of women reported to have been diagnosed with endometriosis surgically (12%). Despite laparoscopy being the gold standard at the time of recruitment[65], and therefore at the time of diagnosis for these women, this small percentage probably reflects the fact that specialised endometriosis laparoscopy is not available in Northern Cyprus. Therefore, women would have to be diagnosed in the Republic of Cyprus, Turkey or elsewhere. The majority of women (83%) were diagnosed using imaging techniques, which as previously discussed can only detect endometriomas, which are classified as stage III/IV according to the ASRM[7]. However, it is important to note that staging does not correlate with disease symptomatology such a pain and infertility. When examining the laparoscopically diagnosed

cases further, there were no significant differences in demographics compared to the cases not diagnosed surgically, though the surgical cases did have a smaller proportion of Turkish Cypriot women, which follows through from the fact that specialised laparoscopy is not available in Northern Cyprus. The most frequent symptom women who were diagnosed surgically experienced was pain, followed by infertility.

Using the information self-reported on date symptoms first appeared and date diagnosed to calculate diagnostic delay gave a mean delay of 1.6 years. This is much lower than other published studies in the United Arab Emirates (UAE) (11.6 years)[91], New Zealand (8.7 years)[332], the Netherlands (7.4 years)[333], Austria and Germany (10.4 years)[71] and the Global Women's Health study (6.7 years)[72]. Furthermore, the average age reported for symptoms starting in the COHERE study was high at 26 years compared to a study in New Zealand[332], which reported the mean age at symptom onset to be 16.9 years, and another study in Brazil[69], which saw that the mean age for pelvic pain symptoms was 20.5 years. This suggests that awareness of pain being a symptom of endometriosis in this population was low. Using earliest age of pain (dysmenorrhea, dyspareunia or non-cyclic pelvic pain) as age symptoms (mean=16 years) started gave an overall diagnostic delay of 9.3 years, which is more similar to other published literature. There was no significant difference between diagnostic delay and symptoms reported, which is in agreement with a study in Austria and Germany[71] but contrary to other studies[334,70] that have reported diagnostic delay to be longer in women with pelvic pain as opposed to

infertility. In this study, women in the youngest age group had the shortest diagnostic delay compared to women in the oldest age group, which could reflect one of two things. Firstly, that awareness for endometriosis and its symptoms has improved over time and that women are receiving their diagnosis quicker or secondly (and most likely) is that women in the youngest age group have not received an endometriosis diagnosis yet, so a long diagnostic delay is not observed. These women may have endometriosis symptoms but will have not yet received a diagnosis, so are not defined as cases in this study which could bias estimates. Reasons for a long diagnostic delay were not examined in this study, but other research[71,323] saw associations with patient's impression of not being taken seriously, normalisation of symptoms from both the patient and the doctor, intermittent suppression of symptoms using hormones and patient's mothers considering menstruation as a negative event.

The most common reported symptom prompting healthcare appointment in the self-reported endometriosis cases was pain (50%). But when examining the pain characteristics of women who said pain was not a reason that made them seek healthcare, 50% of those who had dysmenorrhea in the last 3 months, 54% of those who had pelvic pain in the last 3 months and 38% and 20% who had pain during or after the last time they had intercourse scored above 4 on the relevant NRS, further highlighting the fact that in this population, pain may not be recognised as a symptom of endometriosis. All but one of the incident endometrioma cases reported severe dysmenorrhea, and a substantial proportion also reported pelvic pain and dysmenorrhea. Evidence[335] suggests

that around 50% of women presenting with chronic pelvic pain may be diagnosed as having endometriosis. An online survey[336] completed by 3,735 women living in Northern Cyprus revealed that only 27.7% of women knew what endometriosis was with just over half (58.5%) reporting to know what a chocolate cyst was. A study in a UK secondary school[337] that included girls aged between 15-19 years old revealed that only 8% were able to describe endometriosis, 27% did not know whether their period was typical, and 30% did not know whether it was regular. Other research on health behaviours in the Turkish Cypriot population also point towards a general lack of awareness of reproductive and sexual health. A survey[338] that aimed to capture knowledge on contraception in first year medical students at a local university saw that 63.1% did not know the definition of emergency contraceptive pills and 85.6% were not aware of the most effective time period to take emergency contraception.

Misdiagnoses in this population were high and of the women who said pain was not a symptom that prompted them to seek healthcare but who experienced pelvic pain, only 50% had received a diagnosis for their pain. Reasons for pain in this group and for the incident endometrioma cases who experienced pain but had received a diagnosis included fibroids, IBS, ovarian cysts, PID and stress, amongst other reasons. Misdiagnoses for endometriosis-related pain in other populations is also common; a study in Austria and Germany[71] saw that 74.3% of patients had been misdiagnosed with the misdiagnoses ranging from irritable bladder to PID and intolerances. Co-morbidities associated with endometriosis in this population are discussed in *Chapter 6*, but the

complexities associated with endometriosis and other conditions, as well as the overlap in symptoms, may also be a reason that contributes to the high diagnostic delay associated with endometriosis.

Use of hormones to treat endometriosis in this study was low. Research[339] on endometriosis patients from Latin America and Spain showed a similar number of participants had ever used hormonal treatments (47%). According to the ESHRE guidelines[51], hormone treatment, including combined hormonal contraceptives, progestogens, GnRH agonists or GnRH antagonists, should be offered to women who are experiencing endometriosis-associated pain. In addition to this, a non-steroidal anti-inflammatory drugs (NSAIDs)[340] can also be offered, either alone or in combination with other treatments. However, for women who are wanting to get pregnant, hormonal treatment is not an option. This low use of hormones in endometriosis patients suggests that there may be an opportunity to improve access to hormone medications that have been proven to provide relief to endometriosis-associated pain.

Prevalence of dysmenorrhea, dyspareunia and pelvic pain were 48%, 6% and 13% in endometriosis cases and 38%, 4% and 6% in the control group. Compared to a study in Puerto Rico[81], these prevalence were lower and in community samples, prevalence of chronic pain has been estimated in women of reproductive age as 14.7% in the USA[334], 24% in the UK[341] and 25.4% in New Zealand[342]. A large number of women in the endometriosis group reported to have not experienced pain. A systematic review and meta-analysis[343] used a

total of 9 studies to estimate the prevalence of asymptomatic women with endometriosis at 23%, but in this study, being asymptomatic was defined as no symptoms at all, not just no pain symptoms. One-quarter of the asymptomatic pain cases reported to have had their endometriosis treated at their last surgery which may mean that if they were suffering from pain symptoms, the surgery was successful in alleviating their pain. It is also likely that the study suffers from recall bias, in that when women are recalling pain in the past, they may not remember correctly. Research[344] investigating the accuracy of endometriotic pain recall for pain over a 30-day period saw that women with endometriosis were able to reliably report their pain with relative accuracy. However, in the present study, women are asked to report their pain over longer time periods e.g., 3 months for pelvic pain and 12 months for dysmenorrhea, so may be less accurate, and for older women who are perimenopausal, it may be that the more recent pain symptoms they are reporting are a lot less compared to those experienced when they were younger.

Due to the complexities of endometriosis, the difficulties in diagnosis and the apparent low awareness of symptoms and treatment of endometriosis in this population, it is very likely that there are undiagnosed endometriosis cases in the control group. However, since this misclassification is due to the lack opportunities for women to be diagnosed with endometriosis, this would bias any results towards the null. Despite reporting high levels of pain, only 0.2% of women reported to have had surgery to look for endometriosis; though this is expected because as previously discussed, there is no diagnostic laparoscopy

for endometriosis available in Northern Cyprus. Hormone use in the symptomatic control group was similar to overall hormone use in the cohort (23.6%; *Chapter 2*) and low considering the high levels of pelvic pain this group report to be experiencing. It has been argued[345] that symptoms suggestive of endometriosis (e.g. high levels of pelvic pain) should be treated empirically rather than performing laparoscopy to investigate for endometriosis before treatment.

Women with endometriosis were on average older than the symptomatic control group so it may be that the undiagnosed endometriosis cases in the symptomatic control group have not yet received their endometriosis diagnosis or have not yet tried to become pregnant and hence not realised that they have issues with becoming pregnant. On average, women with endometriosis were more likely to employed and more likely to have a higher educational attainment compared to the symptomatic and asymptomatic control group, which could reflect socioeconomic biases in that more educated women have more knowledge on reproductive health and are more aware of their symptoms and can receive an endometriosis diagnosis easier and quicker than the women in the endometriosis group.

As discussed in the methods section, analysis beyond descriptive statistics of dysuria as an endometriosis pain condition was not possible in this study due to the question only asking about bladder pain in the last 7 days, rather than over a longer time. However, the presence of bladder pain over the last 7 days was

explored, and there was no significant difference in the prevalence of bladder pain compared to endometriosis cases and symptomatic controls, while cases had a higher prevalence compared to asymptomatic controls. This suggests that this presence of bladder pain is not likely to be a function of endometriosis *per se* but is a co-occurrence in people with pelvic pain in general. The prevalence of dysuria in COHERE was lower than that of a study in the UEA[91] which saw a prevalence of bladder pain as 27% in endometriosis cases and 16.2% in symptomatic controls. A study in Taiwan[189] saw that the hazard ratio for developing bladder pain syndrome over a 3-year period for subjects with endometriosis compared to those without was 3.74 and a systematic review[99] of 9 studies estimated that around two-third of women presenting with chronic pelvic pain have bladder pain syndrome. However, although these studies show bladder pain is more common in individuals with endometriosis compared to those without, they fail to have an appropriate control group to reveal if this increased risk is due to endometriosis itself or the fact that endometriosis is a chronic pain condition, and bladder pain prevalence in this group is increased due to an already heightened sensitivity to pain.

There was a higher prevalence of IBS relating to pelvic pain in endometriosis cases compared to symptomatic and asymptomatic controls, but when examining prevalence of IBS related to the pain during menstrual cycle, the only difference was between endometriosis cases and asymptomatic controls, suggesting that the higher prevalence of IBS relating to the menstrual cycle is not a result of an endometriosis diagnosis itself, but due to pain experienced

during the menstrual cycle. These results are similar to another cross-sectional study[346], but the small sample size of 254 endometriosis cases and 102 controls, should be taken into consideration when interpreting these findings. Endometriosis pain symptoms and IBS symptoms are very similar, and endometriosis shared several features with IBS such as low-grade inflammation and visceral hypersensitivity[347] and endometriosis is often misdiagnosed as IBS[348]. A systematic review and meta-analysis[192] concluded that whilst there is a coexistence of gastrointestinal symptoms fulfilling the Rome IV criteria in endometriosis patients, it is uncertain whether there is a true comorbidity between endometriosis and IBS, or whether the gastrointestinal symptomatology in endometriosis depends on medication. In the absence of medical records in COHERE and the fact that endometriosis and IBS are very similar, it is possible that some women in the case group are misclassified as endometriosis cases when they have IBS and some women in the control group are misclassified as controls with IBS when they have undiagnosed endometriosis.

Pain catastrophising scores were similar between endometriosis cases and symptomatic controls, but significantly higher in cases compared to asymptomatic controls. Furthermore, a similar number of endometriosis cases and symptomatic controls reached the cut-off for severe pain, suggesting that the way both groups think about their pain is similar, regardless of whether they have received a diagnosis for their pain. Similarly, there were no significant differences between endometriosis cases and symptomatic controls, but cases

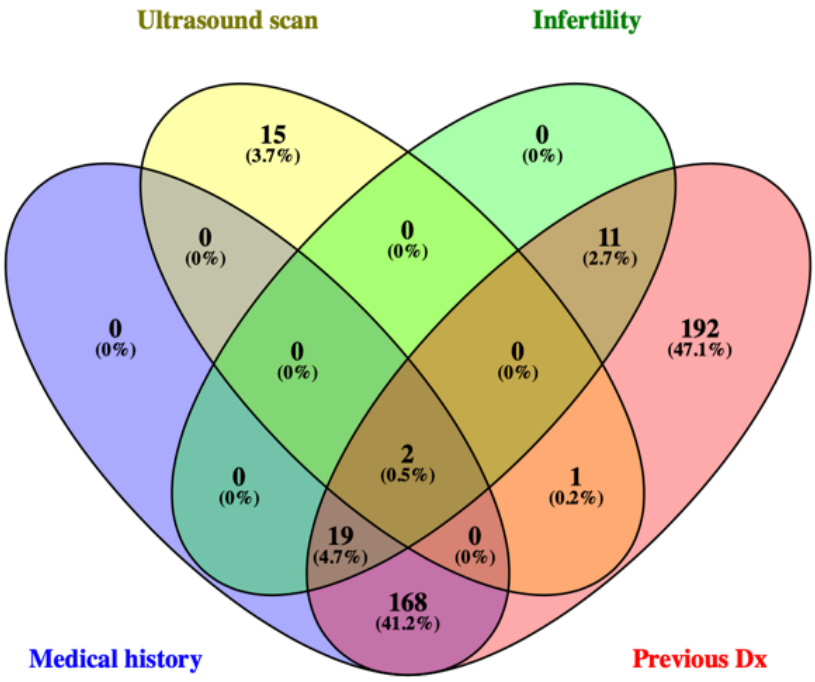
scored significantly higher compared to asymptomatic controls. Higher levels of pain catastrophizing in endometriosis patients have been found to be associated with a poorer response to surgery[349] and persistent pain after 1 year of follow-up[350].

Women with endometriosis more commonly experience migraines compared to those without endometriosis in this study. These findings are consistent with other research demonstrating a comorbid relationship between endometriosis and migraines. A study[183] that included the largest known collection of families containing multiple women with surgically confirmed endometriosis saw a significantly increased risk of migraine in women with endometriosis compared to those without endometriosis (OR: 1.57, 95%CI: 1.12-2.21) and another study that used inpatient and outpatient records saw that participants with migraines were 1.7 times more common in women with endometriosis than those without[351]. Karp *et al.,*[352] saw that migraines were more common in women suffering from chronic pelvic pain independent of having an endometriosis diagnosis and this is in line with the results presented here, as although risk of migraine was attenuated after adjusting for pelvic pain, those with endometriosis were still at an increased risk of migraine. This finding has also been replicated in adolescents with endometriosis[182]. It has been suggested that central sensitisation (*Chapter 1*) associated with chronic pelvic pain contributes to the increased odds of migraine in endometriosis patients but the relationship between endometriosis and migraine in this study still existed even after adjustment for pelvic pain.

Prevalence of infertility in the endometriosis group was double that of both control groups at 15%, though as stated in the methods, this study only asked about difficulties in getting pregnant in the last 6 months, which is different to other studies that used the classical definition of 12 months, so direction comparisons cannot be made here. In those studies, infertility was estimated at 65% in a study in the UAE[91] which recruited 518 endometriosis cases using a combination of hospital and community based participants, 30% in a cross-sectional study in Sweden[353] that recruited 1,228 endometriosis cases and around 30% in a prospective cohort study in the USA[57] that included 658 laparoscopically confirmed cases of endometriosis. The latter estimated that the rate of infertility in endometriosis cases was approximately twice the rate among women without endometriosis, similar to what has been observed in this study. It is difficult to compare prevalence rates as they will vary depending on the study setting, for example, hospital recruited patients are likely to be more complex or severe cases of endometriosis i.e., may suffer with infertility compared to women who do not seek care due to their symptoms being mild and therefore if anything, prevalence of symptoms will be underestimated in this study. Odds of infertility in the endometriosis group remained high even after adjustment for demographics compared to the symptomatic control group, which suggests that this increase in risk is attributed to the disease itself.

After adjustment for demographics, endometriosis cases were more likely to seek tests for infertility compared to both control groups. These women will be

regular users of the healthcare system due to already having been diagnosed and therefore might be more comfortable with visiting the gynaecologists and having tests and procedures. There was one case in the symptomatic and one case in the asymptomatic group who stated that endometriosis was a cause of their difficulties getting pregnant; however, an *a priori* decision to only include cases that reported their diagnosis in the endometriosis-specific section of the questionnaire meant that these participants were not classified as cases. Again, if these are true cases, estimates will be biased towards the null. Endometriosis cases were significantly more likely to report adhesions as a reason for their infertility; endometriosis is considered the most common cause of pelvic adhesions in women[354] and can cause infertility. Both control groups were more likely to report not being given a reason for their infertility.



Dx; Diagnosis

Figure 1. Venn diagram showing the overlap of different parts of the questionnaire where participants reported their endometriosis diagnosis as well as new incident cases from the ultrasound scans as part of this study

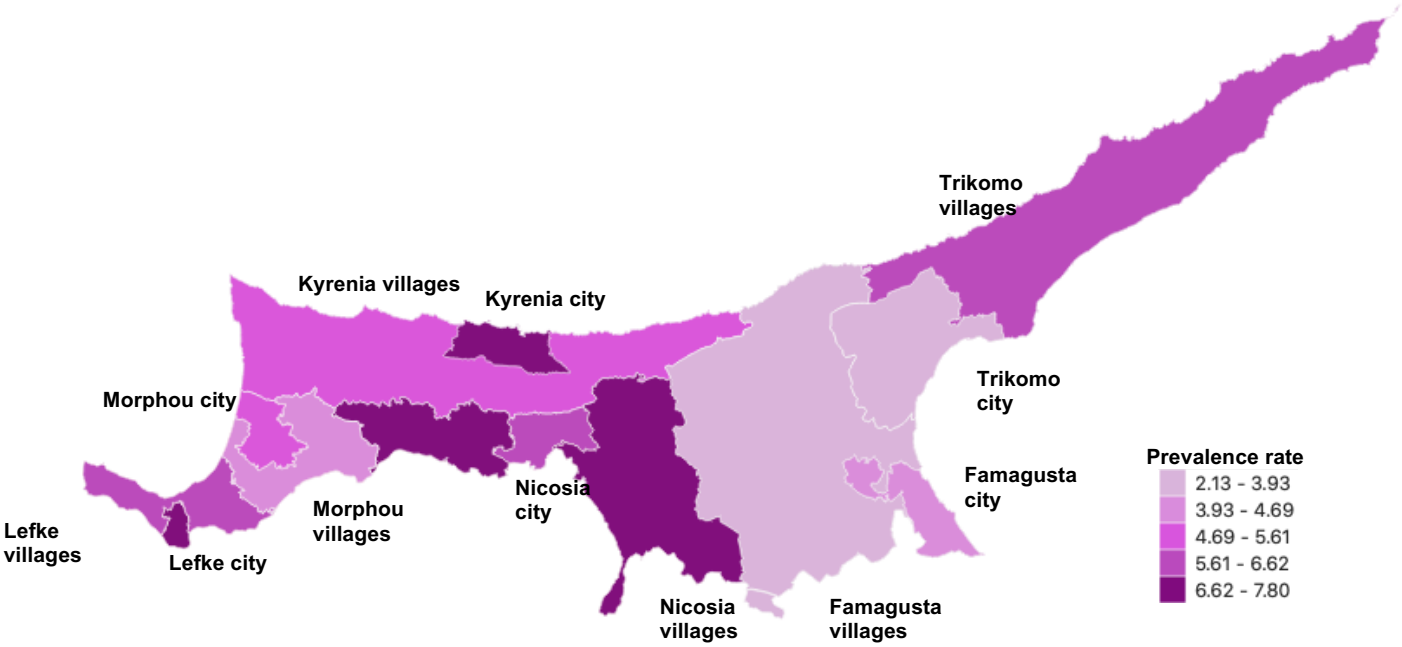


Figure 2. Map of Northern Cyprus created in QGIS showing prevalence rates of endometriosis across the island at the sub-district level.

Table 1. Demographic comparison between self-reported endometriosis cases and incident endometrioma cases with and without adjustment for age

	Self-reported endometriosis (n=395)	New incident cases (n=15)	p-value	
			Crude	Adjusted for age
Mean age (years), n (SD)	37.9 (8.2)	34.7 (8.8)	0.140	-
Ethnicity, n (%)			0.069	0.070
Turkish Cypriot	301 (78.4%)	9 (60.0%)		
Turkish	65 (16.9%)	4 (26.7%)		
Other/Mixed	18 (4.7%)	2 (13.3%)		
Residence type, n (%)			0.167	0.164
Village	205 (51.9%)	5 (33.3%)		
City	190 (48.1%)	10 (66.7%)		
District of residence, n (%)			0.913	0.779
Famagusta	64 (16.2%)	2 (13.3%)		
Kyrenia	65 (16.5%)	3 (20.0%)		
Lefke	17 (4.3%)	0 (0.0%)		
Morphou	27 (6.8%)	1 (6.7%)		
Nicosia	203 (51.4%)	9 (60.0%)		
Trikomo	19 (4.8%)	0 (0.0%)		
Employment, n (%)			0.251	0.419
Not in paid employment	40 (10.4%)	3 (20.0%)		
In paid employment	344 (89.6%)	12 (80.0%)		
Education level, n (%)			0.626	0.500
Primary/Middle school	26 (7.0%)	3 (20.0%)		
High school/Post-secondary	115 (30.8%)	3 (20.0%)		
Undergraduate degree	147 (39.4%)	5 (33.3%)		
Postgraduate degree	85 (22.8%)	4 (26.7%)		
Civil status, n (%)			0.955	0.510
Single	75 (19.7%)	2 (13.3%)		
Divorced / Separated	43 (11.3%)	3 (20.0%)		
Married	262 (68.9%)	10 (66.7%)		
Displaced, n (%)*			0.410	-
No	378 (95.7%)	15 (100.0%)		
Yes	17 (4.3%)	0 (0.0%)		
Migrant Status, n (%)**			0.382	0.310
Migrant	90 (23.4%)	5 (33.3%)		
Non-migrant	294 (76.6%)	10 (66.7%)		

**Defined as those reporting to have been born in Republic of Cyprus*
***Defined as those reporting to have not been born in Northern Cyprus, or those who were born in Northern Cyprus but whose parents were not*

Table 2. Demographic comparison between endometriosis cases and controls with and without adjustment for age

	Controls (n=7,236)	Cases (n=410)	p-value	
			Crude	Adjusted for age
Mean age (years), n (SD)	36.9 (9.7)	37.8 (8.3)	0.054	-
Ethnicity			0.125	0.141
Turkish Cypriot	5,068 (73.5%)	310 (77.7%)		
Turkish	1,456 (21.1%)	69 (17.3%)		
Other/Mixed	368 (5.3%)	20 (5.0%)		
Residence type			0.459	0.430
Village	3,842 (53.1%)	210 (51.2%)		
City	3,394 (46.9%)	200 (48.8%)		
District of residence			0.071	0.086
Famagusta	1,545 (21.4%)	66 (16.1%)		
Kyrenia	1,195 (16.5%)	68 (16.6%)		
Lefke	244 (3.4%)	17 (4.1%)		
Morphou	557 (7.7%)	28 (6.8%)		
Nicosia	3,089 (42.7%)	212 (51.7%)		
Trikomo	606 (8.4%)	19 (4.6%)		
Employment			**<0.001**	**<0.001**
Not in paid employment	1,340 (19.4%)	43 (10.8%)		
In paid employment	5,564 (80.6%)	356 (89.2%)		
Education level			**<0.001**	**<0.001**
Primary/Middle school	816 (12.0%)	29 (7.5%)		
High school/Post-secondary	2,439 (35.9%)	118 (30.4%)		
Undergraduate degree	2,431 (35.7%)	152 (39.2%)		
Postgraduate degree	1,115 (16.4%)	89 (22.9%)		
Civil status			0.147	0.593
Single	1,676 (24.4%)	77 (19.5%)		
Divorced / Separated	638 (9.3%)	46 (11.6%)		
Married	4,567 (66.4%)	272 (68.9%)		
Displaced*			0.821	0.416
No	6,919 (95.6%)	393 (95.9%)		
Yes	317 (4.4%)	17 (4.1%)		
Migrant Status**			0.444	0.388
Migrant	95 (23.8%)	1,759 (25.53%)		
Non-migrant	304 (76.2%)	5,132 (74.5%)		

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Table 3. Diagnostic method and symptoms prompting healthcare appointment for the self-reported endometriosis cases

Diagnostic method*	**N (%**)**
Laparoscopy or other surgical procedure	46 (11.6%)
Ultrasound/MRI	331 (83.8%)
Based on symptoms	60 (15.2%)
Other (during delivery, surgery, general check-up)	17 (4.3%)
Missing	4 (1.0%)
Symptoms prompting healthcare appointment*	
Pain	205 (51.9%)
Infertility	23 (5.8%)
No symptoms	63 (15.9%)
Other (changes in menstruation, during check-up)	81 (20.5%)
Missing	80 (20.3%)

**Participants able to select multiple so percentage do not add up to 100%*
***Denominator (n=395) excludes the 15 incident cases picked as part of the ultrasound visit in this study.*

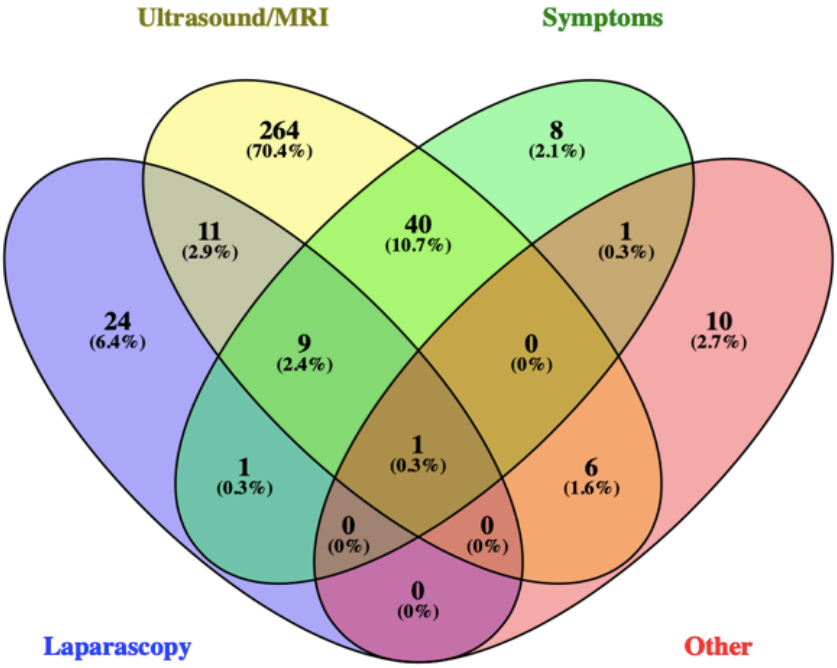

Figure 3. Venn diagram showing the overlap of reported diagnostic method for the self-reported endometriosis cases (n=395)

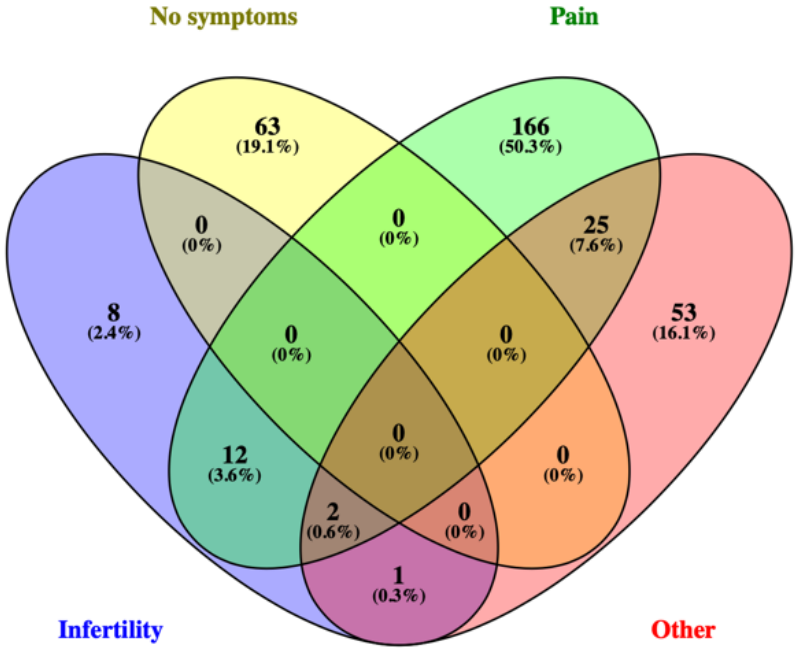

Figure 4. Venn diagram showing the overlap of symptoms endometriosis cases reported experience that prompted them to seek a healthcare appointment and subsequent endometriosis diagnosis

Table 4. Demographic comparison between self-reported endometriosis cases diagnosed surgically and not diagnosed surgically, with and without adjustment for age

	Not diagnosed surgically (n=349)	Diagnosed surgically (n=46)	p-value	
			Crude	Adjusted for age
Mean age (years), n (SD)	37.7 (8.3)	39.4 (7.3)	0.200	-
Ethnicity, n (%)			0.088	0.083
Turkish Cypriot	269 (79.6%)	32 (69.6%)		
Turkish	55 (16.3%)	10 (21.7%)		
Other/Mixed	14 (4.1%)	4 (8.7%)		
Residence type, n (%)			0.129	0.136
Village	186 (53.3%)	19 (41.3%)		
City	163 (46.7%)	27 (58.7%)		
District of residence, n (%)			0.549	0.641
Famagusta	58 (16.6%)	6 (13.0%)		
Kyrenia	56 (16.0%)	9 (19.6%)		
Lefke	16 (4.6%)	1 (2.2%)		
Morphou	25 (7.2%)	2 (4.3%)		
Nicosia	179 (51.3%)	24 (52.2%)		
Trikomo	15 (4.3%)	4 (8.7%)		
Employment, n (%)			0.684	0.808
Not in paid employment	36 (10.7%)	4 (8.7%)		
In paid employment	302 (89.3%)	42 (91.3%)		
Education level, n (%)			0.624	0.463
Primary/Middle school	23 (7.0%)	3 (6.8%)		
High school/Post-secondary	102 (31.0%)	13 (29.5%)		
Undergraduate degree	131 (39.8%)	16 (36.4%)		
Postgraduate degree	73 (22.2%)	12 (27.3%)		
Civil status, n (%)			0.387	0.646
Single	67 (20.0%)	8 (17.8%)		
Divorced / Separated	40 (11.9%)	3 (6.7%)		
Married	228 (68.1%)	34 (75.6%)		
Displaced, n (%)*			0.988	0.690
No	334 (95.7%)	44 (95.7%)		
Yes	15 (4.3%)	2 (4.3%)		
Migrant Status, n (%)**			0.412	0.464
Migrant	261 (88.8%)	77 (85.6%)		
Non-migrant	33 (11.2%)	13 (14.4%)		

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Table 4. Demographic comparison between self-reported endometriosis cases diagnosed surgically and not diagnosed surgically, with and without adjustment for age

	Not diagnosed surgically (n=349)	Diagnosed surgically (n=46)	p-value	
			Crude	Adjusted for age
Mean age (years), n (SD)	37.7 (8.3)	39.4 (7.3)	0.200	-
Ethnicity, n (%)			0.088	0.083
Turkish Cypriot	269 (79.6%)	32 (69.6%)		
Turkish	55 (16.3%)	10 (21.7%)		
Other/Mixed	14 (4.1%)	4 (8.7%)		
Residence type, n (%)			0.129	0.136
Village	186 (53.3%)	19 (41.3%)		
City	163 (46.7%)	27 (58.7%)		
District of residence, n (%)			0.549	0.641
Famagusta	58 (16.6%)	6 (13.0%)		
Kyrenia	56 (16.0%)	9 (19.6%)		
Lefke	16 (4.6%)	1 (2.2%)		
Morphou	25 (7.2%)	2 (4.3%)		
Nicosia	179 (51.3%)	24 (52.2%)		
Trikomo	15 (4.3%)	4 (8.7%)		
Employment, n (%)			0.684	0.808
Not in paid employment	36 (10.7%)	4 (8.7%)		
In paid employment	302 (89.3%)	42 (91.3%)		
Education level, n (%)			0.624	0.463
Primary/Middle school	23 (7.0%)	3 (6.8%)		
High school/Post-secondary	102 (31.0%)	13 (29.5%)		
Undergraduate degree	131 (39.8%)	16 (36.4%)		
Postgraduate degree	73 (22.2%)	12 (27.3%)		
Civil status, n (%)			0.387	0.646
Single	67 (20.0%)	8 (17.8%)		
Divorced / Separated	40 (11.9%)	3 (6.7%)		
Married	228 (68.1%)	34 (75.6%)		
Displaced, n (%)*			0.988	0.690
No	334 (95.7%)	44 (95.7%)		
Yes	15 (4.3%)	2 (4.3%)		
Migrant Status, n (%)**			0.412	0.464
Migrant	261 (88.8%)	77 (85.6%)		
Non-migrant	33 (11.2%)	13 (14.4%)		

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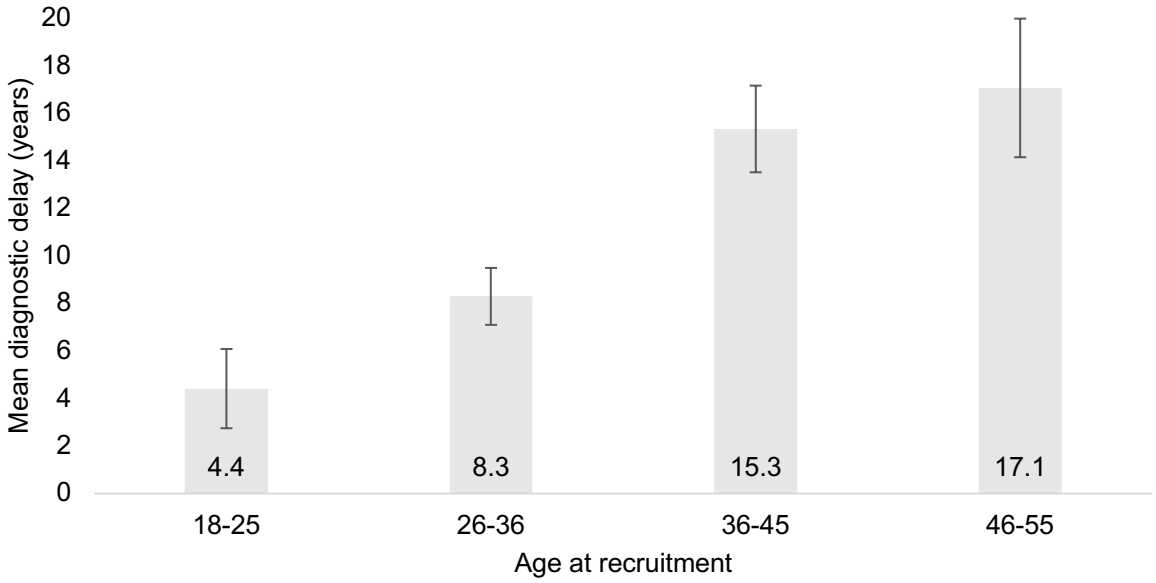
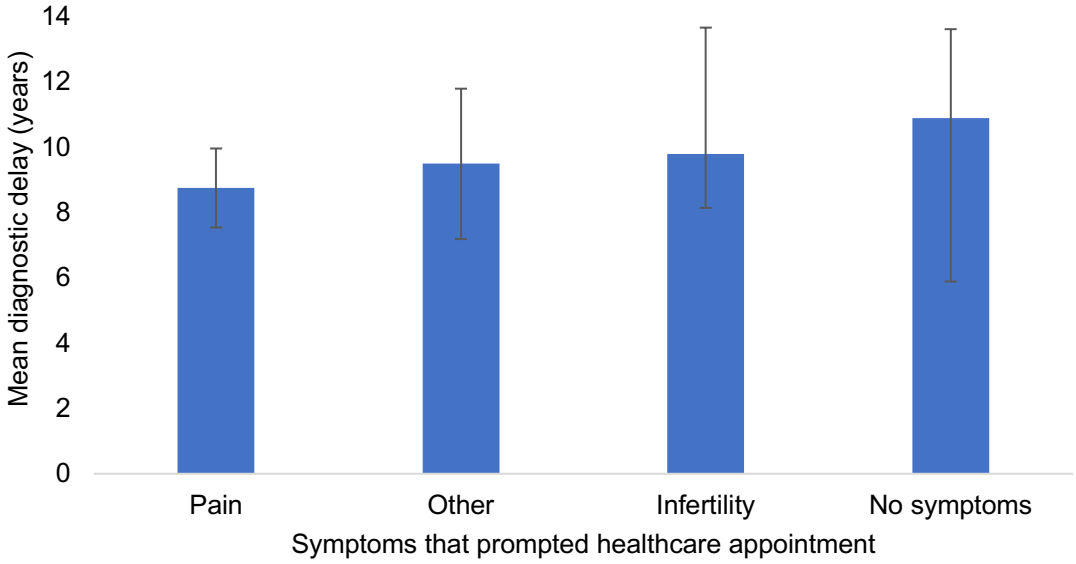
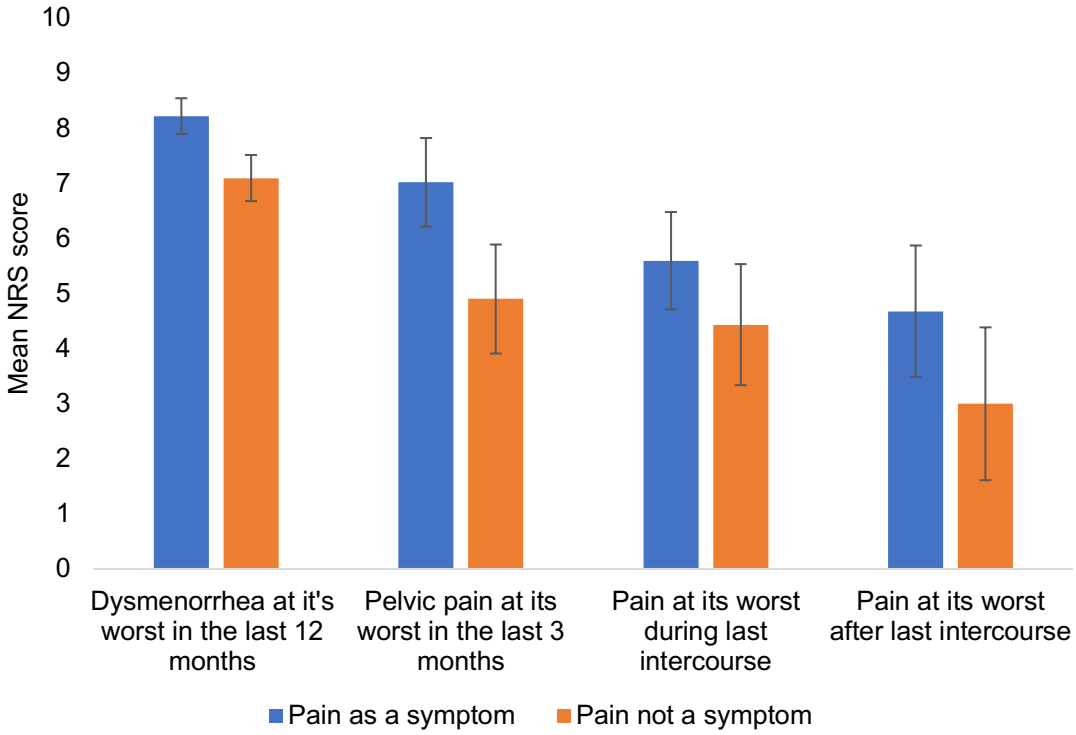


Figure 5. Bar chart showing mean diagnostic delay by age of recruitment. Adjusted for ethnicity, education, civil status, and employment. Error bars are 95% Confidence Intervals.



Other includes any other reason not listed such as changes in menstruation, during a general check-up

Figure 6. Bar chart showing mean diagnostic delay by reported symptoms. Adjusted for ethnicity, education, civil status, residence, and employment. Error bars are 95% confidence intervals.



NRS; Numerical Rating Scale

Figure 7. Bar chart showing mean Numerical Rating Score (NRS) of self-reported endometriosis cases who reported pain to be a symptom prompting their healthcare appointment (blue) and those who reported pain not to be a symptom that prompted their healthcare appointment (orange).

Table 5. Frequency of pain characteristics in incident endometrioma cases (n=15)

	N (%) of women reporting		**N (%) with NRS>4 (severe pain)**
Ever had dysmenorrhea	15 (100%)	Dysmenorrhea at its worst in the last 12 months	14 (93.0%)
Ever had pelvic pain	4 (26.7%)	Pelvic pain at its worst in the last 3 months	2 (50.0%)
Pain during last intercourse	1 (33.3%)	Pain at its worst during last intercourse	1 (25.0%)
Pain in the 24 hours following intercourse	2 (66.7%)	Pain at its worst after last intercourse	1 (25.0%)

NRS; Numerical Rating Scale

Table 6. Diagnoses that had been received for pelvic pain experienced by women who reported pain as a symptom for them seeking healthcare and those who did not report pain

	Pain as a symptom	Pain not as a symptom	p-value
Received diagnosis for pelvic pain, N (%)	68 (81.0%)	20 (50.0%)	**<0.001**
Fibroids, N (%)	14 (20.6%)	2 (10.0%)	0.280
IBS, N (%)	3 (4.4%)	1 (5.0%)	0.912
Ovarian cysts, N (%)	22 (32.4%)	8 (40.0%)	0.526
Painful bladder, N (%)	3 (4.4%)	3 (15.0%)	0.099
PCOS, N (%)	1 (1.5%)	1 (5.0%)	0.352
PID, N (%)	3 (4.4%)	2 (10.0%)	0.343
Stress, N (%)	8 (11.8%)	2 (10.0%)	0.827

IBS; Irritable Bowel Syndrome, PCOS; Polycystic Ovary Syndrome, PID; Pelvic Inflammatory Disease

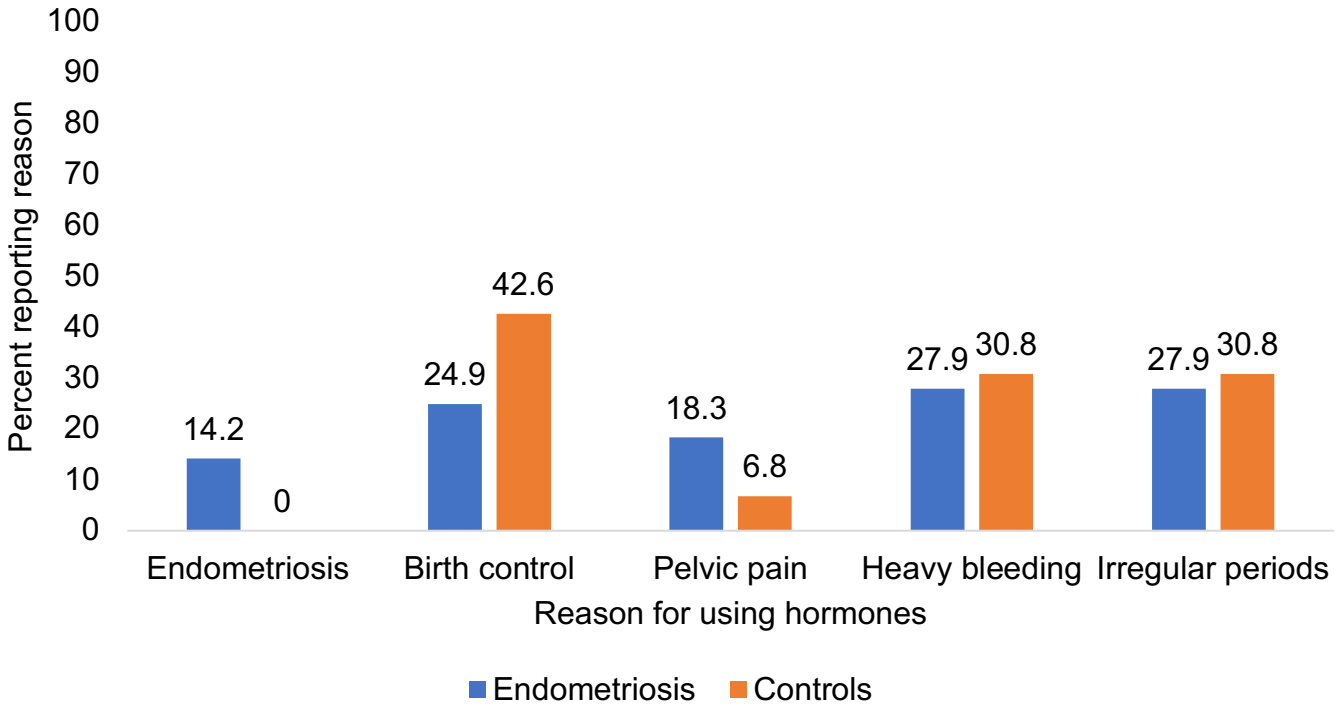


Figure 7. Bar chart showing the proportion of endometriosis cases (blue) and controls (orange) who reported various reasons for using hormones.

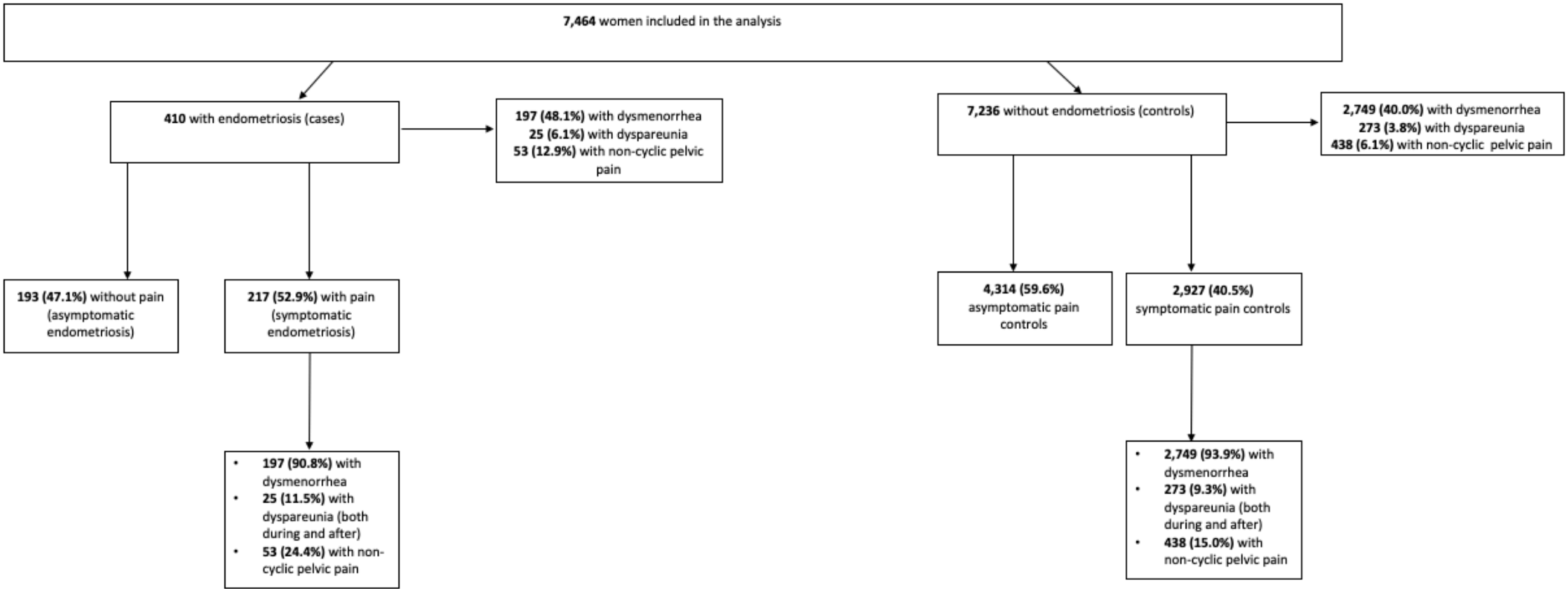


Figure 8. Flow chart depicting ascertainment of case and control groups. Symptomatic cases and controls were defined as those who scored above 4 on the relevant Numerical Rating Scale (NRS) for one of the following: dysmenorrhea, dyspareunia and/or non-cyclic pelvic pain.

Table 7. Comparison of demographics between cases and the two control groups

	(A) Endometriosis (n=410)	(B) Symptomatic pain controls (n=2,927)	A vs B p-value	A vs B age adjusted p-value	(C) Asymptomatic controls (n=4,314)	A vs C p-value	A vs C age adjusted p-value
Age, mean (SD)	37.8 (8.3)	32.8 (8.7)	**<0.001**		39.6 (9.4)	**<0.001**	
Ethnicity, n (%)			**0.041**	0.053		0.27	0.231
Turkish Cypriot	310 (77.7%)	2,053 (72.2%)			3,015 (74.5%)		
Turkish	69 (17.3%)	625 (22.0%)			831 (20.5%)		
Other/Mixed	20 (5.0%)	166 (5.8%)			202 (5.0%)		
Residence type, n (%)			0.822	0.745		0.287	0.327
City	200 (48.8%)	1,408 (48.2%)			1986 (46.0%)		
Village	210 (51.2%)	1,514 (51.8%)			2328 (54.0%)		
Residence, n (%)			0.083	0.242		0.074	**0.047**
Famagusta	66 (16.1%)	641 (21.9%)			904 (21.0%)		
Kyrenia	68 (16.6%)	467 (16.0%)			728 (16.9%)		
Lefke	17 (4.1%)	91 (3.1%)			153 (3.5%)		
Morphou	28 (6.8%)	220 (7.5%)			337 (7.8%)		
Nicosia	212 (51.7%)	1256 (43.0%)			1833 (42.5%)		
Trikomo	19 (4.6%)	247 (8.5%)			359 (8.3%)		
Employment, n (%)			**<0.001**	**0.001**		**<0.001**	**<0.001**
In employment	356 (89.2%)	2,219 (78.0%)			3345 (82.4%)		
Unemployed	43 (10.8%)	627 (22.0%)			713 (17.6%)		
Education, n (%)			**0.007**	**<0.001**		**<0.001**	**<0.001**
Primary/Middle school	29 (7.5%)	283 (10.1%)			533 (13.4%)		
High school/Post-secondary	118 (30.4%)	947 (33.7%)			1492 (37.4%)		
Undergraduate	152 (39.2%)	1066 (37.9%)			1365 (34.2%)		
Postgraduate	89 (22.9%)	516 (18.3%)			599 (15.0%)		

	(A) Endometriosis (n=410)	(B) Symptomatic pain controls (n=2,927)	A vs B p-value	A vs B age adjusted p-value	(C) Asymptomatic controls (n=4,314)	A vs C p-value	A vs C age adjusted p-value
Civil status			**<0.001**	0.195		**0.009**	0.247
Single	77 (19.5%)	1067 (37.6%)			609 (15.1%)		
Divorced/ Separated	46 (11.6%)	224 (7.9%)			414 (10.2%)		
Married	272 (68.9%)	1550 (54.6%)			3017 (74.7%)		
Displaced, n (%)			**0.008**	0.446		0.132	0.622
No	393 (95.9%)	2863 (98.0%)			4056 (94.0%)		
Yes	17 (4.1%)	59 (2.0%)			258 (6.0%)		
Migrant status			0.350	0.116		0.542	0.677
Migrant	95 (23.8%)	739 (26.0%)			1,020 (25.0%)		
Non-migrant	304 (76.2%)	2,104 (74.0%)			3,028 (74.8%)		

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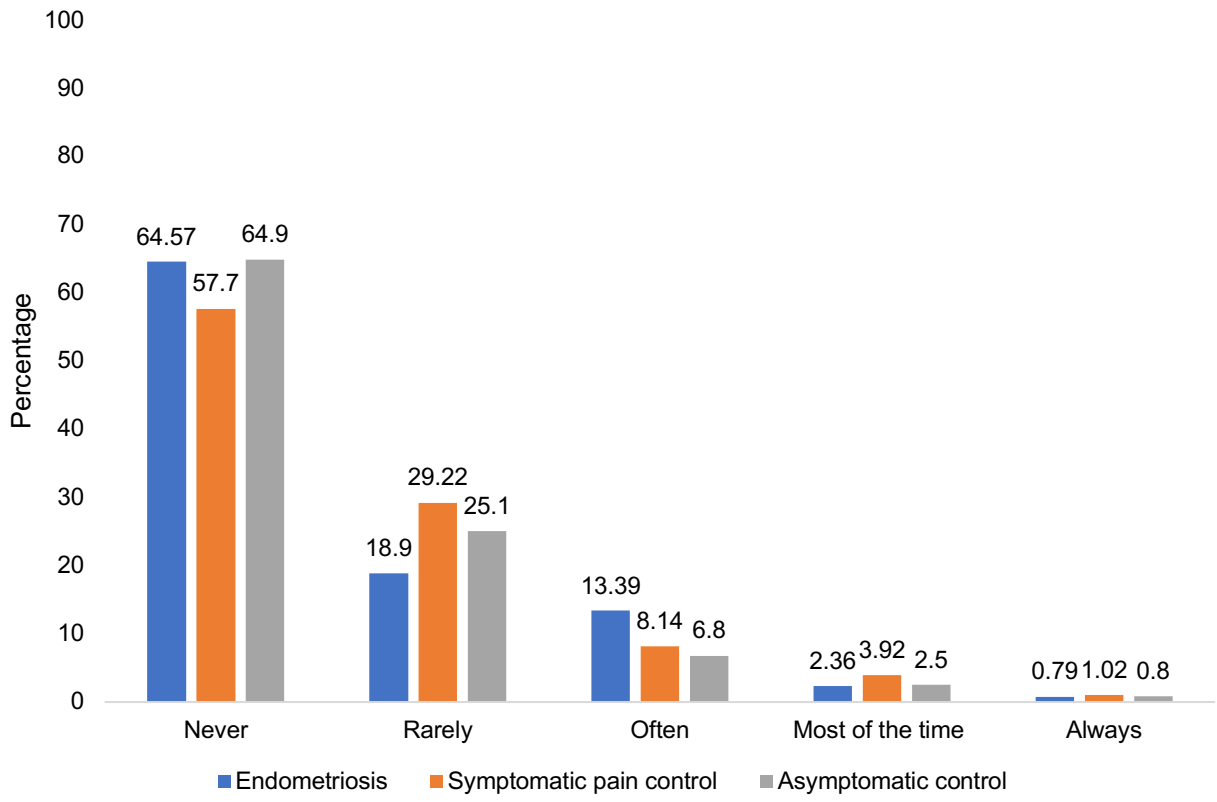


Figure 9A. Frequency of responses to the following question regarding the last 7 days: 'when you urinated how often was it because of pain in your bladder?'

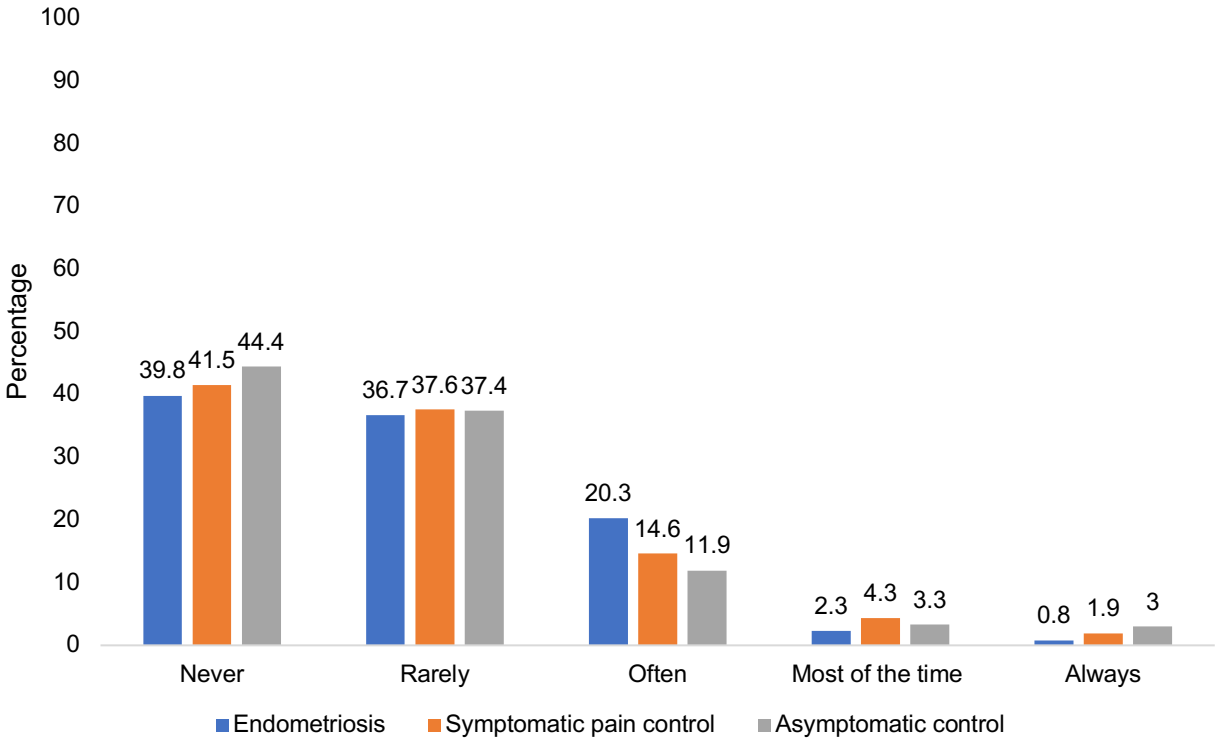


Figure 9B. Frequency of responses to the following question regarding the last 7 days: 'how often did you still feel the need to urinate just after you urinated?'

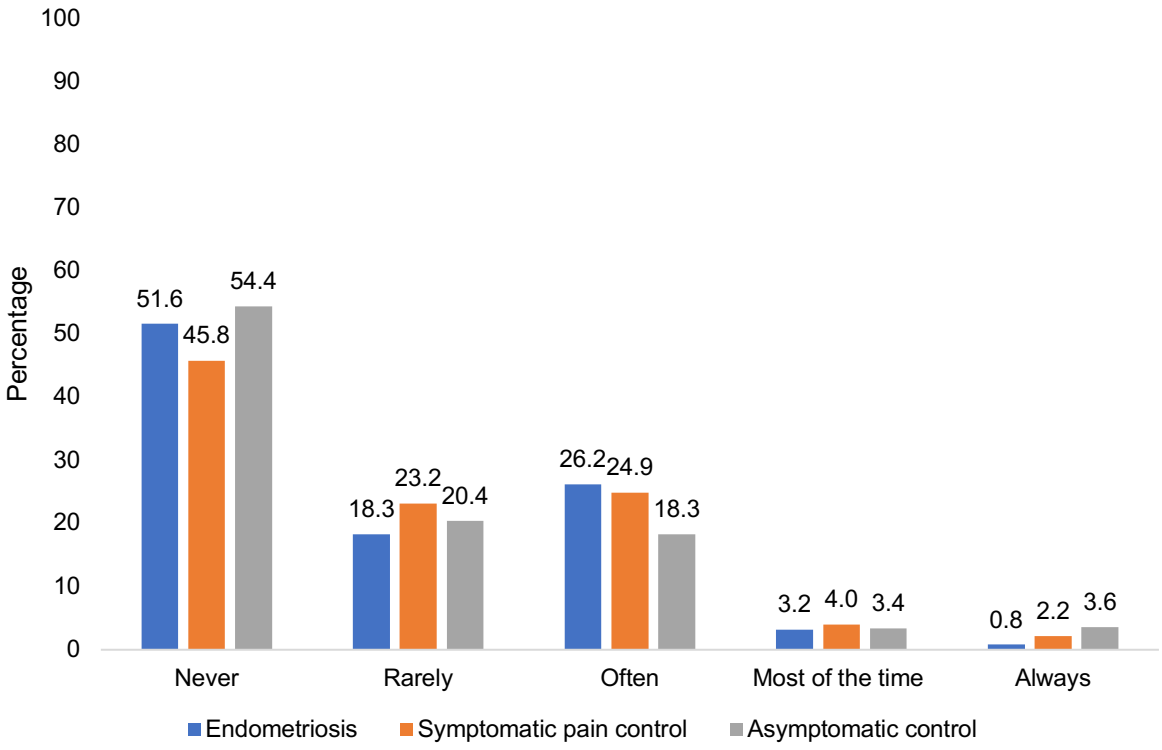


Figure 9C. Frequency of responses to the following question regarding the last 7 days: 'how often did you urinate to avoid pain in your bladder from getting worse?'

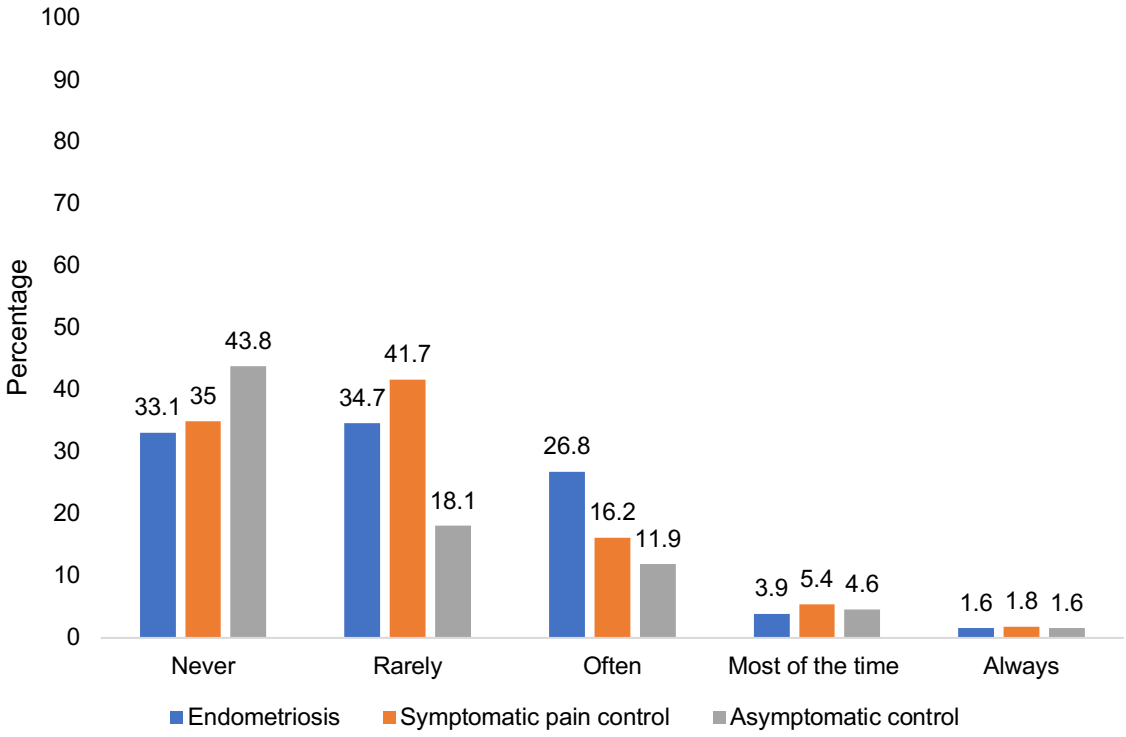


Figure 9D. Frequency of responses to the following question regarding the last 7 days: 'how often did you have a feeling of pressure in your bladder?'

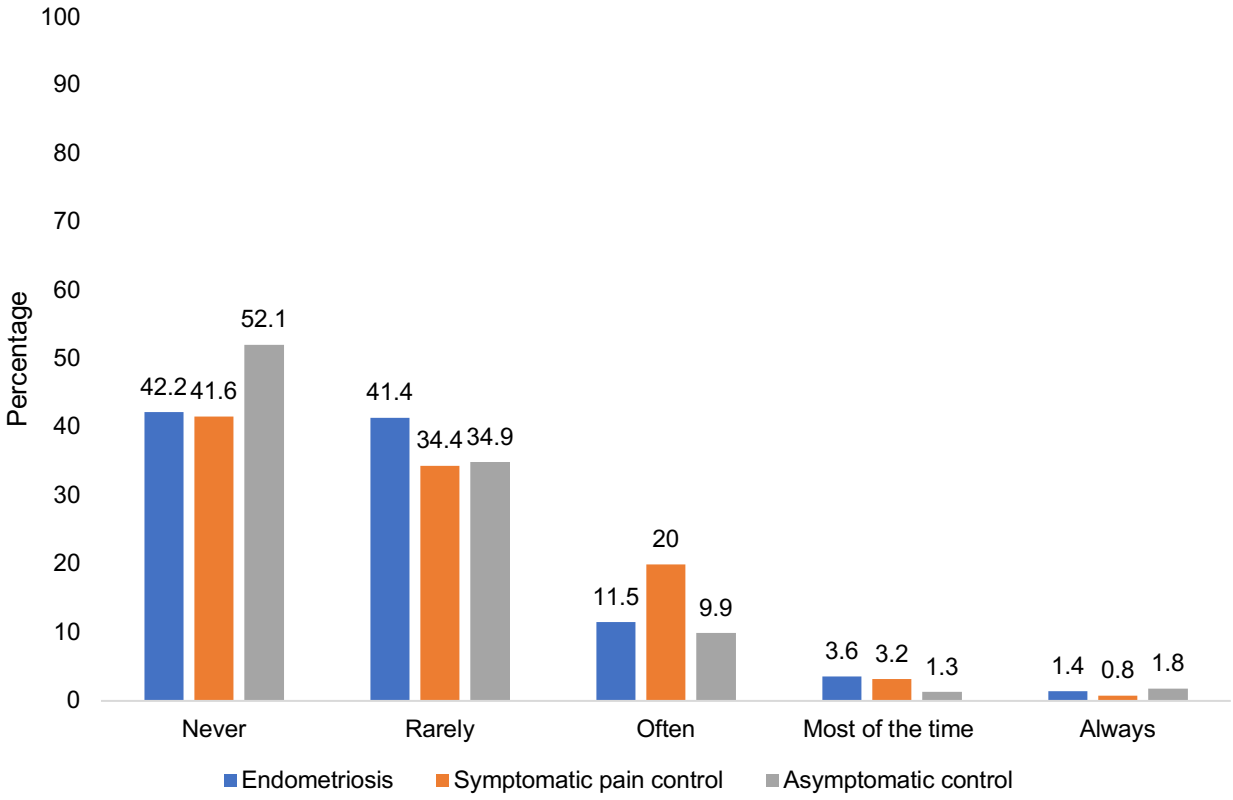


Figure 9E. Frequency of responses to the following question regarding the last 7 days: 'how often did you have pain in your bladder?'

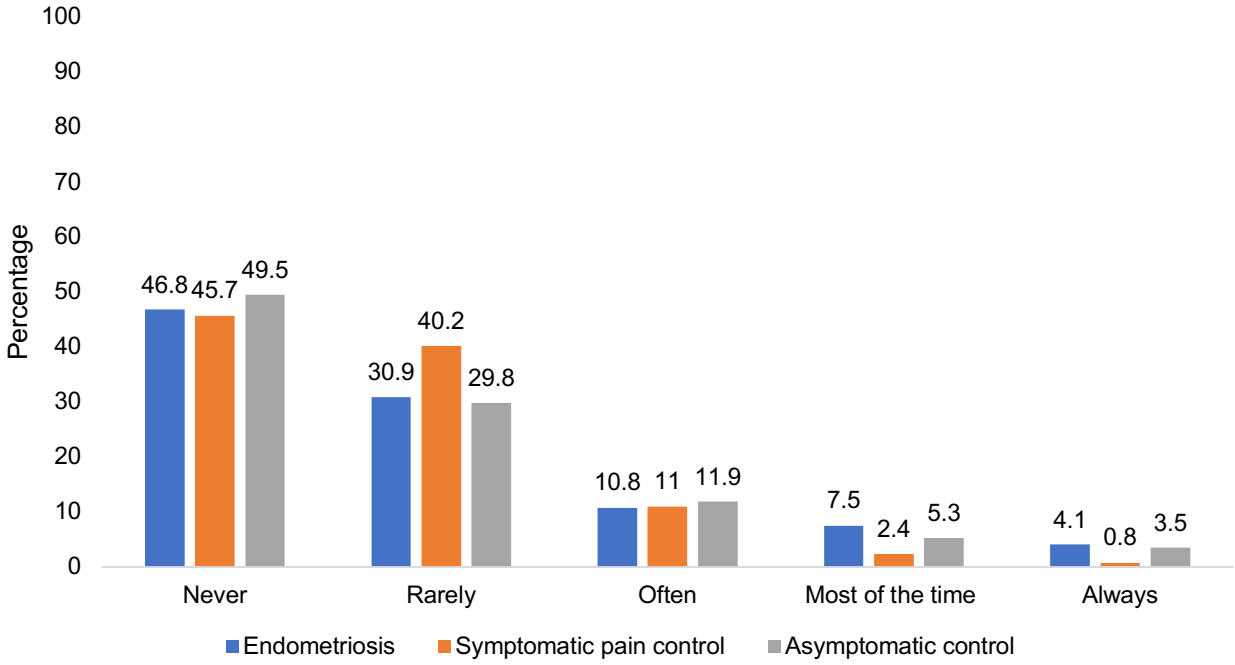


Figure 9F. Frequency of responses to the following question regarding the last 7 days: 'how bothered were you by frequent urination during the daytime?'

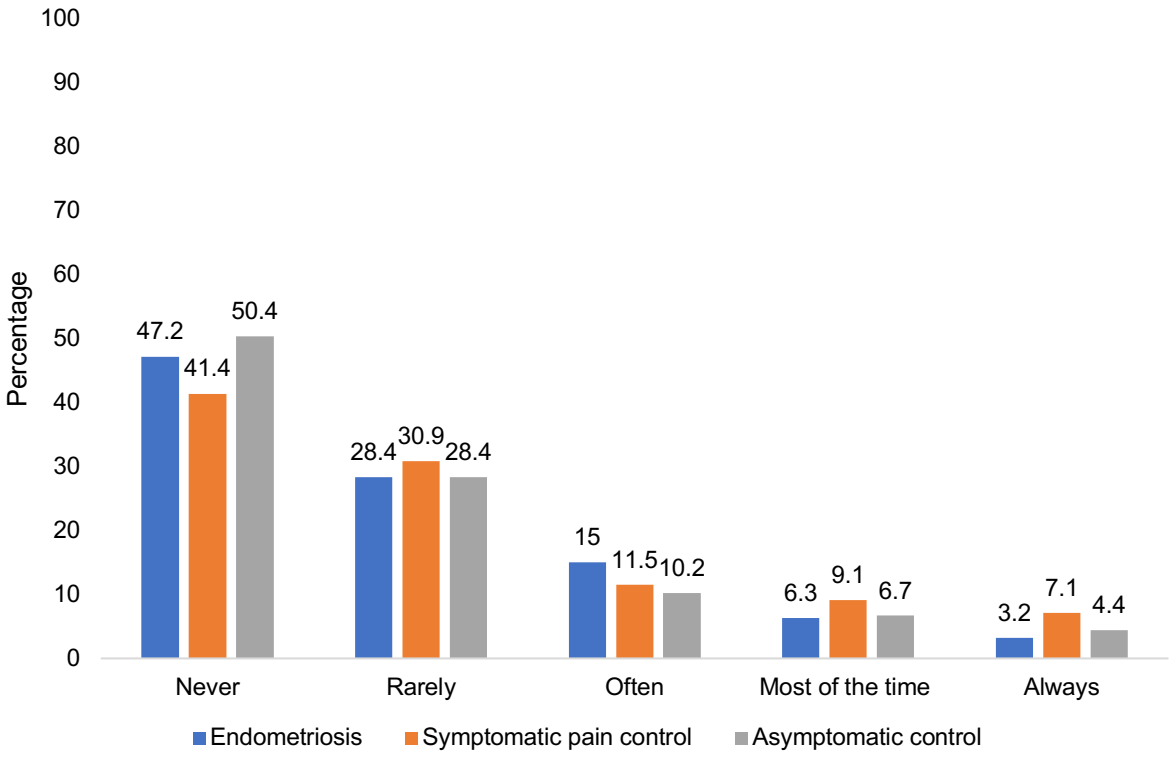
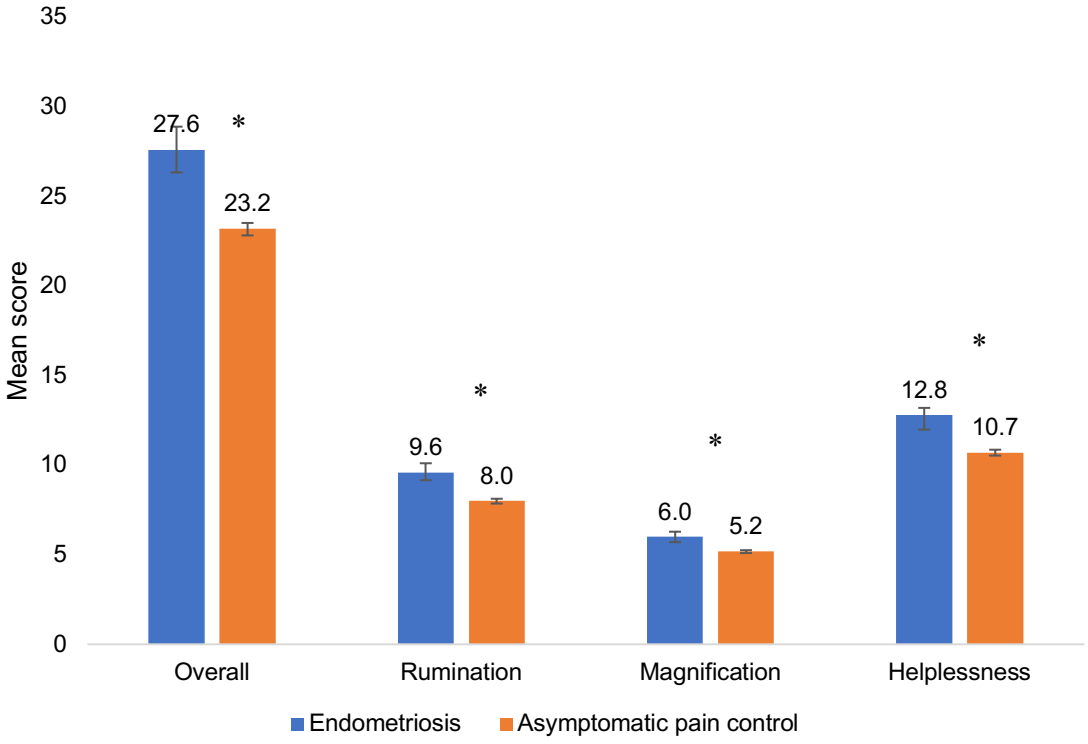


Figure 9G. Frequency of responses to the following question regarding the last 7 days: 'how bothered were you by having to get up during the night to urinate?'



Error bars are 95% Confidence Intervals
**Significant after adjustment for age, ethnicity, residence, employment, education, and civil status*

Figure 10. Mean scores for the four elements of the pain catastrophizing scale (PCtS)– overall score, rumination, magnification and, helplessness.

Table 8. Mean affective, sensory, and overall scores for endometriosis cases, symptomatic and asymptomatic controls for the Short-Form McGill Pain Questionnaire (SF-MPQ)

	Endometriosis (n=44)	**Symptomatic control (n=324)**	**p-value**	**Asymptomatic control (n=75)**	**p-value**
Affective, mean (SD)	9.0 (4.5)	8.5 (4.0)	0.370	4.8 (1.5)	**<0.001**
Sensory, mean (SD)	24.6 (9.4)	23.6 (8.1)	0.460	15.0 (4.0)	**<0.001**
Overall, mean (SD)	33.1 (13.8)	31.9 (11.4)	0.550	19.8 (5.3)	**<0.001**

Table 9. Crude and adjusted odds ratios (OR) with 95% Confidence Intervals (95% CI) of migraine in relation to endometriosis cases and controls.

	Crude (complete case n=5,619)		Model 1 (complete case n=5,619)		Model 2 (complete case n=5,619)	
	OR	**(95% CI)**	**OR**	**(95% CI)**	**OR**	**(95% CI)**
Endometriosis						
No	1	-	1	-	1	-
Yes	1.62***	(1.24, 2.11)	1.49**	(1.13, 1.95)	1.39*	(1.06, 1.83)
Age	-	-	1.02***	(1.01, 1.02)	1.02***	(1.01, 1.03)
Ever used hormones						
No	-	-	1	-	1	-
Yes	-	-	1.23**	(1.05, 1.44)	1.20*	(1.02, 1.41)
Pain during last period						
None/Mild	-	-	-	-	1	-
Moderate/Severe	-	-	-	-	1.21*	(1.04, 1.41)
Pelvic pain in the last 3 months						
No	-	-	-	-	-	-
Yes	-	-	-	-	1.78***	(1.47, 2.16)

****p<0.001, **p<0.01, *p<0.05*

Table 10. Fertility characteristics of endometriosis cases, symptomatic and asymptomatic controls

	Endometriosis (n=410)	Symptomatic controls (n=2,922)	p-value	Asymptomatic controls (n=4,314)	p-value
Tried to get pregnant for 6 months in a row without succeeding, n (%)	64 (15.6%)	206 (7.1%)	**<0.001**	315 (7.3%)	**<0.001**
Mean length tried to get pregnant for, mean (SD)*	21.6 (29.0%)	22.0 (31.8%)	0.948	23.3 (37.8%)	0.838
Had tests/investigations as to why not getting pregnant, n (%)*	55 (87.5%)	149 (73.0%)	**0.020**	235 (77.1%)	0.070
Results from investigations into why participants were not getting pregnant, n (%)^**					
Endometriosis	35 (63.6%)	1 (0.7%)	**<0.001**	1 (0.4%)	**<0.001**
Adhesions	12 (21.8%)	6 (4.0%)	**<0.001**	10 (4.3%)	**<0.001**
Blocked tubes	14 (25.5%)	23 (15.4%)	0.099	43 (18.3%)	0.229
Polycystic ovary syndrome (PCOS)	6 (10.9%)	23 (15.4%)	0.411	32 (13.6%)	0.592
Pelvic inflammatory disease	0 (0.0%)	1 (0.7%)	0.542	0 (0.0%)	-
No/irregular ovulation	3 (5.5%)	20 (13.4%)	0.110	23 (9.8%)	0.311
Poor sperm count/quality	6 (10.9%)	26 (17.5%)	0.254	61 (26.0%)	**0.017**
Uterine fibroids	1 (1.8%)	5 (3.4%)	0.564	13 (5.5%)	0.247
No cause was found	7 (12.7%)	40 (26.9%)	**0.034**	59 (25.1%)	**0.049**
I can't remember	1 (1.8%)	6 (4.0%)	0.442	5 (2.1%)	0.885

**Denominators are 64, 206 and 315 for endometriosis cases, symptomatic controls, and asymptomatic controls, respectively*

***Denominators 55, 149 and 235 for endometriosis cases, symptomatic controls, and asymptomatic controls, respectively.*

^Participants able to select multiple reasons so percentages do not add up to 100%

Table 11. Crude and adjusted odds of infertility as defined as not being able to get pregnant for 6 months or longer in relation to endometriosis cases and controls

	Crude (complete case n=3,191)		Model 1 (complete case n=3,191)			Crude (complete case n=4,365)		Model 1 (complete case n=4,365)	
	OR	(95% CI)	OR	(95% CI)		OR	(95% CI)	OR	(95% CI)
Case group					**Case group**				
Symptomatic pain control	1.00	-	1.00	-	Asymptomatic pain control	1.00	-	1.00	-
Endometriosis	2.49***	(1.83, 3.39)	1.94***	(1.40, 2.68)	Endometriosis	2.39***	(1.77, 3.22)	2.55***	(1.87, 3.46)
Age	-	-	1.00	(0.98, 1.02)	**Age**	-	-	1.01	(1.00, 1.03)
Ethnicity					**Ethnicity**				
Turkish Cypriot	-	-	1	-	Turkish Cypriot	-	-	1.00	-
Turkish	-	-	1.08	(0.76, 1.55)	Turkish	-	-	1.32	(0.98, 1.78)
Other/Mixed	-	-	1.08	(0.61, 1.90)	Other/Mixed	-	-	1.68*	(1.08, 2.63)
Employment		-			**Employment**		-		
Not in paid employment	-	-	1	-	Not in paid employment	-	-	1.00	-
In paid employment	-	-	2.00*	(1.18, 3.39)	In paid employment	-	-	0.96	(0.66, 1.40)
Education		-			**Education**		-		
Primary school	-	-	1	-	Primary school	-	-	1.00	-
High school/Post-secondary	-	-	0.80	(0.49, 1.37)	High school/Post-secondary	-	-	1.94**	(1.21, 3.10)
Undergraduate degree	-	-	1.05	(0.62, 1.78)	Undergraduate degree	-	-	2.74***	(1.68, 4.45)
Postgraduate degree	-	-	1.11	(0.63, 1.96)	Postgraduate degree	-	-	2.59**	(1.51, 4.42)
Civil Status					**Civil Status**				
Married	-	-	1	-	Married	-	-	1.00	-
Single	-	-	0.03***	(0.01, 0.08)	Single	-	-	0.05***	(0.02, 0.15)
Divorced/separated	-	-	0.39***	(0.23, 0.66)	Divorced/separated	-	-	0.73	(0.50, 1.06)

****p<0.001, **p<0.01, *p<0.05*

Chapter 4 – Endometriosis and health-related quality of life

4.1 Introduction

Quality of life (QoL) and Health-related quality of life (HRQoL) are often used interchangeably, and are both terms that view positive and negative aspects of life[355]. However, although HRQOL is an aspect and potentially the strongest determinant of QoL, HRQoL is a patient reported outcome measure defined as "*an individual's or a groups' perceived physical and mental health over time"*[356]*.* There are several instruments available to evaluate HRQoL, and the best tools will seek to summarise the three main domains of HRQoL in one measure – biological functioning, social functioning, and psychological functioning. HRQoL measures can be generic, or can examine specific disease states, as well as being either evaluative (measures how HRQoL has changed over time) or discriminative (looks at the difference between people who have better HRQoL compared to those who have worse HRQoL). The tool used in this study is the Short Form-36-version-2 (SF-36v2)[357] which has both evaluative and discriminative properties.

To aid interpretation of the data, the developers recommend that a normative-based scoring method, using US weights, is used to provide a standard with which scores from other populations can be compared. However, there is much discussion[286] surrounding whether it is appropriate to use weights that may not

be culturally specific, especially when there are differences in health states. When cultural factors affect how individuals respond to self-reported health status questionnaires, the comparability of the outcomes between different cultural groups may be limited. This constrains the validity of these instruments in determining differences in actual health status between different cultural groups. *Chapter 2* used the SF-36v2 to investigate HRQoL in women in the COHERE sample by using normative data that was produced by the COHERE dataset and illustrated the differences in mean scores using both UK and US normative values.

Women suffering from endometriosis have been previously well documented as having a lower HRQoL compared to women without endometriosis due to the chronic, complex and debilitating nature of the disease[91,358,359]. The cross-sectional GSWH[72] took place in 10 countries in women who were undergoing laparoscopy for symptoms suggestive of endometriosis and saw that women with endometriosis had a lower HRQoL as measured by the SF-36 compared to women without endometriosis. Furthermore, it has also been shown that women who experience long diagnostic delays for their endometriosis also suffer from a greater impairment to HRQoL due to not having effective treatment and support options[72]. Prevalence of anxiety and depression is also thought to be high in women suffering from endometriosis, but again has not been reported or estimated in Northern Cyprus.

As this is the first study to investigate the prevalence and profile of endometriosis in Northern Cyprus, this is also the first time the HRQoL of women suffering from this condition has been investigated. Collecting and investigating this type of data from previously undescribed populations is crucial in determining if there are any differences between patient populations due to differences in healthcare, culture, environment and socioeconomic factors.

Aims

The aims of this chapter were as follows:

- Investigate the HRQoL of women with endometriosis and compare with symptomatic and asymptomatic pain control groups.
- Investigate if HRQoL varies by symptoms experienced.
- Investigate if HRQoL differs between self-reported and incident cases identified as part of this study (*Chapter 3*).
- Assess whether there is an association between HRQoL and diagnostic delay in endometriosis cases.
- Estimate the prevalence of anxiety and depression in women with endometriosis and compare this to symptomatic and asymptomatic controls.

4.2 Methods

The methods used to score and analyse the SF-36v2 have been described previously in *Chapter 2*. In addition to the normative values produced as part of the COHERE study[258], normative data from the Third Oxford Health and Lifestyles Survey[289] as well as data from the US[309] are utilised in this chapter as reference populations, in order to allow meaningful comparison of the results presented here with other published studies. Methods detailing how pain was ascertained and diagnostic delay was calculated are described in *Chapter 3*.

Self-reported diagnoses of anxiety and depression were extracted from the baseline questionnaire with non-response being coded as not having received a diagnosis. Prevalence of anxiety and depression was calculated as number of self-reports over the total number of women in each case or control group.

4.2.1 Missing values

Missing values were dealt with by listwise deletion where observations containing missing values were dropped completely when analysing that variable.

4.2.3 Statistical analyses

As per the developer's guidelines, mean scores are presented for the eight health domains and two overall summary measures (PCS and MCS). Differences in mean scores between the case and control groups were

investigated using multivariate linear regression. Spearman rank correlation was used to ascertain the relationship between HRQoL domains and diagnostic delay. All regression models accounted for age (continuous), ethnicity (Turkish Cypriot, Turkish, other/mixed), education (primary/middle school, high school/post-secondary, undergraduate degree, postgraduate degree), employment (in paid employment, not in paid work), civil status (single, married, divorced/widowed) as HRQoL varies depending on demographics (*Chapter 2*). Additionally, models were adjusted for age of first period pain (continuous) since length of pain experienced can impact HRQoL.

4.3 Results

Overall scores for the eight health domains as well as the two component summary scores (PCS and MCS) using COHERE normative values were presented and described in *Chapter 2*. From here now on, only mean scores will be presented in the text, but standard deviations can be viewed in the corresponding tables.

4.3.1 Health-related quality of life in endometriosis and control groups

Table 1 shows differences in mean scores for the eight-health domain sub-scales in endometriosis cases, asymptomatic controls and symptomatic controls, crude significance level, significance level after adjustment from demographics alone and adjustment for demographics and first age of period pain. For the physical functioning sub-scale, women with endometriosis had the

lowest mean scores (87.39) when compared to symptomatic controls (89.05) (p=0.899) and asymptomatic controls (87.84) (p=0.030). Women with endometriosis had significantly lower mean scores for the role physical subscale compared to both symptomatic (76.83 vs 80.50, p=0.022) and asymptomatic controls (81.14, p<0.001). For bodily pain, although scores were lower in the endometriosis group compared to the symptomatic controls (63.75 vs 65.42) this difference was not significant after full adjustment (p=0.274), but the asymptomatic control group did have significantly higher mean scores for bodily pain, compared to women with endometriosis (70.54, p<0.001). Women with endometriosis had similar scores to symptomatic controls for the general health sub-scale (61.49 vs 61.44, p=0.810), and significantly lower scores than the asymptomatic control group (65.62, p<0.001). For the vitality sub-scale, scores in symptomatic women were lower than endometriosis cases (54.47 vs 56.58, p=0.315) and there was a significant difference between endometriosis mean scores and asymptomatic controls (59.66, p=0.011). Endometriosis cases had similar mean scores to symptomatic controls for the social functioning sub-scale (74.16 vs 74.67, p=0.368) and significantly lower scores when compared to the asymptomatic control group (79.56, p<0.001). For role emotional, there was no significant difference between the endometriosis cases and symptomatic controls (75.08 vs 73.96, p=0.901) but asymptomatic controls had significantly higher scores compared to the endometriosis cases (79.44, <0.001). Scores for mental health were similar between endometriosis cases and symptomatic controls (62.87 vs 61.09, p=0.141) and significantly higher in asymptomatic controls (66.20, p=0.018).

Regarding the overall PCS and MCS scores, despite women with endometriosis having lower mean scores when compared to the symptomatic controls for PCS using both Northern Cyprus (48.44 vs 50.32) and US (50.42 vs 51.86) normative values, these differences were not significant after adjustment for demographics and age of first period pain (p=0.070 and p=0.056, respectively) (*Table 1*). However, when using UK values, women with endometriosis had significantly lower PCS scores compared to symptomatic controls (46.79 vs 48.54, p=0.034) after full adjustment. Compared to the asymptomatic control group, women with endometriosis had significantly lower scores after full adjustment (p<0.001 for all three comparisons). Women with endometriosis had significantly higher unadjusted mean MCS scores compared to symptomatic control group using Northern Cyprus (49.72 vs 48.14, p=0.005), US (43.35 vs 41.63, p=0.010) and UK (46.45 vs 44.76, p=0.006) values, but after adjustment these differences were no longer significant (p=0.073 0.077 and 0.071, respectively). After full adjustment, women in the asymptomatic control group had significantly higher MCS scores compared to the endometriosis group using Northern Cyprus (45.22, p=0.019), US (45.22, p=0.017) and UK (48.10 p=0.033) values.

4.3.2 HRQoL stratified by pain

In order to examine whether differences in HRQOL scores previously seen between endometriosis cases and symptomatic controls were related to symptoms or the disease *per se*, differences in mean scores between these

groups, stratified by dysmenorrhea, chronic pelvic pain and dyspareunia, are presented in *Table 2.* On average, compared to the symptomatic pain control group with dysmenorrhea, women with endometriosis and dysmenorrhea had significantly lower mean scores for role physical (70.94 vs 74.07, p=0.002), bodily pain (58.77 vs 65.66, p<0.001), social functioning (70.64 vs 74.92, p=0.015) and role emotional (70.94 vs 74.07, p=0.030) sub-scales. The endometriosis group with dysmenorrhea also had on average lower scores than the symptomatic control group with dysmenorrhea for the physical functioning (87.09 vs 89.41, p=0.070), general health (59.55 vs 61.66, p=0.109) and mental health (60.26 vs 61.24, p=0.310) sub-scales, but after adjustment for demographics, these differences were not significant. Women in the symptomatic control group with dysmenorrhea had a slightly lower score for the vitality sub-scale compared to the endometriosis with dysmenorrhea group (54.67 vs 55.04), but again this was not significant (p=0.756).

Women with endometriosis and chronic pelvic pain had on average lower scores compared to symptomatic control women with pelvic pain for the role physical (66.51 vs 74.01, p=0.017), bodily pain (45.75 vs 58.66, p=0.009), general health (49.50 vs 56.74, p=0.015), vitality (44.88 vs 50.09, p=0.021) and mental health (51.27 vs 55.50, p=0.042) sub-scales after full adjustment for demographics and age of first period pain (*Table 2*). Women with endometriosis and pelvic pain also had lower scores on average compared to women with pelvic pain who were symptomatic controls for the physical functioning (81.25 vs 83.25, p=0.800), social functioning (62.50 vs 68.16, p=0.117) and role

emotional (64.85 vs 68.85, p=0.085) sub-scales, but after adjustment for demographics and age of first period pain these differences were not significant.

For women with endometriosis and dyspareunia, compared to symptomatic controls with dyspareunia, their average scores were significantly lower for role physical (61.25 vs 71.55, p=0.017), bodily pain (46.76 vs 56.82, p=0.009), general health (46.20 vs 56.38, p=0.015) and mental health (52.29 vs 52.76, p=0.042) sub-scales after adjustment for demographics and age of first period pain (*Table 2*). Women with endometriosis and dyspareunia also had lower scores on average compared to symptomatic controls with dyspareunia for physical functioning (80.60 vs 83.17, p=0.599), social functioning (57.50 vs 65.01, p=0.117) and role emotional (59.33 vs 63.37, p=0.085) but these differences were not significant after full adjustment. The symptomatic control group with dyspareunia on average had a significantly lower score than the endometriosis group with dyspareunia for the vitality sub-scale (46.96 vs 47.50, p=0.021).

Using the Northern Cyprus normative values and after stratifying by pain symptoms and adjusting for demographic factors, women with endometriosis had significantly impaired PCS scores, for dysmenorrhea only, in comparison to symptomatic controls (47.45 vs 50.48, p<0.001) (*Table 2*). Women with endometriosis and pelvic pain had lower PCS scores compared to symptomatic controls with pelvic pain (42.62 vs 46.96), but after adjustment for

demographics this was not significant (p=0.053); the same was true for women with dyspareunia (41.76 vs 46.04, p=0.203). MCS scores were similar between women with endometriosis and the symptomatic controls for each of the three pain phenotypes. Patterns using the US values were similar; women with endometriosis and dysmenorrhea had significantly lower PCS scores compared to symptomatic controls with dysmenorrhea (41.85 vs 51.97, p=0.001) as well as in those suffering with pelvic pain (45.83 vs 49.70, p=0.025). Using the US normative values, MCS scores were very low for women with chronic pelvic pain (endometriosis = 37.92, symptomatic control = 38.76, p=0.472) and dyspareunia (35.60, 36.35, p=0.970)

4.3.3 Number of pain symptoms and HRQoL

There was an inverse relationship between the number of pain symptoms experienced and HRQoL in both endometriosis cases and in the symptomatic control group. Mean PCS score in women experiencing one pain was 48.83 in women with endometriosis and 50.97 in the symptomatic control group, 45.00 and 47.94 for women experiencing two pains, 45.81 and 43.53 for three pains and 29.15 and 41.80 for four pains (*Figure 1*). Mean MCS scores in women with endometriosis and symptomatic controls were as follows: for one pain, 50.06 and 48.78, two pains, 43.42 and 45.61, three pains, 45.11 and 41.81 and four pains, 44.27 and 41.61 (*Figure 2*). After adjustment for demographic factors, for every increase in the number of pains experienced, women with endometriosis had a decrease in mean PCS and MCS scores of 3.17 (p<0.001) and 2.12 (p=0.001), respectively. After adjustment for demographics, for every increase

in the number of pains experienced, women in the symptomatic control group had a decrease in mean PCS and MCS scores of 3.13 ($p<0.001$) and 2.96 ($p<0.001$), respectively. After full adjustment for demographics, the only difference in mean HRQoL scores experienced in endometriosis and symptomatic controls, stratified by number of pains was in the average PCS score of one pain ($p=0.035$).

4.3.4 Incident endometrioma cases vs self-reported endometriosis cases

Differences in mean scores for the eight-health domain sub-scales for incident endometriosis cases picked up in the pelvic USS in the study (n=15) in comparison to self-reported endometriosis cases (n=395) are shown in *Table 3*. For the physical functioning sub-scale, incident endometrioma cases had lower scores (86.00) compared to self-reported cases (87.44) ($p=0.384$). Their scores were slightly higher for the role-physical scale (77.50 vs 76.80, $p=0.428$) and lower for the bodily pain scale (57.73 vs 63.98, $p=0.554$). Incident cases also had lower mean scores for the general health scale (59.53 vs 61.57, $p=0.821$), vitality scale (53.33 vs 56.71, $p=0.910$), social functioning (68.33 vs 74.39, $p=0.532$), role emotional (66.11 vs 75.43, $p=0.542$) and mental health sub-scale (58.67 vs 63.04, $p=0.705$). For PCS, women with incident endometriomas had on average higher PCS and MCS scores compared to the women who self-reported to have endometriosis, but these differences were not significant crudely, or after full adjustment. (PCS: 48.46 vs 47.84, 0.835; MCS: 49.86 vs 46.60, $p=0.632$).

4.3.5 Diagnostic delay and HRQoL

Though PCS and MCS were both negatively correlated with length of diagnostic delay of endometriosis, there was no significant relationship present between the two (PCS correlation coefficient: -0.0139, p=0.820, MCS correlation coefficient: -0.0045, p=0.9419).

4.3.6 Psychological disorders

Because endometriosis can negatively affect women's psychological wellbeing, so it follows that there may be an increased prevalence of anxiety and depression in affected women. The questionnaire allowed participants to indicate whether they had been diagnosed with anxiety or depression. Of the women with endometriosis, 8.5% (n=35) reported anxiety, compared to 5.4% (n=157) of the symptomatic controls and 3.8% (n=165) of the asymptomatic controls. For depression, 5.4% (n=22) of endometriosis cases reported depression, compared to 4.1% (n=121) of the symptomatic controls and 2.7% (n=116) of the asymptomatic controls. After adjustment for demographics, the odds of women being diagnosed with anxiety were 1.56 (95%CI: 1.03-2.38) times higher than the symptomatic controls (p=0.034) and 1.95 (95%CI: 1.30-2.92) times higher than the asymptomatic controls (p=0.001). There was no significant association between increased risk of depression with endometriosis compared to symptomatic controls (OR: 0.90, 95%CI: 0.54-1.52, p=0.707) or asymptomatic controls (OR: 1.61, 95%CI: 0.96-2.70, p=0.069) after adjustment for demographics.

4.4 Discussion

This is the first study to estimate the impact of endometriosis and endometriosis-associated pain on HRQoL in women living in Northern Cyprus and in the Eastern Mediterranean region. Prior research into the relationship between HRQoL and endometriosis has been mainly concentrated in Western populations, so this research helps to fill an important gap. Despite research into how endometriosis affects HRQoL being plentiful, comparisons between studies are difficult[360] due to the vast number of QoL instruments there are to choose from and for tools like the SF-36v2, comparisons are only valid if the same reference population values are used. The analysis described in this chapter attempted to increase the validity of comparisons by using both normative values derived from the Northern Cyprus population, as well as values derived from both the US and the UK.

Women with endometriosis had significantly lower scores for all of the eight health domains and the two overall summary scores, PCS and MCS, compared to asymptomatic controls, which has been previously shown in a number of other studies[72,91,90,89,361]. However, though endometriosis cases had significantly lower mean scores for many of the physical subscales and the PCS score compared to the symptomatic control group, the only significant difference after adjustment was for the role physical sub-scale, which asks questions on difficulties and time spent on performing work or other activities. This is contrary to other studies[72,91] which saw significantly impaired physical health in endometriosis cases compared to a symptomatic control group. As shown in the

previous chapter (*Chapter 3*), only around half the endometriosis group reported to suffer from pain symptoms, so this could be a contributing factor as to why the PCS scores in COHERE are not as low as expected, despite still being significantly lower than the asymptomatic control group. Having women who were asymptomatic for pain in the endometriosis group would bias the estimate towards the null and could explain why no different in mean PCS scores was seen between the endometriosis and symptomatic pain control group. Furthermore, the SF-36v2 asks questions based on HRQoL in the present and it may be that some women with endometriosis no longer experience pain symptoms for various reasons e.g., they have gone through the menopause or on treatment, so the questionnaire may not be capturing HRQoL at a time when symptoms of endometriosis were at their worst.

Compared to the normative values, the mental health scores were impaired in both the endometriosis and symptomatic control group, which is an important area that should be considered when examining support that could be related to endometriosis treatment. Furthermore, the symptomatic control group had slightly lower scores compared to the endometriosis group for some of the mental health subscales, and for the overall MCS measure, though this was not significant. This result corroborates with what was found in the GSWH[72]. Though the level of physical health impairment experienced by endometriosis cases and symptomatic controls is similar, the symptomatic control group may suffer slightly more from mental health impairment, perhaps because these are a group of women who are experiencing pain but may not have a diagnosis or

treatment plan for their pain management. The case groups may also suffer from misclassification bias and there may be symptomatic controls in the endometriosis group which would bias any estimates towards the null and potentially explain why no difference was seen between the two groups. Uncertain temporal relationships between endometriosis and HRQoL mean that a longitudinal cohort study would be more suited to investigate these associations.

US-standardised PCS scores were higher in COHERE compared to a study that recruited women of Arab ancestry[91] whereas the MCS scores are very similar, which may be an artefact of having such a high proportion of endometriosis cases who are asymptomatic for pain in the case group, as discussed above. There are also some methodological differences between the two studies. COHERE has predominantly relied on self-reported data of endometriosis, whereas the study in the Middle East used surgical visualisation by laparoscopy to validate incident endometriosis cases, so there may be some reporting bias and misclassification of cases in each of the three groups in COHERE. In addition, since recruitment into the study in the Middle East took place in hospitals, women in the case group are likely to be the more severe cases and therefore have worse quality of life. Comparing the COHERE UK-standardised results with that of GSWH[72], showed that PCS scores were similar but that MCS scores in the endometriosis group were somewhat higher in COHERE compared to the GSWH study. This may reflect the difference between the sampling populations, as the GSWH population was comprised of women with

severe symptoms who were undergoing laparoscopy and differences in demographics between the two groups as the mean age in the GSWH of endometriosis cases is lower than the mean age in COHERE, and as seen in *Chapter 2*, mental health scores increase as age increases.

To elucidate whether differences in HRQoL scores between endometriosis cases and pain symptomatic controls was due to symptoms or the disease *per se*, scores were stratified by pain experienced. This revealed that women with endometriosis who experienced dysmenorrhea had significantly lower physical health compared to women experiencing dysmenorrhea who were not endometriosis cases and though scores were lower in the endometriosis group for chronic pelvic pain and dysuria, these differences were not significant. This difference in HRQoL between endometriosis cases and symptomatic controls with regards to dysmenorrhea could be explained by endometriosis cases experiencing a higher severity of dysmenorrhea compared to the symptomatic controls, which was illustrated in the previous chapter. When examining differences in mean MCS scores by endometriosis cases and symptomatic controls, stratified by pain experienced, scores appeared to be similar. This suggests that although physical health in women with endometriosis who experience dysmenorrhea may be worse, women without a diagnosis for pain experience a similar burden on their mental health and that this does not differ depending on the type of pain experienced. However, the finding in that HRQoL is only related to dysmenorrhea is similar to that of a study in Turkey which saw that only the severity of dysmenorrhea was associated with lower

HRQoL but that presence of chronic pelvic pain and dyspareunia were not[358]. In addition, a cross-sectional study of 57 patients observed that women with chronic pelvic pain had decreased quality of life irrespective of their endometriosis diagnosis[362]. Compared to a study that included women of Arab ancestry[91] that used US normative values and stratified by pain, women with endometriosis and women in the symptomatic control group in COHERE had higher PCS values for all three pains and similar MCS values for dysmenorrhea, but much lower MCS values for chronic pelvic pain, suggesting that women with chronic pelvic pain in Northern Cyprus are affected more by the mental aspect of pain than women in the UAE in this study.

Unsurprisingly, both women with endometriosis and women in the symptomatic pain group had worse HRQoL scores as the number of pains they experienced increased, similar to other studies[363] which have examined multi-site pain and HRQoL. The results suggest that women with endometriosis suffer from a more reduced physical HRQoL compared to the symptomatic controls for one pain only. This could be due to endometriosis cases often suffering from pain for a long time, for example, since the first menstrual period. However, caution must be taken in the interpretation of results due to the wide confidence intervals and small sample size.

There was no difference in HRQoL in women who self-reported to have been diagnosed with endometriosis compared to women who were picked up as having an endometrioma during their clinical visit as part of the study. However,

endometriomas are classified by the ASRM[7] as Stage III and there is little to no evidence[364] that staging of endometriosis is correlated to pain severity, and given there will be women in the self-reported group who are also Stage III, it may not have been expected for there to have been a difference in the physical aspect of HRQoL. Differences in mental health score could have been hypothesised as the women in the endometrioma group may have been likely to have been living with the symptoms of their endometriosis for a long time, which could impact the mental health component of HRQoL. However, since the sample size of the endometrioma group is very small (n=15) it is possible that there was not enough statistical power to see a difference between the two groups.

Though PCS and MCS were negatively correlated with diagnostic delay of endometriosis, as seen in other studies[91], this difference was not significant. This lack of significance could be due to the fact that in constructing the diagnostic delay variable, data was drawn from several sources as described in the previous chapter (*Chapter 3*). However, the trend of a longer diagnostic delay and lower HRQoL is an important finding and further adds weight to the fact that more awareness of endometriosis is needed in this population to diagnose women as soon as possible, treat them and ensure adequate support is provided to them to ensure they do not have a diminished quality of life.

Prevalence of anxiety in endometriosis cases in COHERE was lower (8.5%) than estimates from Austria[90], in an Arab population (28.0%)[91], the United

States (77.0%)[361], and Australia (46.0%)[365]. Similar to anxiety, prevalence of depression in COHERE in endometriosis cases (5.4%) was again lower than worldwide estimates of 54% in Australia[365], 26.3% in the UAE[91] and United States (47.7%)[366], though differences in methodologies means these estimates may not be totally comparable. In addition, prevalence of anxiety and depression in the asymptomatic control group (3.9% and 2.7%, respectively), was lower than other worldwide estimates. In the Republic of Cyprus, a study examining prevalence of depression in college students estimated it at 27.9%[367], a study in Turkey, suggested that point prevalence was between 13-20% and a study in Northern Cyprus that included 978 people found a point prevalence of 23.4% for clinical depression[368]. It is likely that prevalence in the case groups is also underreported, resulting in misclassification which would bias any effect estimates towards the null. These lower estimates may be due to the perceived stigma in this population around mental health. A study in Greek Cypriots who were living in London[369] found that they had less contact with mentally ill people, were less knowledgeable about mental illness and had more stigmatising views compared to English born participants and that there were little differences between first and second generation Greek Cypriots. Furthermore, it is difficult to make comparisons of prevalence of mental health conditions between studies due to differences in definitions and methodologies between studies.

Women with endometriosis were at a higher risk of reporting to have anxiety compared to both symptomatic and asymptomatic control groups, results which

are consistent with previously published studies. In the Taiwan National Health Insurance Research Database, women with endometriosis had a greater risk of anxiety disorder (Hazard Ratio: 1.44, 95%CI: 1.22-1.70) compared to women without endometriosis[370] and a retrospective matched-cohort study in the United States that used health claims database saw that the risk of anxiety was higher in women with endometriosis compared to those without (HR: 1.38, 95%CI: 1.34-1.42)[366]. The fact that women with endometriosis had higher anxiety than the symptomatic control group suggests that this is not due to any pain symptoms they are experiencing, and is more likely due to endometriosis-specific factors such as symptoms occurring early on in life and the long diagnostic delay associated with the disease[361,371]. For both the endometriosis and symptomatic control group, chronic pain can lead to social isolation which affects emotional wellbeing[370,372]. Other research has shown that women with endometriosis usually have a higher risk of developing depression, contrary to the results from this study. However, as discussed above, misclassification of women with depression may be responsible for this result and only further adds weight to the argument that more support is needed for women with endometriosis and their mental health.

Table 1. Associations between endometriosis and HRQoL compared to symptomatic and asymptomatic pain controls

		Endometriosis	Symptomatic controls	p-value			Asymptomatic controls	p-value		
		Mean (SD)	**Mean (SD)**	**Unadjusted**	**Adjusted***	**Adjusted^**	**Mean (SD)**	**Unadjusted**	**Adjusted***	**Adjusted^**
	Physical functioning (PF)	87.39 (14.98)	89.05 (15.40)	0.041	0.640	0.899	87.84 (16.20)	0.593	**0.022**	**0.030**
	Role Physical (RP)	76.83 (23.76)	80.50 (22.89)	0.003	0.190	**0.022**	81.14 (22.62)	**<0.001**	**<0.001**	**<0.001**
	Bodily pain (BP)	63.75 (24.48)	65.42 (24.55)	0.831	0.843	0.274	70.54 (24.00)	**<0.001**	**<0.001**	**<0.001**
	General health (GH)	61.49 (20.14)	61.44 (20.54)	0.962	0.926	0.810	65.62 (19.08)	**<0.001**	**<0.001**	**<0.001**
	Vitality (VT)	56.58 (21.11)	54.47 (20.64)	0.058	0.314	0.315	59.66 (20.46)	**0.005**	**0.001**	**0.011**
	Social functioning (SF)	74.16 (23.74)	74.67 (23.91)	0.691	0.734	0.368	79.56 (22.55)	**<0.001**	**<0.001**	**<0.001**
	Role emotional (RE)	75.08 (24.09)	73.96 (24.51)	0.390	0.572	0.901	79.44 (23.15)	**<0.001**	**<0.001**	**<0.001**
	Mental health (MH)	62.87 (19.80)	61.09 (19.88)	0.094	0.141	0.250	66.20 (19.49)	**0.001**	**0.001**	**0.018**
Northern Cyprus	**PCS**	48.44 (9.67)	50.32 (9.91)	**0.001**	0.255	0.070	50.11 (10.02)	**0.002**	**<0.001**	**<0.001**
US		50.42 (7.53)	51.86 (7.71)	**0.001**	0.192	0.056	51.78 (7.61)	**0.001**	**<0.001**	**<0.001**
UK		46.79 (8.62)	48.54 (8.84)	**<0.001**	0.178	**0.034**	48.31 (8.83)	**0.002**	**<0.001**	**<0.001**
Northern Cyprus	**MCS**	49.72 (10.11)	48.14 (10.15)	**0.005**	0.073	0.187	51.34 (9.69)	**0.002**	**0.004**	**0.019**
US		43.35 (11.84)	41.63 (12.08)	**0.010**	0.077	0.206	45.22 (11.46)	**0.003**	**0.005**	**0.017**
UK		46.45 (10.96)	44.76 (11.15)	**0.006**	0.071	0.165	48.10 (10.61)	**0.005**	**0.010**	**0.033**

MCS, Mental Component Score; PCS, Physical Component Score; SD, Standard Deviation
**Adjusted for age, ethnicity, education, employment, civil status*
^Adjusted for age, ethnicity, education, employment, civil status, and age of first period pain

Table 2. Association between endometriosis and health-related-quality-of-life (HRQoL) compared to symptomatic pain controls, stratified by pain

		Dysmenorrhea				Chronic Pelvic Pain				Dyspareunia			
		Endometriosis (n=177)	Symptomatic pain control (n=2,592)	Crude	Adjusted*	Endometriosis (n=46)	Symptomatic pain control (n=397)	Crude	Adjusted *	Endometriosis (n=24)	Symptomatic pain control (n=247)	Crude	Adjusted *
		Mean (SD)		p-value		Mean (SD)		p-value		Mean (SD)		p-value	
	Physical functioning (PF)	87.09 (15.56)	89.41 (15.06)	**0.037**	0.070	81.25 (17.31)	83.25 (18.27)	0.455	0.800	80.60 (19.54)	83.17 (17.85)	0.495	0.599
	Role Physical (RP)	70.94 (25.48)	74.07 (24.52)	**0.001**	**0.002**	66.51 (22.20)	74.01 (24.34	**0.033**	**0.017**	61.25 (29.20)	71.55 (24.97)	**0.033**	**0.017**
	Bodily pain (BP)	58.77 (24.02)	65.66 (24.56)	**<0.001**	**0.001**	45.75 (21.53)	58.66 (24.51)	**<0.001**	**0.009**	46.76 (24.78)	56.82 (24.44)	**<0.001**	**0.009**
	General health (GH)	59.55 (21.04)	61.66 (20.46)	0.165	0.109	49.5 (22.58)	56.74 (20.68)	**0.019**	**0.015**	46.20 (20.13)	56.38 (21.69)	**0.019**	**0.015**
	Vitality (VT)	55.04 (21.45)	54.67 (20.54)	0.809	0.756	44.88 (22.04)	50.09 (19.68)	0.081	**0.021**	47.50 (22.10)	46.96 (21.13)	0.081	**0.021**
	Social functioning (SF)	70.64 (24.94)	74.92 (23.87)	**0.016**	**0.015**	62.5 (24.64)	68.16 (24.67)	0.116	0.117	57.50 (25.77)	65.01 (24.23)	0.116	0.117
	Role emotional (RE)	70.94 (25.48)	74.07 (24.52)	0.090	**0.030**	64.58 (24.91)	68.85 (24.71)	0.241	0.085	59.33 (27.88)	63.37 (25.31)	0.241	0.085
	Mental health (MH)	60.26 (20.17)	61.24 (19.86)	0.507	0.310	51.27 (19.98)	55.50 (19.87)	0.153	**0.042**	52.29 (18.36)	52.76 (21.52)	0.153	**0.042**
Northern Cyprus	PCS	47.45 (10.28)	50.48 (9.81)	**<0.001**	**<0.001**	42.62 (10.50)	46.96 (11.17)	**0.012**	0.053	42.37 (12.14)	46.88 (11.11)	0.061	0.203
	MCS	48.59 (10.19)	48.18 (10.14)	0.598	0.871	45.03 (9.62)	46.00 (10.03)	0.534	0.365	43.35 (10.27)	44.04 (10.74)	0.534	0.365
US	PCS	49.81 (7.82)	51.97 (7.67)	**<0.001**	**0.001**	45.83 (8.25)	49.70 (8.50)	**0.004**	**0.018**	46.03 (8.67)	49.87 (8.43)	**0.035**	0.105
	MCS	41.85 (11.94)	41.68 (12.09)	0.853	0.682	37.92 (11.28)	38.76 (12.00)	0.650	0.472	35.60 (12.31)	36.35 (12.67)	0.781	0.970

MCS, Mental Component Score; PCS, Physical Component Score; SD, Standard Deviation; US, United States
**Adjusted for age, ethnicity, education, employment, civil status*

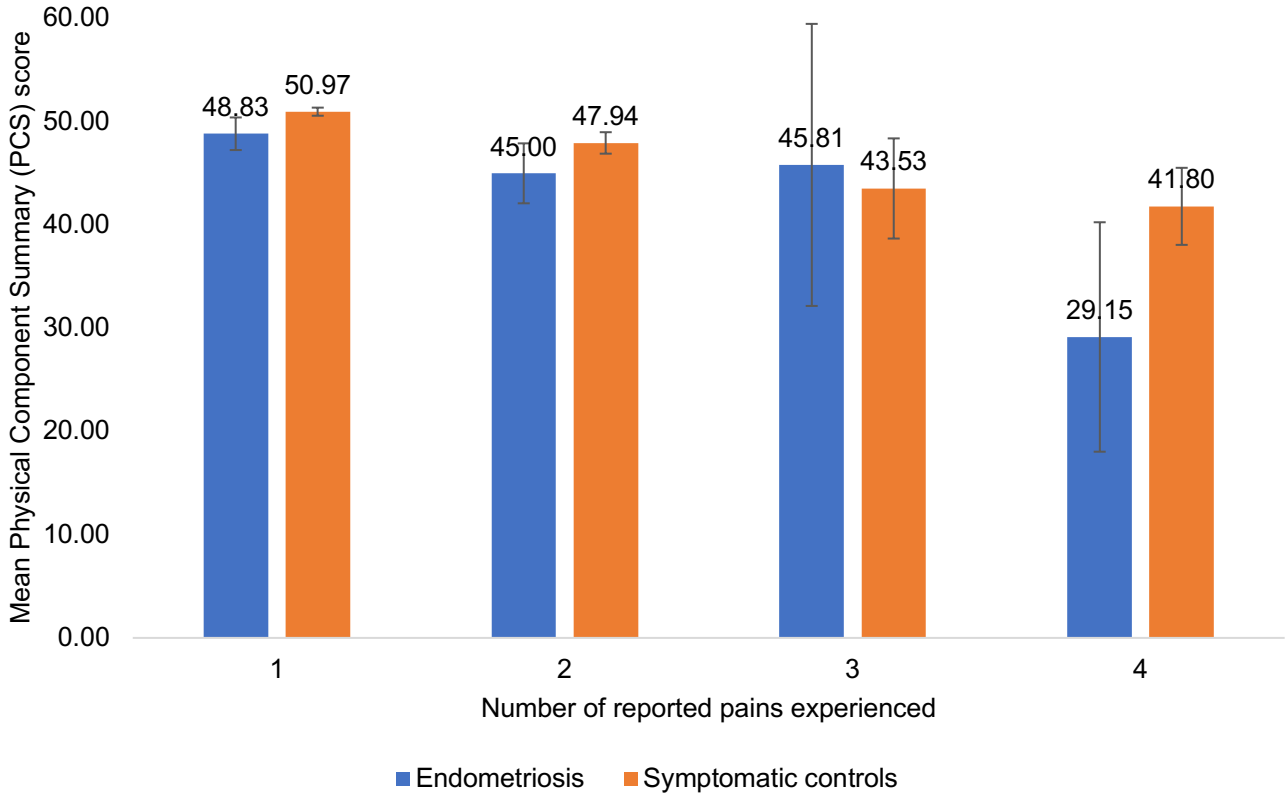


Figure 1. Mean Physical Component Summary (PCS) score by number of pains experienced in women with endometriosis (blue) and symptomatic controls (orange). Error bars are 95% Confidence Intervals.

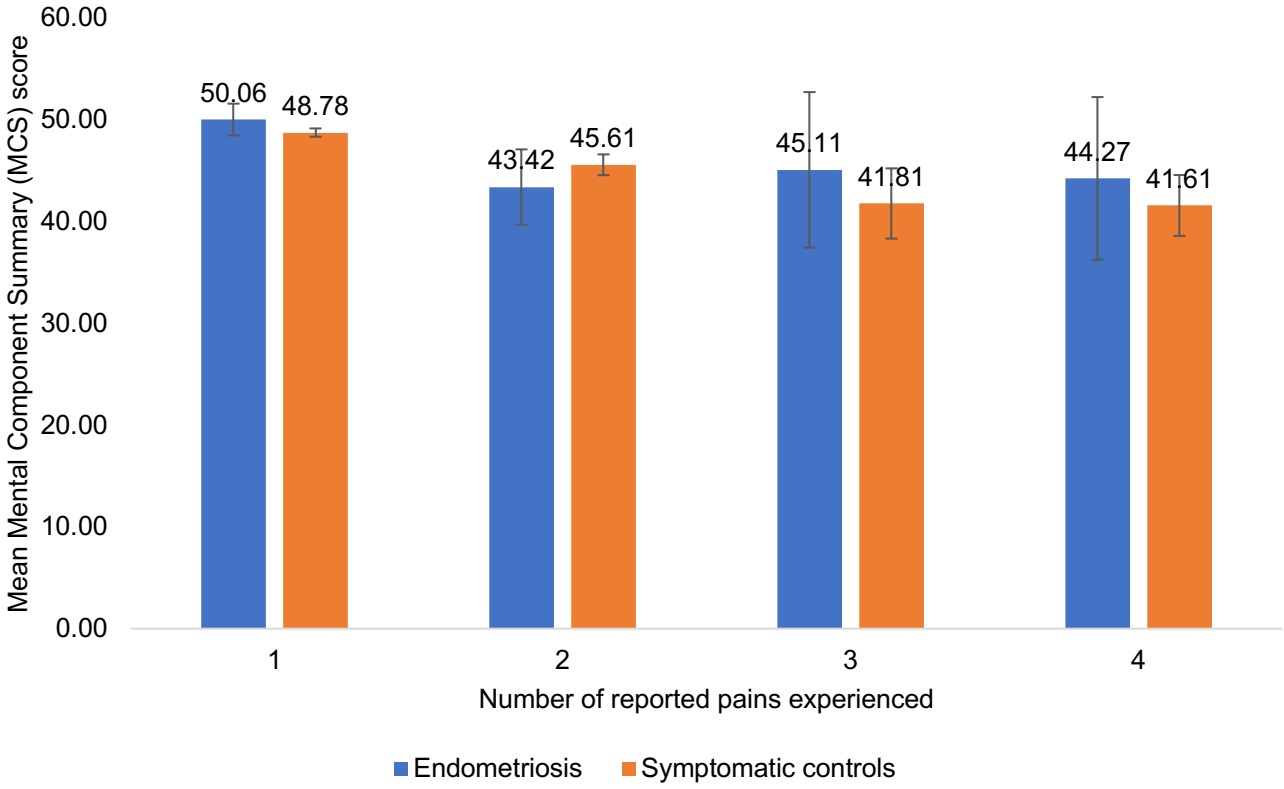


Figure 2. Mean Mental Component Summary (MCS) score by number of pains experienced in women with endometriosis (blue) and symptomatic controls (orange). Error bars are 95% Confidence Intervals.

Table 3. Association between self-reported endometriosis cases and health-related-quality-of-life (HRQoL) compared to incident endometrioma cases picked up as part of this study.

	Self-reported endometriosis		Incident endometrioma cases		p-value		
	Mean	**Standard deviation**	**Mean**	**Standard deviation**	**Crude**	**Adjusted***	**Further adjusted****
Physical functioning (PF)	87.44	14.60	86.00	23.39	0.715	0.656	0.384
Role Physical (RP)	76.80	23.85	77.50	22.01	0.911	0.862	0.428
Bodily pain (BP)	63.98	24.22	57.73	31.05	0.332	0.603	0.554
General health (GH)	61.57	20.16	59.53	20.00	0.702	0.998	0.821
Vitality (VT)	56.71	21.05	53.33	23.01	0.544	0.900	0.910
Social functioning (SF)	74.39	23.49	68.33	29.83	0.333	0.543	0.532
Role emotional (RE)	75.43	23.96	66.11	26.44	0.142	0.208	0.542
Mental health (MH)	63.04	19.61	58.67	24.46	0.402	0.648	0.705
PCS	47.84	13.11	48.46	9.52	0.808	0.916	0.835
MCS	46.60	13.70	49.86	9.93	0.222	0.419	0.632

MCS, Mental Component Score; PCS, Physical Component Score
**Adjusted for age, ethnicity, education, employment and, civil status*
***Adjusted for age, ethnicity, education, employment, civil status, and age of first period pain*

Table 4. Odds ratios of anxiety and depression in women with endometriosis vs symptomatic and asymptomatic pain controls.

	Endometriosis cases vs symptomatic pain 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		1		1		1	
Yes	1.64 (1.12, 2.41)	**0.011**	1.56 (1.03, 2.38)	**0.034**	2.35 (1.61, 3.43)	**<0.001**	1.95 (1.30, 2.92)	**0.001**
Depression								
No	1		1		1		1	
Yes	1.31 (0.82, 2.09)	0.253	0.90 (0.54, 1.52)	0.707	2.05 (1.29, 3.27)	**0.003**	1.61 (0.96, 2.70)	0.069

**Adjusted for age, ethnicity, education, employment, and civil status*
95%CI. 95% Confidence Intervals

Chapter 5 – Economic burden

5.1 Introduction

Given the high symptom burden and negative effect on physical and mental quality life endometriosis has on women (demonstrated in *Chapters 3* and *4*), it can be assumed that there would be a substantial negative impact on the day-to-day life of women whilst at work and during their regular activities. Work productivity loss can be defined as either absence from work (absenteeism) or loss of productivity during work (presenteeism)[266]. The GSWH estimated overall work productivity loss to be 10.8 hours/week (SD 12.2) in women with endometriosis compared to 8.4 hours/week (SD 10.6) in symptomatic control women[72]. A study that included women of Arab ancestry reported that work productivity was significantly impaired in women with endometriosis, who lost on average 16.8% (SD=12.7%) of time from work compared to 14.8% (SD=12.6) in a symptomatic control group[91]. In the USA, there was a significant positive correlation between the number of endometriosis symptoms experienced and hours of both household and employment productivity loss due to absenteeism and presenteeism[94].

Work productivity loss also comes at a price. Unpaid time off work due to symptoms not only impacts the individual but also the employer, with loss of productivity at work potentially adversely affecting the gross domestic product (GDP) of countries[373]. On top of this, the long diagnostic delay associated with endometriosis (*Chapter 3*), increased risk of infertility, and costly treatment

options means that costs associated with endometriosis are considerable. The GSWH estimated the average yearly cost of endometriosis to be €9,579 (95%CI: €8,559-€10,599) and a study in Australia saw that the average cost incurred by women with endometriosis was Int $20,898 (95% CI Int $18,999-$23,213), with productivity costs being the biggest contributor.

There is currently no data on how endometriosis affects work productivity in Northern Cyprus or any estimates for economic burden. Such studies are useful not only on an individual level but can help guide policy and define priorities in healthcare. Data from cost studies can also help guide evaluations that aim to assess cost-effectiveness approaches to diagnosis and treatment of endometriosis. Therefore, the aims of this part of the study were to:

- Estimate the work productivity and activity impairment associated with endometriosis and compare this with pain symptomatic and asymptomatic control groups
- Estimate the direct and indirect costs of endometriosis and compare this with pain symptomatic and asymptomatic control groups
- Investigate how direct and indirect costs vary across the age groups
- Assess whether cost varies with pain severity experienced

5.2 Methods

5.2.1 Assessment of work productivity and activity impairment

The Work Productivity and Activity Impairment General Health (WPAI:GH) questionnaire was incorporated into the baseline questionnaire and was used to assess the impact of symptoms on absence from work (absenteeism) and reduced productivity whilst working (presenteeism) in endometriosis cases, symptomatic and asymptomatic controls. Questions were asked with regards to the past 4 weeks since endometriosis symptoms can fluctuate across the menstrual cycle. Analysis of the WPAI:GH followed standard methods for the calculation of the dimensions[266]. Absenteeism was calculated as [hours missed due to symptoms/(hours missed due to symptoms + hours actually worked)] x 100. Presenteeism was calculated as [reduced productivity while working] x 100. Overall productivity loss was calculated as [((hours missed due to symptoms + (percent reduced productivity while working x hours actually worked))/ (hours missed due to symptoms + hours actually worked)] x 100. Mean percentage values for these dimensions were compared for working women (employed/self- employed) between endometriosis cases, symptomatic and asymptomatic control groups.

5.2.2 Economic burden

Costs included both direct health care costs[374] and indirect costs related to loss of productivity or time off work. Costs relating to care were not calculated given the small number of individuals who reported to have a carer to assist them with

their daily activities (n=63/7,646; 0.82%). Since this was a prevalence analysis, costs were estimated regardless of the time of diagnosis. Average per-person costs were estimated separately for (i) endometriosis cases, (ii) symptomatic pain controls and (iii) asymptomatic pain controls. Costs were estimated in Turkish Lira using 2022 prices and then converted into International Dollars (Int $), which are tied to the US dollar by dividing the price in Turkish Lira by 2.61, which was the conversion factor taken from the World Bank at the time of analysis[375].

Costs were extrapolated to estimated costs over one year; the technique used was specific to the type of cost considered, outlined below:

Direct costs

Primary care

Costs included in primary care were pharmaceuticals and specialist visits. For medication relating to period pain, information on whether the pain medication was bought over the counter or obtained via prescription was gathered and an average dosage was assumed. For medication relating to pelvic pain, additional information on how long participants had this medication for in the last 3 months was collected and calculated to give a total time per 3 months, as follows – (i) less than one day ~ 0.5, (ii) one day – 1, (iii) two to three days ~ 2.5, (iv) one day a week ~ 4, (v) more than one day a week ~ 3.5 and (vi) every day ~ 91.

For hormones. If participants were asked if they had ever used selected hormones and if a respondent answered yes to either the combined birth control pill or the progesterone only pill, it was assumed that this was for at least one year and the cost was taken into account accordingly.

To extrapolate to annual costs, it was assumed that costs incurred would repeat over the course of the year. Therefore, for period pain, it was assumed women would have 12 periods in one year, so the cost was multiplied by 12. For pelvic pain, costs were multiplied by 4. Information was collected on specialist visits during the last 6 months, it was assumed these would repeat throughout the year, so this number was multiplied by 2.

Secondary care costs

This includes all hospital in-patient and out-patient care, including diagnostics, surgeries, visits to emergency care and hospitalisations. To extrapolate to annual costs, different assumptions were used dependent on the type of cost incurred. For diagnostics (blood tests, ultrasounds, and MRI/CT scans), use of these was reported in the last 6 months, and it was assumed that this would not be repeated continuously throughout the year, so these estimates were not extrapolated further, similar to the methods by Armour *et al.,* 2019[97].

For surgery costs, the baseline questionnaire collected data on the type and number of surgeries each respondent reported to have had so far in their life.

To calculate an annual cost for this, it was assumed that the earliest age any surgery would have taken place was 16 years. For each type of surgery, the following calculation was used:

$$\left(\frac{Number\ of\ surgeries}{Age\ at\ time\ of\ recruitment - 16}\right) x\ price\ of\ surgery$$

For hysterectomies, oophorectomies and tubal ligations, the number of surgeries was replaced with 1 since these surgeries are not able to be repeated. For laparoscopy, it was assumed to be diagnostic for those without endometriosis and assumed to be an endometrioma excision for those who reported to have endometriosis.

Unit costs for pharmaceuticals and specialist visits were obtained through local knowledge. Costs for surgeries and procedures were obtained from the tariff given by the Turkish Cypriot Medical Association[376].

For fertility treatments, the baseline questionnaire collected data on the type and number of fertility treatments (fertility drugs, IVF, intrauterine insemination (IUI)) each respondent reported to have had so far in their life. To calculate an annual cost, the same calculation was performed as for surgery costs, but rather than using 16 for the earliest age, the earliest age of each fertility treatment in the sample was used i.e., 24 for fertility drugs, 30 for IUI and 25 for IVF.

Indirect costs: productivity impact

Initial impact

A ‘human capital approach’ was used where lost working time was valued by lost income to each person. Income information was not collected as part of the baseline questionnaire, so the minimum national income of 84,000 Turkish Lira was used, giving a pro-rata daily income of 230 Turkish Lira. Costs were divided into ‘Absenteeism’ and ‘Presenteeism’, as detailed previously. Absenteeism is measured by days absent from work which was then multiplied by the pro rate daily income rate and the latter was measured from ‘*During the four weeks, how much did your symptoms affect your productivity while you were working?*’ – responses from 0-10 were converted into associated percentages (e.g. 2 = 20%) and then multiplied by the daily income. To extrapolate these costs to annual costs, the one-month absenteeism and presenteeism costs were multiplied by twelve.

Outcomes: average costs per patient

The average cost per person was estimated across the categories described above and collated into both an average for the sample as a whole and by age categories (18-25, 26-35, 36-45 and 46-55) as well as by pain severity during the menstrual cycle when the pain was at its worst (Minimal’ (1–2), ‘Mild’ (3–5), ‘Moderate’ (6–8), ‘Severe’ (9–10)). Analysis was conducted by endometriosis

cases, symptomatic controls, and asymptomatic controls separately. Means and 95% confidence intervals are reported.

Exclusion criteria

To not bias estimates, analysis was restricted to participants who reported to be employed as questions on productivity assume the individual was employed.

5.2.3 Missing values

To calculate absenteeism, data needed to be available for “hours missed due to symptoms” and “hours actually worked” and for presenteeism, data needed to be available for “hours missed due to symptoms”, “reduced productivity while working” and “hours actually worked”. Therefore, if a respondent had stated that they were employed but did not specifically state that they had taken time off work due to symptoms or that their symptoms affected their productivity while working, it was assumed that the answer to these questions was zero. Missing values dealt with by listwise deletion in Stata; any observation missing a value for a specific variable was dropped completely in the analysis of that variable, therefore observations missing any required variable were dropped in the computation of the relevant work productivity parameter.

5.3 Results

5.3.1 Employment status

In the study population, 77.4% (n=5,920) of women reported to be employed; 71.2% (n=5,440) were working in a paid job as an employee and 6.3% (n=480) were self-employed. Of the 1,384 women who were not in paid work, 1,375 (99.3%) gave further details (*Table 1*). The majority were homemakers (57.8%, n=795), 34.1% (n=469) were in full time education and 2.0% (n=28) were unemployed. Five women (0.4%) said they were unable to work because of the symptoms they experienced.

For women with endometriosis, 89.2% (n=356) were in paid employment compared to 10.8% (n=43) who reported to not be in paid employment. Women with endometriosis who were not in paid work were more likely to be between the ages of 18-25 (30.2% vs 5.1%) and less likely to be in the older age groups ($p<0.001$), more likely to have lower educational attainment (primary/middle school education – 30.2% vs 4.6%, high school/post-secondary – 46.5% vs 28.4%, $p<0.001$), more likely to be single (32.6% vs 17.9%, $p=0.039$) and less likely to live in Nicosia (30.2% vs 53.9%) and more likely to live in Trikomo (18.6% vs 3.1%) ($p<0.001$). There were no significant differences between women with endometriosis and employment status when considering ethnicity or residence type (*Table 2*).

5.3.2 Work productivity and impairment

The following analyses are restricted to those women who reported to be employed which includes a total of 5,920 (77.43%) women; 356 (86.83%) endometriosis cases, 2,219 (75.94%) symptomatic controls and 3,345 asymptomatic controls (77.54%).

5.3.3 Hours paid to work

On average, women who reported to be employed were paid to work for a total of 41.4 (95%CI: 40.2-42.6) hours per week but worked slightly less hours at 40.8 (95%CI: 38.7-42.8). Women with endometriosis were paid to work 39.8 (95%CI: 37.5-42.0) hours on average, which was slightly less than the symptomatic control group (42.0 hours, 95%CI: 41.1-43.0) (p=0.079) and the asymptomatic control group (41.1 hours, 95%CI: 39.1-43.0) (p=0.067). In practice, women with endometriosis worked on average for 38.0 (95%CI: 35.7-40.4) hours and symptomatic controls worked on average for 40.7 (95%CI: 39.1-42.3) hours, p=0.195. Women in the asymptomatic control group worked on average for 41.1 (95%CI: 37.5-44.7) hours, which was not significantly different to the endometriosis group, 0.575 (*Figure 1*). Women with endometriosis who experienced symptoms were paid to work on average for 41.0 (95%CI: 37.5-44.6) hours compared to asymptomatic endometriosis cases who were paid to work on average for 38.2 (95%CI: 35.5-40.9) hours, p=0.224. There was no statistical, significant difference between average number of

hours actually worked between endometriosis cases and symptomatic controls (36.4, 95%CI: 34.3-38.6 vs 40.3, 95%CI: 35.7-44.9, p=0.114).

5.3.4 Absenteeism

Absenteeism in the study population was low with women reporting an average absence from work as a result of symptoms for 2.1% (SD=5.6) of contracted work time. Women with endometriosis had lower average absence from work compared to symptomatic control women; reporting 2.2% (SD=5.5) and 2.5% (SD=5.7), respectively, but this was not statistically significant, p=0.111 (*Table 3*). Asymptomatic control women reported a lower average absence of 1.9% (SD=5.6) of contracted work time compared to the endometriosis group, but again this was not statistically significant, p=0.451.

5.3.5 Presenteeism

Women in the study population reported an average 22.4% (SD=26.3) reduction in effectiveness at work due to symptoms. Women with endometriosis reported an average 25.8% (SD=28.4) reduction in effectiveness compared to an average of 27.6% (SD=28.4) in the symptomatic control group, p=0.289. The asymptomatic control group reported an average 18.6% (SD=24.8) reduction in effectiveness at work due to symptoms, and this was significantly lower when compared to the endometriosis group, p<0.001 (*Table 3*).

5.3.6 Overall work productivity loss

Overall work productivity loss was on average 24.2% (SD=27.2) in the study population. Women with endometriosis had an overall work productivity loss on average of 27.5% (SD=28.5) which was lower than the symptomatic control group who had an overall loss on average of 29.7% (SD=28.8), p=0.376, but higher than the asymptomatic control group who averaged at 19.7% (SD=25.0), p<0.001 (*Table 3*).

5.3.7 Activity impairment

Overall, women reported an average 19.8% (SD=24.6) reduction in ability to carry out their regular daily activities due to symptoms. Women with endometriosis reported an average 23.4% (SD=26.0) reduction and symptomatic controls reported an average 15.4% (SD=26.7) reduction, p=0.725. The asymptomatic control group had a significantly lower average reduction in ability to carry out regular daily activities compared to the endometriosis group at 15.3% (SD=21.8), p<0.001.

5.3.8 Economic burden

The economic burden of endometriosis was on average Int $9,864.35 (95%CI: $8,811.55-$10,917.15) annually, which was not significantly different to the symptomatic control group, who spent a total of Int $10,429.68 (95%CI: $10,004.18-$10,855.17) annually (p=0.332). Women in the asymptomatic

control group spent significantly less than the endometriosis group on average – Int $6,587.63 (95%CI: $6,294.19-$6,881.08) annually, p<0.001 (*Table 4*).

The average annual health cost in women with endometriosis was Int $2,244.30 (95%CI: $1,934.06-$2,554.54), which included Int $724.67 (95%CI: $525.69-$923.64) on primary health costs and Int $1,519.63 (95%CI: $1,295.92-$1,743.34) on secondary health costs. These costs were significantly higher than the symptomatic control group, who spent on average a total of Int $1,578.02 (95%CI: $1,475.85-$1,680.18) annually on healthcare (p<0.001) which included Int $402.95 (95%CI: $365.74-$440.16) on primary health costs (p<0.001) and Int $1,175.07 (95%CI: $1,085.54-$1,264.59) on secondary health costs (p=0.005). The asymptomatic control group also spent significantly less than the endometriosis group, spending an average of Int $1,245.17 (95%CI: $1,169.37-$1,320.97) anually on health costs (p<0.001) which included Int $289.42 (95%CI: $269.92-$308.92) on primary health care (p<0.001) and Int $955.75 (95%CI: $887.78-$1,023.73) on secondary care (p<0.001) (*Table 4*).

For economic costs associated with productivity (absence from work and loss of productivity), the total annual cost for women with endometriosis was Int $7,620.05 (95%CI: $6,667.88-$8,572.23) which comprised of Int $523.32 (95%CI: $364.74-$681.90) lost through absenteeism and Int $7,096.73 (95%CI: $6,187.13-$8,006.34) lost through presenteeism. The symptomatic control group had a significantly higher cost of productivity loss, spending an average of Int $8,851.66 (95%CI: $8,456.30-$9,247.03) annually (p=0.023) which

included Int $572.90 (95%CI: $507.18-$638.62) lost through absenteeism (p=0.581) and Int $8,278.76 (95%CI: $7,904.09-$8,653.44) lost through presenteeism (p=0.021). The asymptomatic control group lost significantly less on average compared to the endometriosis group, incurring an average annual cost of loss of productivity of Int $5,342.46 (95%CI: $5,074.14-$5,610.78) (p<0.001) which included Int $473.98 (95%CI: $412.04-$535.93) spent on absenteeism (p=0.623) and Int $4,868.48 (95%CI: $4,618.23-$5,118.72) on presenteeism (p<0.001) (*Table 4*).

When stratifying the costs by age, the annual average cost in women with endometriosis was Int $10,742.43 (95%CI: $7,258.69-$14,226.18) for those aged 18-25, Int $12,159.78 (95%CI: 10,261.25-$14,058.32) for those aged 36-45, Int $9,389.21 (95%CI: $7,718.75-$11,059.67) for those aged 36-45 and Int $6,628.53 (95%CI: $4,652.91-$6,756.73) in those aged 46-55. The same pattern was observed in the average health costs which increased from Int $2,132,01 (95%CI: $1,161.69-$3,102.33) in those aged 18-25, to Int $2,728.11 (95%CI: $2,161.26-$3,294.97) in those aged 26-35 before decreasing to Int $2,125.82 (95%CI: $1,573.41-$2,678.22) in those aged 36-45 and Int $1,670.76 (95%CI: $1,294.88-$2,046.65) in those aged 36-45 as well as in productivity costs which were on average Int $8,610.42 (95%CI: $5,403.71-$11,817.11) for those aged 18-25, Int $9,431.67 (95%CI: $7,722.80.10-$11,140.54) in those aged 26-35, Int $7,263.40 (95%CI: $5,735.37-$8,791.42) in those aged 36-45 and Int $4,957.77 (95%CI: $3,158.80-$6,756.73) in those aged 46-55 (*Table 5*).

Although the average annual overall cost was lower in the symptomatic control group compared to the endometriosis group for women aged 18-25, averaging Int $9,553 (95%CI: $8,553.59-$10,553.66), it was markedly higher for those women in the oldest age group, 45-55 at Int $10,156.58 (95%CI: $8,800.24-$11,512,92), costs were Int $10,546 (95%CI: $9,911.18-$11,181.55) in 26-35 year olds and Int $10,803.20 (95%CI: $9,997.81-$11,608.59) in the 36-45 year olds. Here, the decrease in costs did not occur until women were around the age of menopause. Compared to the endometriosis group, the total annual costs were lower in all age groups for the asymptomatic controls, and the costs remained steady over the age groups; Int $7,136.41 (95%CI: $5,817.47-$8,455.35) in 18-25 year olds, Int $6,732.77 (95%CI: $6,203.50-$7,262.05) in 26-35 year olds, Int $6,146.57 (95%CI: $5,668.85-$6,624.30) in 36-45 year olds and Int $6,904.44 (95%CI: $6,340.69-$7,468.18) in 45-55 year olds (*Table 5*).

When examining the total average annual costs for all women (n=5,920) by pain severity, regardless of case group, the total cost incurred increased as pain increased. On average, women with minimum pain spent a total of Int $5,165.14 (95%CI: $4,449.56-$5,880.71), women with mild pain spent a total of Int $6,772.70 (95%CI: $6,290.26-$7,255.15), those with moderate pain Int $8,705.46 ($8,284.46-$9,126.63) and those with severe pain spent Int $10,800.74 (95%CI: $10,270.00-$11,331.49). Total annual health costs increased from Int $977.38 (95%CI: $805.24-$1,149.51) in the minimal pain group, to Int $1,129.05 (95%CI: $1,036.56-$1,221.53) in the mild pain group, to Int $1,478.97 (95%CI: $1,369.20-$1,588.73) in the moderate pain group to Int

$1,891.03 (95%CI: $1,746.82-$2,035.24) in the severe pain group. Similarly, average annual cost incurred due to absenteeism and presenteeism was Int $4,187.76 (95%CI: $3,516.28-$4,859.24) in the minimal pain group, Int $6,772.70 (95%CI: $6,290.26-$7,255.15) in the mild pain group, Int $8,705.46 (95%CI: $8,284.29-$9,126.63) in the moderate pain group and Int $10,800.74 (95%CI: $10,270.00-$11,331.49) in the severe pain group (*Table 6*).

5.4 Discussion

This is the first-time work productivity loss and economic burden has been estimated for women with endometriosis in Northern Cyprus. In addition to this, data on work and activity productivity loss and economic burden of endometriosis is scarce, especially in the Eastern Mediterranean region. Recall bias was minimised by asking questions relating to absence from work and productivity loss over the past 4 weeks.

In women who were employed, absenteeism from work was low in this population (average 2.1%), and there was no significant difference between absenteeism in the endometriosis group (2.2%), compared to the symptomatic (2.5%) and asymptomatic (1.9%) control group. These values are much lower than estimates in Arab women[91], which saw a significant difference in absenteeism between endometriosis cases (16.7%) and symptomatic controls (14.8%) and estimates from the GSWH[72], which estimated the mean percent of time absent from work as 11.2% in endometriosis cases and 8.5% in symptomatic controls; however, these differences were not significant. A study

of 1,138 women with endometriosis in the US[94] saw that the average percent of absenteeism in the study was 15.2% and another study that included 193 women from Puerto Rico[89] found women with endometriosis suffered from 22% of loss of work time on average.

Mean percentage of time lost due to loss of productivity in the symptomatic control group (27.6%) was not significantly different from the endometriosis group (25.8%). Asymptomatic controls (18.6%) had significantly lower loss of productivity compared to the endometriosis group. In contrast, the study in Arab women[91] had a similar percent of presenteeism in endometriosis cases at 22.7%, but significantly lower loss of presenteeism in the symptomatic control group at 18.7%. The GSWH[72] also saw a greater loss of presenteeism in the symptomatic control group (25.8%) compared to the endometriosis group (17.9%), but this was not significant after full adjustment. Women with endometriosis in Puerto Rico[89] were estimated to have a 60% productivity loss.

Activity impairment in women with endometriosis was much greater compared to the symptomatic control group (23.4% vs 15.4%), but again this was not significant. Activity impairment in the asymptomatic control group was similar to that of the symptomatic control group at 15.3%, and significantly lower than the endometriosis group. The GSWH[72] also saw a greater loss of activity impairment in the symptomatic control group compared to the endometriosis group (19.6% vs 28.5%) but similar to COHERE, this was not significant. Conversely, the aforementioned study in Arab women[91] saw no significant

difference between activity impairment between endometriosis cases and symptomatic controls (36.9% vs 34.0%) and the Puerto Rico study[89] estimated mean activity impairment to be 54%.

This similar loss of absenteeism, presenteeism and overall work productivity loss in the endometriosis and symptomatic control group suggests that it is the symptoms that are causing these losses, rather than having a diagnosis of endometriosis, *per se.* However, it is important to consider the fact that endometriosis cases in this study were ascertained using predominantly self-reported data, and results from *Chapter 3* showed that knowledge of endometriosis and its symptoms are low, so the likelihood of endometriosis cases being in the control group and inflating the percentages in the symptomatic control group, which would bias results towards the null, is high. In addition, *Chapter 3* also revealed that around half of endometriosis cases do not or have not experienced moderate-severe pain, and so this could bias results in the endometriosis group downwards and make the percentages similar to those in the symptomatic control group. However, the fact that activity impairment was so much greater in the endometriosis group compared to the symptomatic control group suggests that the effect of symptoms experienced by both groups are equal.

It is important to consider the specifics of each included study population. For example, both the GSWH[72] and the study of women of Arab ancestry[91], the case group was comprised of incident endometriosis cases who were attending

hospital to undergo a diagnostic or therapeutic laparoscopy or for sterilisation. Therefore, these case groups will be biased towards women with more severe symptoms who consequently will be more likely to need time of work or have reduced productivity because of their symptoms. Even if the demographics of these case groups are similar to that of census data, they are not fully representative of the endometriosis population and so are not generalisable. Since COHERE is a population-based study it does not suffer from these biases, but could be biased in other ways, as discussed in the previous paragraph.

Women with endometriosis spent a total of Int $9,864.35 on average which was lower than the average spend for symptomatic control women who spent Int $10,429.68, but significantly higher than the average spend for asymptomatic control women Int $6,587.63. This average cost in women with endometriosis was lower than in a study from Australia[97], which estimated an average annual cost of $20,898, and $16,573 in 113,506 women with endometriosis in the USA[377].

When attempting to make comparisons between the results presented here and other published studies, it is important to note that differences in costs could reflect multiple things. Firstly, methodology must be considered; the studies above all used the validated WERF ENDOCOST[378] tool which allows for valid comparisons between the studies that use that tool. The actual prices that individuals paid for services could not be obtained in this study, and although

efforts were made to use current prices, it cannot be ruled out that these may have been incorrect. The study in Australia also factored in a 'multiplier impact' to their costing analysis, which is a knock-on effect that reduced productivity has on the wider economy for example, reduced spending in the area a workplace is located if an individual takes time off work due to illness. Though this is an important consideration, there are no multiplier impacts that have been calculated for Northern Cyprus or the Eastern Mediterranean region. Estimates used in the study by Armor *et al.,* (2019) originated from research in Sweden[379] which may not be applicable to our study due to differences in workplaces, work patterns and economies. Secondly, it is important to note that healthcare systems and financing of healthcare will differ between countries and here, we assumed all costs were out-of-pocket expenses and did not consider price of insurance or whether any of these costs would be covered by the insurance. Thirdly, we did not have salary information for participants and used the minimum wage in Northern Cyprus for all participants, which would underestimate indirect costs. Fourthly, several assumptions were made with regards to frequency of treatments and in the type of treatment used, in the absence of this data being collected as part of the study (see Methods). Lastly, due to quick and uncontrolled inflation, the purchasing power parity (PPP) of the Turkish Lira has substantially increased over the last 10 years, and it is likely that prices paid for procedures or drugs that were incurred several years ago would not only be different to today's prices, but the equivalent in International Dollars would likely also be different. Therefore, the estimations presented here may be under- or over-estimated. However, this is the first study that has

attempted to estimate economic burden for endometriosis and what is important is the magnitude of the difference between endometriosis cases, symptomatic and asymptomatic controls, which shows women with endometriosis and women with symptoms have a high economic burden.

The biggest component of the annual cost for all women was loss of productivity, which has also been shown to be the biggest driver of costs associated with endometriosis in other published research described above. When considering overall healthcare costs, secondary costs were higher than primary costs as they encompass more expensive procedures. Although the average healthcare cost was highest in women with endometriosis, the average total loss of productivity costs was highest in the symptomatic control group. Women with endometriosis may have higher healthcare costs as their diagnosis may have more specialised treatment whereas the symptomatic control group, in the absence of a diagnostic or specialist treatment plan, may need to take more time off work or will face a higher loss of productivity as they live with their symptoms.

As age increased, the total average cost for women with endometriosis decreased from Int $10,742.43 to Int $6,628.53 and were highest for women between the ages of 26-35 at Int $12,159.78. For the symptomatic control group costs did not vary as much and were higher than women with endometriosis between the ages of 36-45 and 46-55. These results could be explained by the fact that since average age of endometriosis diagnosis in this population is 26

(*Chapter 3*), women with endometriosis may be undergoing multiple tests and procedures which will incur high costs. This is also likely the age that women will undergo fertility investigations and treatments if necessary. However, after diagnosis, women may be on an effective treatment regime and so costs related to decreased productivity and absence from work may be lower. Once they reach ages 46-55, women will become perimenopausal and menopausal which due to the change in hormones, means that their symptoms may decrease, or resolve completely, so their health costs are lower and, they are likely to retire from work. On the contrary, the symptomatic control group continue to have high costs between the ages of 26-45 as they continue to have investigative tests and incur costs due to absence from work and loss of productivity as they will be experiencing a higher symptom burden. However, other factors such as the small case group for women with endometriosis between 18-25 (n=18) must be considered because this small sample size means that the average costs may not be as accurate as if a larger sample size was used which would reduce the variance. In an ideal scenario a matched case control study would be undertaken, but in the absence of an abundance of data that is required to do this, the results presented here do give a good indication of how costs relating to endometriosis and pelvic pain vary across the life course.

The findings here showed that as reported period pain at its worst (NRS score) increased in all women, the total annual cost also increased from Int $6,165.14 to Int $10,800.74 and the main contributing factor here were costs relating to loss of productivity. Similar findings were seen in an economic burden study of

women with pelvic pain in Australia[97]. Research has shown that women with endometriosis in particular experience a greater loss of productivity as their pain experienced increases[94] and that chronic pain is one of the greatest contributors to loss of absenteeism and presenteeism in the workplace[95]. This can be explained by the fact that women with chronic pelvic pain often have difficulty with prolonged sitting[380] and in general, the availability of sick leave, because they may have already used all of their sick leave up. Women have reported that endometriosis has resulted in a negative impact on their educational and professional achievements through missed opportunities for promotions and feelings of not reaching their full potential[87,381].

Results from *Chapter 3* revealed that hormones, one of the main treatments for endometriosis, are not widely used in this population. Access to appropriate treatment for endometriosis could be improved in this population and would, in turn, help to drive the high loss of productivity costs down. Estimates on percentage reduction needed on pain scales vary but are estimated to be between 10 and 30%[382,383].

Table 1. Frequency and percentage of reasons for not being in paid work for all women

Reason for not being in paid work	Frequency	Percent
Undertaking voluntary work	24	1.8%
Homemaker	795	57.8%
In full time education	469	34.1%
Undertaking an internship	10	0.7%
Maternity leave	4	0.3%
Retired	23	1.7%
Unable to work because of the symptoms	5	0.4%
Unable to work for other reasons	17	1.2%
Unemployed	28	2.0%
Total	1,375	100.0%

Table 2. Demographic comparison between women with endometriosis in paid employment and not in paid employment

	All	Not in paid employment (N = 43)	In paid employment (N = 356)	p-value
		Number (percent)		
Age category				**<0.001**
18-25		13 (30.2%)	18 (5.1%)	
26-35		10 (23.3%)	125 (35.1%)	
36-45		13 (30.2%)	140 (39.3%)	
46-55		7 (16.3%)	73 (20.5%)	
Ethnicity				0.570
Turkish Cypriot		33 (76.7%)	277 (78.0%)	
Turkish		9 (20.9%)	59 (16.6%)	
Other/Mixed		1 (2.3%)	19 (5.4%)	
Education				**<0.001**
Primary/Middle school		13 (30.2%)	16 (4.6%)	
High school/Post-secondary		20 (46.5%)	98 (28.4%)	
Undergraduate degree		5 (11.6%)	147 (42.6%)	
Postgraduate degree		5 (11.6%)	84 (24.4%)	
Civil status				**0.039**
Single		14 (32.6%)	63 (17.9%)	
Divorced / Separated		2 (4.7%)	44 (12.5%)	
Married		27 (62.8%)	245 (69.6%)	
City				**<0.001**
Famagusta		8 (18.6%)	57 (16.0%)	
Kyrenia		8 (18.6%)	59 (16.6%)	
Lefke		2 (4.7%)	13 (3.7%)	
Morphou		4 (9.3%)	24 (6.7%)	
Nicosia		13 (30.2%)	192 (53.9%)	
Trikomo		8 (18.6%)	11 (3.1%)	
Residence				0.105
Village		27 (62.8%)	177 (49.7%)	
City		16 (37.2%)	179 (50.3%)	

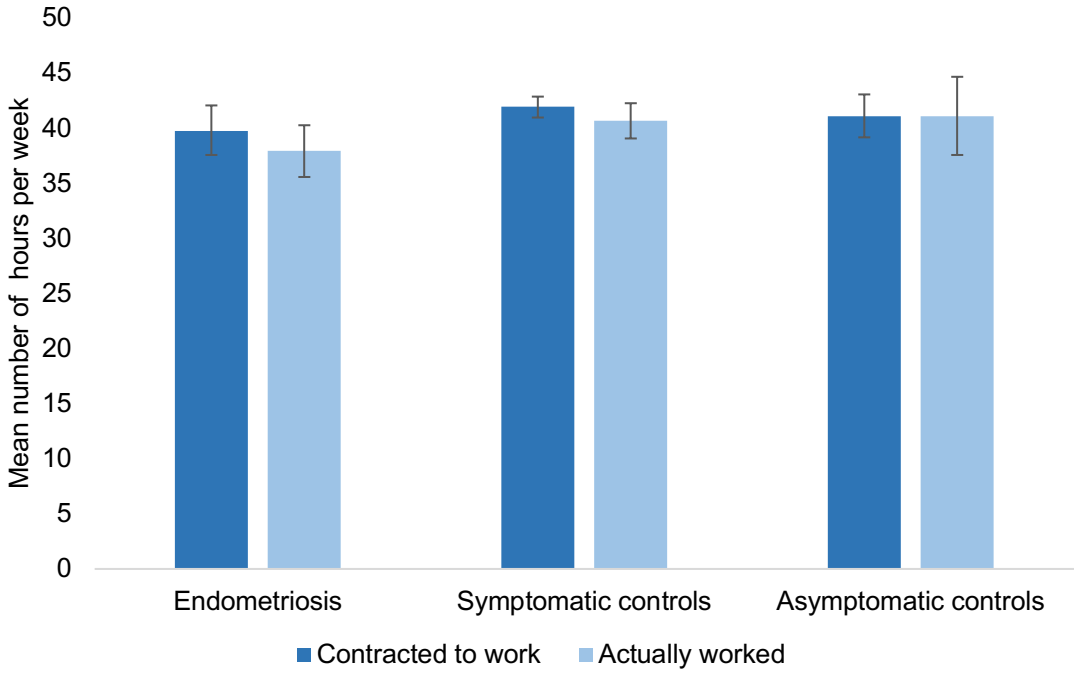


Figure 1. Bar chart showing mean number of hours contracted to work (dark blue) vs number of hours reported to actually work for (light blue)

Table 3. Work productivity and activity impairment in women with endometriosis compared to symptomatic and asymptomatic controls.

	Endometriosis, mean (SD)	Symptomatic controls, mean (SD)	Unadjusted p-value	Adjusted p-value*	Asymptomatic controls, mean (SD)	Unadjusted p-value	Adjusted p-value*
Absenteeism	2.2 (5.5)	2.5 (5.7)	0.496	0.111	1.9 (5.6)	0.269	0.451
Presenteeism	25.8 (28.4)	27.6 (28.4)	0.254	0.289	18.6 (24.8)	**<0.001**	**<0.001**
Overall work productivity loss	27.5 (28.5)	29.7 (28.8)	0.248	0.376	19.7 (25.0)	**<0.001**	**<0.001**
Activity impairment	23.4 (26.0)	15.4 (26.7)	0.205	0.725	15.3 (21.8)	**<0.001**	**<0.001**

**Adjusted for age, education, employment, ethnicity, civil status*
Absenteeism; Time absent from work due to symptoms, Presenteeism; Reduced effectiveness at work due to symptoms, Overall work productivity loss; Absenteeism and presenteeism combined, Activity impairment; Reduced effectiveness doing non-work-related activities

Table 4. Cost of health and productivity measures in endometriosis cases, symptomatic controls, and asymptomatic controls per annum. Currency is International Currency (Int $).

	A) Endometriosis (n=356)			**B) Symptomatic controls (n=2,219)**				**C) Asymptomatic controls (n=3,345)**			
	Mean	95% CI		Mean	95% CI		p-value (A vs B)	Mean (95% CI)	95% CI		p-value (A vs C)
Health											
Primary care	724.67	525.69	923.64	402.95	365.74	440.16	**<0.001**	289.42	269.92	308.92	**<0.001**
Secondary care	1,519.63	1,295.92	1,743.34	1,175.07	1,085.54	1,264.59	**0.005**	955.75	887.78	1,023.73	**<0.001**
Total	2,244.30	1,934.06	2,554.54	1,578.02	1,475.85	1,680.18	**<0.001**	1,245.17	1,169.37	1,320.97	**<0.001**
Productivity costs											
Absenteeism	523.32	364.74	681.90	572.90	507.18	638.62	0.581	473.98	412.04	535.93	0.623
Presenteeism	7,096.73	6,187.13	8,006.34	8,278.76	7,904.09	8,653.44	**0.021**	4,868.48	4,618.23	5,118.72	**<0.001**
Total	7,620.05	6,667.88	8,572.23	8,851.66	8,456.30	9,247.03	**0.023**	5,342.46	5,074.14	5,610.78	**<0.001**
Grand total	**9,864.35**	**8,811.55**	**10,917.15**	**10,429.68**	**10,004.18**	**10,855.17**	0.332	**6,587.63**	**6,294.19**	**6,881.08**	**<0.001**

95%CI; 95% Confidence Intervals

Table 5. Cost of health and productivity measures in endometriosis cases, symptomatic controls, and asymptomatic controls, by age group per annum. Currency is International Currency (Int $).

	Age range	**18-25 (n=18)**			**26-35 (n=125)**			**36-45 (n=140)**			**46-55 (n=73)**		
		Mean	95% CI		Mean	95% CI		Mean	95% CI		Mean	95% CI	
Endometriosis	**Health**												
	Primary care	**420.10**	172.99	667.21	**1,000.49**	603.65	1,397.33	**694.73**	2,161.26	1,045.59	**384.87**	267.74	502.01
	Secondary care	**1,711.91**	883.25	2,540.58	**1,727.63**	1,325.46	2,129.79	**1,431.08**	1,039.82	1,822.35	**1,285.89**	952.15	1,619.63
	Total	**2,132.01**	1,161.69	3,102.33	**2,728.11**	2,161.26	3,294.97	**2,125.82**	1,573.41	2,678.22	**1,670.76**	1,294.88	2,046.65
	Productivity costs												
	Absenteeism	**206.84**	(65.63)	479.32	**703.39**	369.54	1,037.25	**504.78**	264.36	745.19	**328.57**	102.20	554.95
	Presenteeism	**8,403.58**	5,161.62	11,645.53	**8,728.28**	7,122.48	10,334.07	**6,758.62**	5,262.96	8,254.28	**4,629.19**	2,959.00	6,299.39
	Total	**8,610.42**	5,403.72	11,817.11	**9,431.67**	7,722.80	11,140.54	**7,263.40**	5,735.37	8,791.42	**4,957.77**	3,158.80	6,756.73
	Grand total	**10,742.43**	7,258.69	14,226.18	**12,159.78**	10,261.25	14,058.32	**9,389.21**	7,718.75	11,059.67	**6,628.53**	4,652.91	8,604.15
	Age range	**18-25 (n=351)**			**26-35 (n=958)**			**36-45 (n=687)**			**46-55 (n=223)**		
		Mean	95% CI		Mean	95% CI		Mean	95% CI		Mean	95% CI	
Symptomatic controls	**Health**												
	Primary care	**276.70**	218.21	335.19	**408.02**	369.81	446.23	**476.05**	375.11	576.98	**354.69**	288.43	420.95
	Secondary care	**1,006.29**	848.94	1,163.64	**1,183.89**	1,051.11	1,316.68	**1,235.57**	1,043.29	1,427.84	**1,216.38**	980.14	1,452.63
	Total	**1,282.99**	1,108.30	1,457.68	**1,591.92**	1,445.49	1,738.34	**1,711.61**	1,483.86	1,939.37	**1,571.08**	1,310.71	1,831.44
	Productivity costs												
	Absenteeism	412.63	301.84	523.41	**475.10**	397.73	552.46	**720.02**	565.72	874.32	**792.09**	551.09	1,033.09
	Presenteeism	**7,858.01**	6,929.91	8,786.11	**8,479.35**	7,912.78	9,045.92	**8,371.56**	7,690.08	9,053.05	**7,793.41**	6,593.18	8,993.65
	Total	**8,270.63**	7,308.12	9,233.15	**8,954.45**	8,363.76	9,545.14	**9,091.58**	8,359.04	9,824.12	**8,585.50**	7,298.29	9,872.72
	Grand total	**9,553.62**	8,553.59	10,553.66	**10,546.36**	9,911.18	11,181.55	**10,803.20**	9,997.81	11,608.59	**10,156.58**	8,800.24	11,512.92

	Age range	18-25 (n=167)			26-35 (n=951)			36-45 (n=1,234)			46-55 (n=993)		
		Mean	95% CI		Mean	95% CI		Mean	95% CI		Mean	95% CI	
	Health												
	Primary care	**206.90**	137.86	275.94	**354.72**	316.23	393.20	**283.35**	250.55	316.14	**248.30**	214.60	282.00
	Secondary care	**950.12**	655.57	1,244.68	**1,006.37**	877.93	1,134.80	**902.91**	786.40	1,019.41	**973.91**	855.99	1,091.83
Asymptomatic controls	Total	**1,157.03**	843.71	1,470.34	**1,361.08**	1,217.69	1,504.47	**1,186.25**	1,053.62	1,318.88	**1,222.21**	1,094.25	1,350.16
	Productivity costs												
	Absenteeism	**756.73**	378.99	1,134.46	**396.89**	308.73	485.05	**427.45**	324.86	530.05	**558.09**	431.36	684.81
	Presenteeism	**5,222.66**	4,071.10	6,374.22	**4,974.80**	4,515.34	5,434.26	**4,532.87**	4,136.61	4,929.14	**5,124.15**	4,637.62	5,610.67
	Total	**5,979.39**	4,734.68	7,224.09	5,371.69	4,888.16	5,855.23	**4,960.32**	4,530.44	5,390.20	**5,682.23**	5,160.09	6,204.38
	Grand total	**7,136.41**	5,817.47	8,455.35	**6,732.77**	6,203.50	7,262.05	**6,146.57**	5,668.85	6,624.30	**6,904.44**	6,340.69	7,468.18

95%CI; 95% Confidence intervals

Table 6. Cost of health and productivity measures in in all women, by pain severity (period pain at its worst) per annum. Currency is International Currency (Int $)

	Minimum (0-2) (n=392)			**Mild (3-5) (n=1,020)**			**Moderate (6-8) (n=1,873)**			**Severe (9-10) (n=1,602)**		
Age range	Mean	95% CI		Mean	95% CI		Mean	95% CI		Mean	95% CI	
Health												
Primary care	**253.62**	191.18	316.06	**270.87**	237.55	304.18	**382.99**	355.69	410.29	**489.07**	424.59	553.55
Secondary care	**723.76**	569.07	878.44	**858.18**	778.18	938.18	**1,095.98**	997.48	1,194.47	**1,401.96**	1,280.96	1,522.97
Total	**977.38**	805.24	1,149.51	**1,129.05**	1,036.56	1,221.53	**1,478.97**	1,369.20	1,588.73	**1,891.03**	1,746.82	2,035.24
Productivity costs												
Absenteeism	**509.60**	299.18	720.02	**500.54**	390.48	610.59	**544.00**	465.91	622.08	**542.30**	466.18	618.41
Presenteeism	**3,678.16**	3,063.63	4,292.69	**5,143.12**	4,712.33	5,573.90	**6,682.50**	6,318.21	7,046.79	**8,367.41**	7,903.95	8,830.88
Total	**4,187.76**	3,516.28	4,859.24	**5,643.65**	5,177.94	6,109.37	**7,226.50**	6,839.94	7,613.05	**8,909.71**	8,423.44	9,395.98
Grand total	**5,165.14**	4,449.56	5,880.71	**6,772.70**	6,290.26	7,255.15	**8,705.46**	8,284.29	9,126.63	**10,800.74**	10,270.00	11,331.49

95% CI; 95% Confidence Intervals

Chapter 6 – Risk factors, co-morbidities and deficiencies associated with endometriosis

6.1 Introduction

Despite endometriosis having a high prevalence and a significant impact on both quality of life and economic burden[72,97], very little is understood about its disease aetiology[38] and in particular, there is a lack of data on risk factors and co-morbidities from non-Western populations[2].

Early age of menarche has been associated with a higher risk of endometriosis[109,110,384], explained by a change in the hormonal environment or an increase in exposure to menstruation giving support to Sampson's hypothesis of retrograde menstruation[11,18]. Other menstrual characteristics previously shown to be associated with endometriosis are shorter[109] and irregular menstrual cycles[91]. Low BMI, low waist-to-hip ratio[38] and height[114] have also been shown to be associated with endometriosis. Correlations between lifestyle risk factors such as smoking, alcohol and exercise have been inconsistent. Some studies[103,111] have shown that smoking could be a protective factor for endometriosis, explained tobacco's anti-oestrogenic effect[385]. However, a recent systematic review and meta-analysis[157] revealed no association between smoking and endometriosis. A recent systematic review and meta-analysis suggested a positive association between alcohol intake and endometriosis[163], potentially explained by the fact that alcohol increases oestrogen levels which have shown to be elevated in women with

endometriosis[386]. The possible relationships between diet and endometriosis were discussed in detail in *Chapter 1*. The correlation between endometriosis and physical activity has been inconsistent with several case-control studies estimating there to be around a 40-80% decreased risk of endometriosis with regular exercise[111,164,165]. However, the prospective NHSII saw a non-significant decreased risk[169].

In terms of co-morbidities, endometriosis has been associated with an increased risk for several other diseases[180,387] such as auto-immune[30], allergic[388–390] and cardiovascular[55]. In terms of deficiencies, both iron deficiency[220] and vitamin D deficiency[244,391] have been associated with endometriosis risk. These deficiencies are particularly interesting in this population of women in Cyprus due to the high prevalence of thalassemia carriers[218] and large amount of sunlight received by the island. Pigmentary traits such as red hair[392], lighter eyes[227], and increased numbers of naevi[224] have also been investigated as potential risk factors for endometriosis. However, different genetic characteristics in this population may mean the prevalence of these pigmentary characteristics in Northern Cyprus is low.

The difficulties involved in assessing risk-factors for endometriosis were touched on in *Chapter 1*. The cross-sectional study design of COHERE constrains the ability to properly assess risk factors for endometriosis in this population. The study relies on self-reported data which is prone to recall bias and it is not possible to determine whether the occurrence of risk-factors

precede or follow the diagnosis of endometriosis. The long delay between onset of symptoms and diagnosis also poses a unique challenge. Interpretation of the results presented here need to bear the aforementioned limitations in mind. However, in the absence of any data on endometriosis from Northern Cyprus, this study can provide some information on potential risk factors and co-morbidities and provides a basis for future follow-up studies.

Therefore, the aims of this chapter were to investigate potential associations between endometriosis and:

- Menstrual characteristics, lifestyle factors, anthropometric measurements, family history, pigmentary traits, co-morbidities, and deficiencies.

6.2 Methods

6.2.1 Menstrual risk factors

Variables assessed included: age of menarche (≤12 years, 13-14 years, ≥15 years), menstrual cycle length (<24 days, 24-31 days, ≥32 days), menstrual cycle irregularity (regular or irregular), duration of menstrual phase (≤4 days, 5-6 days, ≥7 days) and average intensity of menstrual flow (spotting/light, moderate, heavy).

6.2.2 Anthropometric risk factors

BMI, waist-to-hip-ratio (WHR) and height were calculated as described in *Chapter 2* of this thesis. WHR was adjusted for BMI to give a surrogate measure of abdominal adiposity[393].

6.2.3 Family history

The family histories of the following were assessed as a binary (yes/no) variable: endometriosis, chronic pelvic pain, heavy bleeding, uterine fibroids, PCOS. Participants were coded as having a family history of the disease if they reported their mother, sister, daughter grandparents, aunt or cousin having the disease.

6.2.4 Co-morbidities and deficiencies

Co-morbidities were grouped (*Supplementary Table 1*) into the following to increase power of the analysis and assessed as yes/no variables: reproductive (PCOS, uterine fibroids, ovarian cysts), autoimmune (thyroid disease, systemic lupus erythematosus, Sjogren's, rheumatoid arthritis, multiple sclerosis, irritable bowel disease, psoriasis, type 1 diabetes), allergic (eczema, asthma), obesity and metabolomic-related (type 2 diabetes, insulin resistance, hypoglycaemia, high cholesterol, obesity), cardiovascular (cardiovascular disease, mitral valve prolapse, angina, arrythmia, congenital heart disease, high blood pressure, low blood pressure), thalassemia carrier.

Iron deficiency (yes/no) and vitamin D deficiency (yes/no) were also examined.

6.2.5 Dietary risk factors

Each food item and vitamin/mineral were assessed using dichotomised variables based on the median daily intake (g) reported to be consumed by the FFQ participants. Participants were given a value of 1 if they consumed equal to or over the sample median and a value of 0 if they consumed below the sample median. If a significant association was obtained, then the data were explored using tertiles and linear trend. Derivation of the Mediterranean diet (MD) score was explained in *Chapter 2*.

6.2.6 Lifestyle risk factors

These included ever smoked over 100 cigarettes during a lifetime (yes/no), currently smokes (yes/no), regularly drinks alcohol (yes/no) and regularly exercises (yes/no).

6.2.7 Pigmentary risk factors

Included eye colour (brown, hazel/ blue, green, grey), hair colour (blonde/red, light brown, dark brown, black), skin colour (very light, light intermediate/ dark intermediate, dark, very dark), number of moles (none/1 to 10/11-50/50 or more)

6.2.8 Sun exposure habits as risk factors

Included time outside during the summer age <25 years, time outside during the winter age <25 years, time outside during the summer in the past 2 years, time outside during the winter in the past 2 years were all assessed as categorical variables comprising of less than an hour per week, 2 to 4 hours per week, 5+ hours per week. Use of sunscreen in the summer and winter was assessed as a dichotomised variable (yes/no). Solarium use was not examined due only a small number of women reporting to have ever used them (63/7,646, 0.82%).

6.2.9 Missing values

Analyses were only performed on participants who had no missing data on the outcome and covariates to enable a complete case analysis.

6.2.10 Statistical analysis

Descriptive statistics (frequencies and percentages) were used to summarise the above characteristics between the case and control groups. For the dietary data, endometriosis cases were compared to non-endometriosis controls. For the rest of the analyses, endometriosis cases were compared to symptomatic and asymptomatic controls. Multivariate logistic regression modelling was used to examine potential associations between endometriosis and independent variables. Confounding variables were determined *a priori* and are listed in the corresponding tables. Crude and adjusted odds ratios with 95% confidence

intervals (95%CI) were obtained. A p-value of <0.05 was deemed statistically significant.

6.3 Results

6.3.1 Dietary habits

There was no association between MD score and endometriosis cases and controls. Women consuming above the median daily intake (1,446g) of fruits and vegetables had a 63% lower endometriosis risk (95%CI: 0.21-0.64), compared to those consuming less than the median value, after adjustment (*Table 1*). When this relationship was examined further by splitting total fruit and vegetable intake into tertiles (*Table 2*), women in the highest tertile were 60% less likely to report having endometriosis (95%CI: 0.14-0.64) compared to women in the lowest tertile, but there was no evidence of a trend (*p*-trend=0.273). When splitting the control group into symptomatic and asymptomatic controls, the observed association between total fruit and vegetable intake and endometriosis still held for symptomatic (adjusted OR: 0.51 (95%CI: 0.28-0.96)) and asymptomatic (aOR: 0.33 (95%CI: 0.18-0.60)) controls.

When considering vegetable intake on its own, women consuming over the median daily intake (567g) were 47% less likely to report having an endometriosis diagnosis (95%CI: 0.31-0.89) (*Table 1*) and when splitting total vegetable intake into tertiles, there was no evidence of a trend (p-trend=0.804)

but women in the highest tertile were 52% less likely (95%CI: 0.25-0.93) to report an endometriosis diagnosis compared to women in the lowest tertile (*Table 2*). The association between endometriosis and vegetable intake held when splitting the control group into symptomatic (aOR: 0.51 (95%CI: 0.27-0.94)) and asymptomatic (aOR: 0.54 (95%CI: 0.31-0.95)).

Although no significant association existed between reporting an endometriosis diagnosis and meat intake, the odds of reporting an endometriosis diagnosis and reporting to consume over the median daily intake (36g) of processed and unprocessed red meat were notably high (aOR: 1.49 (95%CI: 0.88-2.50)) compared to consuming below the median intake. This finding was similar when considering processed red meat on its own (aOR: 1.27 (95%CI: 0.75-1.12)) (*Table 2*).

In terms of reported vitamin/mineral consumption and endometriosis, women consuming over the median daily intake of lutein (3g) were 41% (95%CI: (0.36, 0.97)) less likely to report an endometriosis diagnosis compared to women reporting to consume less than the median daily intake (*Table 3*). When examining this association further by splitting daily consumption of lutein into tertiles, no significant association existed (*Table 4*). Women consuming over the median daily intake of vitamin E (25.8g) were 48% (95%CI: 0.28, 0.97) less likely to report an endometriosis diagnosis than women consuming less than the median daily intake (*Table 3*). When examining this association further by splitting daily consumption of lutein into tertiles, no significant association

existed (*Table 4*). Women consuming over the median daily intake of folate (519.5g) were 48% (95%CI: 0.28-0.94) less likely to report an endometriosis diagnosis compared to women consuming less than the median intake (*Table 3*). When examining this association further by splitting daily consumption of lutein into tertiles, no significant association existed (*Table 4*).

6.3.2 Menstrual factors

Women with endometriosis were slightly more likely to report starting their periods at or under the age of 12 years (52.8% vs 50.3% in symptomatic controls and 48.9% in asymptomatic controls) and a greater proportion of endometriosis cases reported to have a menstrual cycle length <24 days compared to symptomatic and asymptomatic controls (17.4% vs 14.4% and 15.2%, respectively) (*Table 5*). However, after adjustment for demographics, there was no relationship between endometriosis cases and either of these characteristics (*Table 6*).

Women with endometriosis were more likely to report to have an irregular menstrual cycle (15.9%) than both symptomatic controls (13.1%) and asymptomatic controls (12.5%) (*Table* 5) and after adjustment for demographics, women with irregular menstrual cycles were 1.45 times (95%CI: 1.05-2.01) more likely to have report endometriosis compared to women with regular menstrual cycles, rather than be in the asymptomatic control group (*Table 6*). A higher proportion of women in the endometriosis group (20.1%) reported that their menstrual phase lasted ≥7 days compared to symptomatic

(17.0%) and asymptomatic controls (12.6%) (*Table 5*). Compared to asymptomatic controls, women with a menstrual phase of ≥7 days were 1.94 (95%CI: 1.39-2.70) times more likely to report endometriosis, when using 5-6 days as the reference category (*Table 6*). When this analysis was restricted to women who self-reported to have regular menstrual cycles, this association still existed (aOR: 1.92 (95%CI: 1.30-2.78)) (*Table 7*). Women with endometriosis reported to have a heavier flow (9.8%) on average compared to symptomatic (8.8%) and asymptomatic controls (5.2%) (*Table 5*) and when compared to asymptomatic controls, women with a heavier flow were 1.92 times (95%CI: 1.27-2.91) more likely to report endometriosis than those with a moderate flow (*Table 6*). When this analysis was restricted to women with regular menstrual cycles, this association still held (aOR: 1.69 (95%CI: 1.04-2.73)) (*Table 7*).

6.3.3 Anthropometric factors

Distributions of BMI and height did not appear to differ too much between endometriosis and control groups, but women with endometriosis had a higher frequency of having a lower WHR than both control groups (*Table 8*). After adjusting for BMI and other demographic factors, women with a WHR ≤80.41cm had an increased odds of reporting endometriosis compared to symptomatic controls (OR: 2.19, 95%CI: 1.21-3.97) using >84.91cm to ≤88.12cm as the reference (*Table 9*). Compared to asymptomatic controls, women with a WHR ≤80.41 (OR: 2.35, 95%CI: 1.32-4.20) and >80.41cm to ≤84.91cm (OR: 2.85, 95%CI: 1.02-3.34) had an increased odds of endometriosis, using >84.91cm to ≤88.12cm as the reference (*Table 9*).

6.3.4 Family history

When considering family history, women with a family history of endometriosis, chronic pelvic pain, heavy bleeding, uterine fibroids and PCOS were more likely to be endometriosis cases compared to both control groups (*Table 10*) and after adjustment for demographics, the odds of endometriosis were significantly higher in women with these family histories compared to both control groups (*Table 11*). The highest odds were observed for endometriosis history (aOR vs symptomatic controls: 6.14, 95%CI: 453-8.34, aOR vs asymptomatic controls: 7.79, 95%CI: 5.81-10.43) and history of chronic pelvic pain (aOR vs symptomatic controls: 2.53, 95%CI: 1.82-3.52, aOR vs asymptomatic controls: 3.61, 95%CI: 2.62-4.98).

6.3.5 Lifestyle factors

A similar proportion of endometriosis cases and symptomatic controls reported to be ever smokers (39.0% vs 34.4%) with a lower proportion of asymptomatic controls reporting this (29.9%) (*Table 12*). After adjusting for demographics, ever smokers were 1.5 (95%CI: 1.24-1.92) times more likely to be endometriosis cases compared to never smokers, when compared with the asymptomatic control group (*Table 13*). As discussed in *Chapter 2*, there were only a small proportion of participants who reported to regularly drink alcohol (27.7%; n=1,121). A similar proportion of endometriosis cases and symptomatic controls reported to regularly drink alcohol (38.0% vs 35.9%) compared to a

lower proportion in the asymptomatic control group (23.4%) (*Table 12*). After demographic adjustment, compared to the asymptomatic control group, women who regularly drank alcohol were 1.73 (95%CI: 1.38-2.16) times more likely to be an endometriosis cases compared to those who did not regularly drink alcohol (*Table 13*). There were no significant associations between current smokers and regular exercise between endometriosis cases and either control group.

6.3.6 Comorbidities and deficiencies

Women with endometriosis reported a higher proportion of all co-morbidities and deficiencies examined in comparison to symptomatic and asymptomatic control groups (*Table 14*). After adjustment for demographics, endometriosis cases were 2.55 (95%CI: 2.02-3.21) and 4.17 (95%CI: 3.33-5.23) times more likely to report a reproductive comorbidity compared to symptomatic and asymptomatic controls, respectively (*Table 15*). Women with endometriosis were also at a greater risk of reporting an allergy-related condition compared to symptomatic (aOR: 1.43 (95%CI: 1.04-1.96)) and asymptomatic (aOR: 2.00 (95%CI: 1.47-2.74)) control groups. Compared to asymptomatic controls, cases were 1.71 (95%CI: 1.29-2.24) and 1.65 (1.26-2.16) times more likely to report obesity/metabolic-related and cardiovascular diseases, respectively. Compared to asymptomatic controls, women who were iron deficient were 1.70 (95%CI: 1.37-2.12) times more likely to report endometriosis and women who were vitamin D deficient were 1.52 (95%CI: 1.18-1.95) times more likely to report endometriosis (*Table 15*).

6.3.6 Pigmentary traits and sun habits

Endometriosis cases and controls had equally distributed proportions of women with similar eye colour, hair colour, moles, and sun habits (*Table 16*). The endometriosis group had higher frequencies of women with lighter skin (85.3% vs 77.9% in symptomatic and 78.3% in asymptomatic controls) and a higher proportion of cases used sunscreen in the summer (63.4%) and winter (43.7%) compared to symptomatic (55.5% and 30.2%) and asymptomatic (47.6% and 28.8%) controls (*Table 17*).

After adjustment for demographics, compared to symptomatic controls, women with darker skin were 40% less likely to report having endometriosis (aOR: 0.60 (95%CI: 0.39-0.92)) compared to women with lighter skin. Compared to asymptomatic controls, use of sunscreen in the summer and winter was associated with an increased endometriosis risk 1.49 (95%CI: 1.08-2.05) and 1.72 (95%CI: 1.26-2.36), respectively, compared to using no sunscreen (*Table 17*).

6.3.7 Relationship between vitamin D deficiency, demographics, pigmentary traits, and sun habits <25 years of age

The relationship between the above factors and endometriosis cases compared to symptomatic controls can be seen in *Table 18.* After adjustment, women with darker skin were 39% (95%CI: 0.39-0.95) less likely to report endometriosis when considering sun exposure in the summer compared to women with lighter

skin and 40% (95%CI: 0.39-0.94) less likely to report endometriosis when considering sun exposure in the winter, compared to women with lighter skin. The relationship between the above factors and endometriosis cases compared to asymptomatic controls can be seen in *Table 19.* Women with a vitamin D deficiency were 1.77 (95%CI: 1.23-2.57) times more likely to report to have endometriosis, after adjustment for demographics, pigmentary traits, and sun habits during the summer when they were under the age of 25. In addition to this, after controlling for these factors and vitamin D deficiency, use of sunscreen increased the risk of endometriosis compared to women who did not report using sunscreen (aOR=1.44, 95%CI: 1.04-1.98).

As opposed to asymptomatic controls, women who reported to be vitamin D deficient were 1.87 (95%CI: 1.29-2.71) times more likely to report endometriosis compared to women who were not vitamin D deficient after adjusting for demographics, pigmentary traits, and sun habits during the winter when they were under the age of 25. Again, use of sunscreen appeared to be associated with a higher endometriosis risk (aOR: 1.68, 95%CI: 1.22-2.31).

6.3.8 Relationship between vitamin D deficiency, demographics, pigmentary traits, and sun habits in the past 2 years.

When investigating the relationship between endometriosis and vitamin D deficiency but considering sun exposure in the past 2 years in the summer, women who were vitamin D deficient were 1.52 and 2.04 (95%CI: 1.01-2.27) times more likely to be endometriosis cases compared to women who were not

vitamin D deficient, when comparing the odds against symptomatic *(Table 20*) and asymptomatic (*Table 21*) controls, respectively. However, when considering winter sun exposure in the last 2 years and sunscreen use during the winter, there were no associations. Compared to the asymptomatic control group, vitamin D deficient women were 2.02 (95%CI: 1.35-3.02) times more likely to be an endometriosis case compared to women who were not vitamin D deficient (*Table 21*).

There were no observed differences between changes in sun exposure in case and control groups from age <25 to in the last 2 years (*Table 22*).

6.4 Discussion

This is the first time that potential risk factors and co-morbidities for endometriosis have been explored in this population. Although the cross-sectional study design means that temporality is an issue, the analysis presented here forms the basis for potential appropriately designed follow-up studies and helps to address a gap in research into co-morbidities and risk factors for endometriosis in the Eastern Mediterranean region.

6.4.1 Menstrual-related risk factors

No significant association was observed between age of menarche, or menstrual cycle length and endometriosis, but women with longer, heavier, and more irregular menstrual cycles were more likely to be endometriosis cases.

There is strong evidence that early age of menarche is related to menstrual cycle risk. The NHSII showed a greater incidence of endometriosis amongst women who had an earlier age of menarche (rate ratio: 1.3 comparing age of menarche age <10 to 12 years, 95%CI: 1.0-1.8)[109] as did a case control study in Australia[394] and a study in the UAE[91]. In addition, a systematic review and meta-analysis[110] including 18 case-control studies saw a small, but non-significant, association between the two, similar to that observed here. As discussed in previous chapters, given the fact that awareness of endometriosis is low in this population, there is likely disease misclassification resulting in undiagnosed endometriosis cases in the control group. This would attenuate risk estimates and bias them towards the null. Additionally, research[395] has shown that validity of self-reported age of menarche when women are middle aged is only moderate compared to adolescent females. Therefore, there may also be misclassification in the outcome variable.

In the present study, there was no significant association between menstrual cycle length and endometriosis. Results from the NHSII saw a greater incidence of endometriosis in women with a shorter cycle length during late adolescence (RR: 1.3 comparing <26 days to 26-31 days, 95%CI: 1.1-1.5)[109]. The present study was not able to specifically assess menstrual cycle length during adolescents so it is not clear if there would be a potential association had this analysis been able to be performed. A meta-analysis[396] that include 11 case-control studies restricted to cases of surgically confirmed endometriosis found that when comparing menstrual cycle length shorter or equal to 27 days against

length longer than or equal to 29 days that the odds were 1.22 (95%CI: 1.05-1.43) and 0.68 (95%CI: 0.48-0.96), respectively. However, it can be argued that 27 days is not necessarily a short cycle, with other studies defining a 'normal' length cycle as between 21-35 days[397]. Notably, one case-control study[398] saw an increased risk of endometriosis with a longer menstrual cycle length (OR: 2.9, 95%CI: 1.3-6.4).

Women with prolonged menstrual bleeding equal to or over 7 days compared to 5-6 days and women with heavy bleeding were more likely to be endometriosis cases, when compared with asymptomatic controls. Similar findings have been reported in the UAE[91] and in a population of white women with primary infertility due to endometriosis[111]. A study of adolescents in Italy[399] who were undergoing investigative ultrasound saw high rates of heavy bleeding in adolescents who were found to have endometriosis. In this study, heavy menstrual bleeding was assessed subjectively based on recall; a strength of the study presented here is that a visual guide was used to aid participants, helping to avoid misclassification of the outcome. Another study examining 27,840 women with endometriosis in six European countries[400] also saw that 50.8% of women experienced heavy/menstrual bleeding. The above menstruation-related risk factors for endometriosis all support Sampson's theory of retrograde menstruation[18] as the origin of endometriosis because they increase the frequency of exposure to menstruation and menstrual reflux.

Endometriosis cases were more likely to report having an irregular menstrual cycle than a regular menstrual cycle when compared to asymptomatic controls only. This is similar to a study in the UAE[91] that also observed a significantly higher degree of menstrual irregularities compared to asymptomatic controls but not symptomatic controls though different from a study in Lombardy, Italy[112] which observed that women with irregular menstrual cycles were at a lower risk of endometriosis. The mechanism by which endometriosis could be related to irregular menstrual cycles is unclear and warrants further epidemiological research, but may lie in dysregulation of control mechanisms[401]. For the menstrual characteristics investigated here, no differences were seen between endometriosis cases and symptomatic controls. This could be due to undiagnosed cases being in the control group thus causing misclassification and biasing estimates towards the null, or since women in the symptomatic control group suffer from pain, they may have other gynaecological problems that also cause menstrual irregularities. In addition, the results in Chapter 3 suggested low awareness of endometriosis symptoms in both clinicians and the public and since a proportion of endometriosis cases were diagnosed off 'symptoms' alone, it is plausible that they have been incorrectly diagnosed. One strength of the research presented here is that so few women reported to have ever taken hormones, which are known to alter menstrual cycles, so this is unlikely to have affected the results.

6.4.2 Anthropometric characteristics

There was no relationship between BMI and endometriosis or height and endometriosis. This is contrary to data using the French E3N cohort[114] which found that women in the highest quartile of height had an increased odds of endometriosis compared to those in the lowest (OR: 1.28, 95%CI: 1.12-1.46) and data from the NHSII[113] which found that in infertile women, those categorised as obese had a 55% (95%CI: 0.30-0.67) and 62% (95%CI: 0.20-0.62) lower risk of endometriosis compared with low-normal categories of BMI. In COHERE, women with a lower WHR had a higher likelihood of reporting to have endometriosis compared to both symptomatic and asymptomatic controls, though this result was not linear. Since genetic studies have shown associations between endometriosis and loci association with WHR but no associations with known BMI variants[116], it has been suggested that associations between endometriosis and body size could be operating through common hormonal pathways responsible for distribution of adipose tissue in particular places[114]. Age at menarche is also related to body size during childhood, though as stated previously, no association between age of menarche and endometriosis was seen in this study. In addition, not all participants of COHERE had their measurements taken as part of the study, so the analysis may not have been sufficiently powered to detect a true difference.

6.4.3 Family history

In this study, having a family history of endometriosis, chronic pelvic pain, heavy bleeding, uterine fibroids, or polycystic ovary increased the likelihood of being an endometriosis case, compared to both control groups. Studies have shown that endometriosis has a heritable component[172–174]. A study that evaluated medical reports of 400 cases and controls in Greece[175], saw the overall risk of first-degree relatives of endometriosis was 10.2% vs 0.7% in controls, supporting the view that genetic factors are involved in the development of endometriosis in the Mediterranean region. Since women with endometriosis in the present study suffer from chronic pelvic pain and heavy bleeding, it could be that when they are reporting a family member with chronic pelvic pain and/or heavy bleeding, they are actually reporting to have an undiagnosed family member with endometriosis or the symptoms of family members with endometriosis. Uterine fibroids and endometriosis have been shown to have shared genetic susceptibility[176], which could explain why endometriosis cases are more likely to have a family history of uterine fibroids. There have also been suggestions that endometriosis and PCOS share similar biomarkers[177] and that certain cancer pathways and biological processes were enriched in women with both diseases[402]. However, there are other shared lifestyle factors that relate to both diseases which also may be responsible[403]. In addition, it is likely that women with endometriosis are more aware of family members who also have gynaecological diseases and symptoms, and thus may be more readily diagnosed. Since information on uterine fibroids and PCOS was collected as part of COHERE, it would be interesting to examine family histories of women

with only one of the three diseases and compare that to women who report to suffer from more than one of the diseases. Genetic data collected as part of COHERE[257] could help to elucidate the potential genetic mechanisms involved in this population of women.

6.4.5 Dietary risk factors

The results on diet suggest that women who reported an endometriosis diagnosis consume more fruits and vegetables. Two case control studies have examined this association; a hospital based case-control study in Italy[122] saw a lower consumption of green vegetables (OR=0.3, 95%CI: 0.2-0.5) and fresh fruit (OR: 0.6, 95%CI: 0.4-0.8) in endometriosis cases and a population-based case-control study in the US[123] observed a greater odds of endometriosis with greater fruit intake (OR=1.5, 95%CI: 1.2-2.3) and no association with vegetable intake. Conversely, the prospective NHSII which had a 22-year follow-up period saw that a high intake of fruits was associated with a 22% lower risk of endometriosis (95%CI: 0.69-0.89), but no association was found between total vegetable intake and consumption of some vegetables actually increased endometriosis risk by 13% (0.95-1.34)[124]. One factor that must be considered is that although these aggregated measures are composed of the same food groups, the relative amount that each food group contributes to the overall measure will vary based on population, local diet, and availability of produce. In addition, the NHSII used a frequency-based measure to analyse dietary intake whereas the present study used a pre-calculated daily amount in grams. Although no association was seen between MD score and endometriosis in this

study, the vegetables consumed in Cyprus will differ to that of other countries in both type and amount, which could yield different results to other research. There is likely residual confounding present in the analysis presented. For example, women who consume high amounts of vegetables may also participate in other activities which could lower risk of endometriosis or may have different sociodemographic characteristics which correlate with a high intake of vegetables.

Consuming equal to or more than the median intake of folate, lutein and vitamin E appeared to reduce the likelihood of being an endometriosis case. The NHSII observed that intakes of folate (RR=0.79, 95%CI: 0.66-0.93) and vitamin E (RR=0.70, 95%CI: 0.59-0.83) were inversely related to endometriosis diagnoses[126], whereas, a case-control study[123] found no associations between folate and vitamin E with endometriosis diagnosis, and the authors suggested that the associations seen were due to consumption of the food itself, rather than the nutrient[126]. A study in Brazil that included surgically diagnosed endometriosis cases saw a significantly lower intake of vitamin E among these women[129]. Folate and lutein are both found in dark leafy vegetables, so it is possible that the observed association is due to high intakes of vegetables in this study. With a bigger sample size, food sources could be adjusted for. Since the FFQ was based on self-reported data, recall bias cannot be eliminated. A strength of the analysis is that the FFQ asked for dietary habits over the whole year to limit seasonal bias. However, a major limitation is that dietary habits were only collected for one year as part of follow-up for COHERE and this was

therefore not preceding women's endometriosis diagnoses. Women may have altered their diets due to symptoms or their diagnosis, so the dietary data presented here cannot act as an accurate exposure to assess endometriosis risk. To investigate this further, women with FFQ data in COHERE and no endometriosis diagnosis could be followed-up according to a prospective cohort design, to investigate who develops endometriosis, which would give more accurate information.

6.4.6 Lifestyle factors

Converse to other studies, women who reported to have ever smoked were more likely to be an endometriosis case when compared to women who had never smoked. A systematic review and meta-analysis that included 13,129 women saw no association between tobacco smoking and endometriosis when considering ever, former, current moderate and heavy smokers[157], similar to a more recent case-control paper from the US[404]. Data from the NHSII saw an inverse relationship between current cigarette smoking and endometriosis, but only in infertile cases[103]. In this case, smoking has been suggested to decrease endometriosis risk due to tobacco's anti-oestrogenic effect[385], with some research suggesting that oestradiol could be a modulator of immune system molecules[405].

Being a regular alcohol drinker appeared to increase the likelihood of being an endometriosis case. Associations between alcohol drinking and endometriosis have been reported since the 1990s[161,162]. A more recent systematic review and

meta-analysis that included a total of 15 case-control and cohort studies showed that women who drank alcohol were 1.24 (95%CI: 1.12-13.6) times more likely to have endometriosis than women who did not drink alcohol.[163] Alcohol increases oestrogen levels through conversion of testosterone so there could potentially be an interaction between alcohol and production of luteinising hormone from the pituitary gland which could cause the ovaries to produce more oestradiol[386], potentially leading to endometriosis.

There were no associations between physical activity and endometriosis. Associations between endometriosis and physical activity in the literature have been inconsistent. Some studies have observed no association between exercise and endometriosis[91,168], including a meta-analysis which included 3,355 female participants[168]. However, several case control studies[111,164,165] have suggested there could be a potential 40-80% decreased risk of endometriosis with exercise. The prospective NHSII saw that although the risk ratio was lower with increased exercise, it was not significant[169]. Potential mechanisms behind exercise lowering endometriosis risk include exercise lowering oestrogens[166] and increasing sex hormone binding globulins which could factor into endometriosis development[406].

One issue with cross-sectional and case control studies is that temporality cannot be accounted for. It is not possible to assess whether smoking, drinking alcohol or exercise preceded the endometriosis diagnosis or whether these lifestyle choices are as a result of endometriosis symptoms or diagnosis. For

example, alcohol drinking could be response to pain or depression, both of which have also been shown to be associated with endometriosis[372,407]. In addition to this, in the absence of medical records, the present study relies on self-reported data which is prone to recall bias. However, information on smoking status in observational studies has been shown to be valid[408–410].

6.4.7 Co-morbidities

There was no significant difference between the prevalence of autoimmune disease between endometriosis cases and asymptomatic controls. A systematic-review and meta-analysis[30] that examined 26 studies saw that endometriosis appeared to be associated with a range of autoimmune diseases but that in general, study quality was low due to the high likelihood of bias in their chosen study designs. In COHERE, endometriosis cases were more likely to report allergic diseases, which included asthma and eczema. A descriptive study in the USA[388], case-control study in Italy[389] and retrospective study in Taiwan[390] have seen this pattern and the use of electronic health records and follow-up by Peng *et al.,* certainly adds strength to their study. Associations between endometriosis and autoimmune and allergic disease support the hypothesis that endometriosis is a condition related to immunological dysfunction[199–202] and a recent meta-analysis of 60,674 cases and 701,926 controls revealed significant genetic correlations between endometriosis and inflammatory conditions including asthma and osteoarthritis (Rahmioglu *et al.,* in press).

Endometriosis cases were more likely to report other reproductive disorders compared to both control groups. The potential heritable component between endometriosis and other gynaecological conditions has already been discussed. It has been argued that endometriosis and PCOS are in fact diametric diseases[411], which would suggest the likelihood of them co-occurring to be low and gives support to the hypothesis that there are shared risk factors[412] between the two diseases rather than a shared pathogenesis. One study[413] investigating co-occurrence of symptomatic endometriosis and symptomatic uterine fibroids showed a higher prevalence of them co-existing together, with an additional study[414] estimating that women with endometriosis report a higher proportion of uterine fibroids than a control group.

Women with endometriosis were more likely to report cardiovascular diseases compared to asymptomatic controls. Evidence from the prospective NHSII[55] showed that women with endometriosis had a higher risk of several cardiovascular diseases, though part of the associations seen were shown to be accounted for by treatments for endometriosis that are also risk factors for CHD, such as hysterectomy/oophorectomy. Two previous studies[415,416] have shown that women with endometriosis have significantly lower values of flow-mediated dilation compared to controls.

Reporting an iron deficiency was associated with a higher likelihood of being an endometriosis case. Studies investigating the association between iron deficiency and endometriosis are limited, but, given the chronic inflammation

and heavy menstrual bleeding often accompanied by endometriosis, there is biological plausibility for iron deficiency to be a comorbidity of endometriosis. The non-significant association between endometriosis cases and symptomatic controls could be due to these women also experiencing menstrual dysregulation which may result in heavy bleeding and iron deficiency. A study[220] that investigated iron deficiency in a non-human primate (NHP) model of endometriosis reported that NHPs had decreased red blood cell counts indicative of anaemia, decreased hepatic and bone marrow iron stores, decreased serum hepcidin and decreased serum iron levels. In Cyprus, iron deficiency is common because thalassemia is prevalent in the Mediterranean[218] and the overall prevalence of iron deficiency in COHERE was 28.9% (n=2,208). Since 1980, pre-marital screening for thalassemia has been mandatory in Northern Cyprus resulting in no new cases with thalassemia since 2001[217]. However, many people are still carriers of the disease and are therefore at risk of being iron deficient[219,417]. If the association between endometriosis and iron deficiency here is true, this could be a unique co-morbidity for the population. When accounting for multiple testing the comorbidities found to be significant here would remain significant (0.05/8 – p=0.006).

6.4.8 Pigmentary traits

Despite the results here suggesting a relationship between increasing number of moles and endometriosis, this was not significant. Several retrospective studies[223,226,228] have seen significant associations between number of moles and endometriosis risk, and this was confirmed with data from the NHSII which

saw endometriosis risk was increased with an increasing number of moles on the lower legs (RR=1.08, 95%CI: 1.02-1.14)[224]. We saw no associations between hair colour or eye colour and endometriosis, contrary to other studies which have seen associations between lighter eyes and endometriosis[227–229] and research that has shown red hair to be associated with increased endometriosis risk[392,231]. However one study only saw an association in women who had never been infertile[230]. These associations were not observed in the French E3N cohort[223] or the prospective NHSII with 10 years of follow-up[224]. It is possible that the small numbers of women with lighter eyes and hair in Northern Cyprus may have restricted the ability to see associations in the data. Phenotypic characteristics were self-reported and not objectively confirmed, therefore the results may suffer from misclassification. However, this is unlikely to be differential between case and control groups so misclassification would attenuate estimates towards the null. In addition, potential associations between number of moles and other gynaecological disease such as uterine fibroids, may have led to an underestimation of the association examined here between moles and endometriosis[418]

6.4.9 Vitamin D deficiency, sun exposure habits and pigmentary traits

After adjustment for demographics, pigmentary traits and sun habits women with a vitamin D deficiency were at an increased odds of being an endometriosis case, as opposed to an asymptomatic control. The relationship between vitamin D deficiency and endometriosis has long been contested with various reviews concluding that the evidence is not clear[244,391,419]. Its biological

plausibility lies in the suggestion that vitamin D could act as an immunomodulator and anti-inflammatory agent in endometriosis pathogenesis[420,421]. Using vitamin D data obtained from diet, the NHSII calculated a score for predicted vitamin D level prior to endometriosis diagnoses and saw that women in the highest quintile of predicted vitamin D level had a 24% lower risk of endometriosis than women in the lowest quintile (RR=0.76, 95%CI: 0.60-0.97)[134]. Though no association between endometriosis and vitamin D from diet was observed in the FFQ data collected from this study, the sample size may not have been large enough to estimate an accurate difference.

The NHSII investigated the effect of recreational and residential sun exposure on endometriosis risk in a population of white women with laparoscopically confirmed endometriosis[239]. The study showed that number of sunburns during adolescence and percentage of time using sunscreen in adulthood were positively associated with endometriosis and in contrast, residential UV exposure across the ages was associated with a decreased risk of endometriosis. In the present study, sunscreen use during summer and winter was associated with endometriosis after adjusting for other factors such as vitamin D deficiency, sun exposure and pigmentary traits. There are several potential reasons for this finding[239]. There has been an association shown between sunscreen use and intention to suntan and so high sunscreen use could represent high levels of sun exposure[422]. Research has shown that sunscreen contains environmental chemicals that have the potential to disrupt

normal endocrine functions[423] and these types of chemicals such as benzophenone-type UV filters have been shown to be associated with an increased risk of endometriosis[424]. People who regularly apply sunscreen are more likely to have a phenotype that is sun-sensitive which as discussed, has been shown to lead to an increased risk of endometriosis. Although the analysis was adjusted for pigmentary traits, there are fewer people in the study who have the sun-sensitive phenotype so there may not have been sufficient power to investigate this fully. In addition, endometriosis cases may represent a proportion of women who are more likely to participate in health protective measures, such as wearing sunscreen, and that could also be responsible for the observed association. Future research could consider a Mendelian randomisation study design[425], which uses genetic variants as instrumental variables for modifiable risk factors, and would have the potential to assess exposures on outcomes free from confounding that exists in observational studies.

Vitamin D deficiency and endometriosis is especially interesting to investigate in Northern Cyprus, given its subtropical climate and exposure to strong sun rays, which would suggest vitamin D deficiency to be low in this population. Self-reported prevalence of vitamin D in COHERE was 17.3% (n=1,325) and a retrospective cross-sectional study[426] investigating the prevalence of vitamin D deficiency in a Greek Cypriot population between the ages of 2-96 years of age showed that 69.3% of the population had inadequate levels of vitamin D. Though reasons were not examined, it has been suggested that modern office

lifestyles of office work with less sun exposure may be a contributing factor to low levels of vitamin D[427,428]. In addition, since the weather in Cyprus is very warm, people tend to avoid being in direct sunlight which would hinder vitamin D synthesis. Further research into this could involve systematic collection of vitamin D measurements from endometriosis patients at various timepoints and ideally before endometriosis diagnoses.

As previously stated, the cross-sectional nature of COHERE means it is not best placed to assess potential risk factors for endometriosis in an unbiased manner. Randomised controlled trials, whereby one group of women are exposed to a potential risk factor and followed-up for disease ascertainment compared to a group of women not exposed to the risk factor, are the strongest type of studies. However, these are not always appropriate and come with ethical considerations. Therefore, longitudinal studies that enrol participants early enough to have a sufficient follow-up time to assess exposures prior to outcomes are best suited. Other methodological considerations include proper ascertainment of cases using hospital records and consideration of diagnostic biases[321]. However, this is the first-time endometriosis has been investigated in this population of women and so provides a basis for future follow-up studies. A limitation of this work is that due to investigative laparoscopy not being available in Northern Cyprus, most endometriosis cases will have been detected via ultrasound methods and their endometriosis is likely to be stage III/IV as ultrasound cannot diagnose superficial endometriosis of the peritoneum. In addition, some studies stratified endometriosis patients based on fertility status

and saw differential associations which could not be investigated here. Potential risk factors identified here may not be applicable to all women with endometriosis due to this and differences in demographics between endometriosis cases and undiagnosed women. Knowing specific risk factors can help to target both informational campaigns and future follow-up studies.

Table 1. Crude and adjusted odds ratios of consuming equal to or above the median intake of each food group in relation to endometriosis cases and controls

	Median value (g/day)	Cases	Crude odds ratio	95% CI	p-value	Adjusted odds ratio*	95% CI	p-value
All fruit and veg								
<Median	1,446	55	1.00	Referent	-	1.00	Referent	-
≥Median		36	0.63	(0.40, 1.01)	0.055	0.37	(0.21, 0.64)	**<0.001**
Vegetables								
<Median	567	51	1.00	Referent	-	1.00	Referent	-
≥Median		40	0.77	(0.49, 1.21)	0.257	0.53	(0.31, 0.89)	**0.017**
Cruciferous vegetables								
<Median	39	40	1.00	Referent	-	1.00	Referent	-
≥Median		50	1.26	(0.79, 1.99)	0.332	1.11	(0.69, 1.80)	0.653
Tomatoes								
<Median	150	44	1.00	Referent	-	1.00	Referent	-
≥Median		46	1.02	(0.65, 1.62)	0.918	0.74	(0.44, 1.23)	0.248
Legumes								
<Median	39	39	1.00	Referent	-	1.00	Referent	-
≥Median		50	1.30	(0.81, 2.06)	0.274	1.14	(0.69, 1.88)	0.614
Fruit								
<Median	815	45	1.00	Referent	-	1.00	Referent	-
≥Median		46	1.06	(0.67, 1.67)	0.803	0.81	(0.48, 1.36)	0.426
Citrus fruits								
<Median	212	47	1.00	Referent	-	1.00	Referent	-
≥Median		44	0.96	(0.61, 1.52)	0.863	0.81	(0.50, 1.33)	0.411
All dairy products								
<Median	244	42	1.00	Referent	-	1.00	Referent	-
≥Median		49	1.17	(0.74, 1.85)	0.495	1.37	(0.83, 2.26)	0.222
Yoghurt								
<Median	81	44	1.00	Referent	-	1.00	Referent	-
≥Median		45	1.02	(0.64, 1.61)	0.942	0.90	(0.55, 1.46)	0.667
Cheese								
<Median	58	35	1.00	Referent	-	1.00	Referent	-
≥Median		56	1.81	(1.14, 2.89)	**0.013**	1.57	(0.93, 2.65)	0.088
Milk and milk products								
<Median	86	45	1.00	Referent	-	1.00	Referent	-
≥Median		40	0.79	(0.49, 1.27)	0.330	0.77	(0.47, 1.26)	0.296
Eggs								
<Median	33	43	1.00	Referent	-	1.00	Referent	-
≥Median		46	1.17	(0.74, 1.86)	0.504	1.09	(0.67, 1.77)	0.727
Processed and unprocessed red meat								
<Median	36	40	1.00	Referent	-	1.00	Referent	-
≥Median		51	1.37	(0.87, 2.17)	0.179	1.49	(0.88, 2.50)	0.134
Unprocessed red meat								
<Median	32	42	1.00	Referent	-	1.00	Referent	-
≥Median		45	1.07	(0.67, 1.70)	0.791	1.10	(0.65, 1.84)	0.726
Processed red meat								
<Median	6	37	1.00	Referent	-	1.00	Referent	-
≥Median		47	1.28	(0.79, 2.05)	0.314	1.27	(0.75, 1.12)	0.372
Poultry								
<Median	95	45	1.00	Referent	-	1.00	Referent	-
≥Median		39	0.79	(0.49, 1.28)	0.341	0.78	(0.46, 1.32)	0.357
Fish								
<Median	11	27	1.00	Referent	-	1.00	Referent	-
≥Median		46	0.69	(0.40, 1.19)	0.182	0.78	(0.44, 1.36)	0.376

** Adjusted for age, total energy intake, BMI, ever smoked, education and employment*

Table 2. Crude and adjusted odds ratios of endometriosis according to intake of food group

	Cases	Crude odds ratio	95% CI	p-value	Adjusted odds ratio*	95% CI	p-value
All fruit and veg							
1	31	1.00	Referent	-	1.00	Referent	-
2	38	1.33	(0.78, 2.26)	0.301	0.90	(0.51, 1.61)	0.729
3	22	0.70	(0.39, 1.28)	0.250	0.30	(0.14, 0.64)	**0.002**
*P-t*rend		0.273					
Vegetables							
1	31	1.00	Referent	-	1.00	Referent	-
2	35	1.26	(0.73, 2.17)	0.404	0.96	(0.54, 1.72)	0.897
3	25	0.81	(0.46, 1.45)	0.482	0.48	(0.25, 0.93)	**0.030**
*P-t*rend		0.805					

** Adjusted for age, total energy intake, BMI, ever smoked, education and employment*

Table 3. Crude and adjusted odds ratios of consuming equal to or above the median intake of each vitamin/mineral in relation to endometriosis cases and controls.

		Median value	Cases	Crude odds ratio	95% CI	p-value	Adjusted odds ratio*	95% CI	p-value
Omega 3		2							
	<Median		45	1.00	Referent	-	1.00	Referent	-
	≥Median		46	1.23	(0.78, 1.94)	0.379	1.16	(0.64, 2.09)	0.624
Retinol		459							
	<Median		45	1.00	Referent	-	1.00	Referent	-
	≥Median		46	1.10	(0.70, 1.73)	0.687	0.91	(0.52, 1.59)	0.739
B-carotene		12							
	<Median		47	1.00	Referent	-	1.00	Referent	-
	≥Median		44	0.94	(0.59, 1.48)	0.777	0.71	(0.42, 1.21)	0.210
Lycopene		2							
	<Median		37	1.00	Referent	-	1.00	Referent	-
	≥Median		38	0.82	(0.50, 1.36)	0.445	0.76	(0.45, 1.29)	0.317
Lutein		3							
	<Median		50	1.00	Referent	-	1.00	Referent	-
	≥Median		37	0.72	(0.45, 1.16)	0.179	0.59	(0.36, 0.97)	**0.038**
Vitamin D		4							
	<Median		40	1.00	Referent	-	1.00	Referent	-
	≥Median		51	1.31	(0.83, 2.08)	0.243	1.24	(0.74, 2.07)	0.421
Calcium		1,364							
	<Median		42	1.00	Referent	-	1.00	Referent	-
	≥Median		49	1.20	(0.76, 1.90)	0.428	0.93	(0.52, 1.67)	0.804
Magnesium		515							
	<Median		43	1.00	Referent	-	1.00	Referent	-
	≥Median		48	1.16	(0.74, 1.84)	0.517	0.81	(0.43, 1.51)	0.500
Phosphorus		1,768							
	<Median		46	1.00	Referent	-	1.00	Referent	-
	≥Median		45	1.01	(0.64, 1.59)	0.97	0.58	(0.30, 1.14)	0.115
Oleic acid		40							
	<Median		39	1.00	Referent	-	1.00	Referent	-
	≥Median		52	1.36	(0.86, 2.16)	0.189	1.47	(0.78, 2.79)	0.237
Cholesterol		385							
	<Median		45	1.00	Referent	-	1.00	Referent	-
	≥Median		46	1.04	(0.66, 1.65)	0.855	0.89	(0.52, 1.54)	0.688
Vitamin A		2,423							
	<Median		47	1.00	Referent	-	1.00	Referent	-
	≥Median		44	0.95	(0.60, 1.49)	0.811	0.65	(0.38, 1.14)	0.132
Vitamin E		26							
	<Median		51	1.00	Referent	-	1.00	Referent	-
	≥Median		40	0.79	(0.50, 1.25)	0.321	0.52	(0.28, 0.97)	**0.039**
Vitamin B1		1							
	<Median		44	1.00	Referent	-	1.00	Referent	-
	≥Median		47	1.12	(0.71, 1.78)	0.615	0.80	(0.42, 1.52)	0.493

		Median value	Cases	Crude odds ratio	95% CI	p-value	Adjusted odds ratio*	95% CI	p-value
Vitamin B2		2							
	<Median		47	1.00	Referent	-	1.00	Referent	-
	≥Median		44	0.97	(0.61, 1.52)	0.88	0.58	(0.31, 1.12)	0.104
Niacin		21							
	<Median		45	1.00	Referent	-	1.00	Referent	-
	≥Median		46	1.03	(0.65, 1.63)	0.89	0.82	(0.46, 1.47)	0.504
Folate		520							
	<Median		50	1.00	Referent	-	1.00	Referent	-
	≥Median		41	0.85	(0.53, 1.34)	0.473	0.52	(0.28, 0.94)	**0.031**
Sodium		2,401							
	<Median		40	1.00	Referent	-	1.00	Referent	-
	≥Median		51	1.33	(0.84, 2.10)	0.225	1.19	(0.67, 2.11)	0.543
Potassium		4,769							
	<Median		46	1.00	Referent	-	1.00	Referent	-
	≥Median		45	1.02	(0.65, 1.61)	0.935	0.67	(0.37, 1.21)	0.184
Iron		18							
	<Median		46	1.00	Referent	-	1.00	Referent	-
	≥Median		45	1.00	(0.63, 1.58)	0.995	0.65	(0.35, 1.24)	0.193
Zinc		15							
	<Median		40	1.00	Referent	-	1.00	Referent	-
	≥Median		51	1.31	(0.83, 2.08)	0.243	1.14	(0.60, 2.15)	0.690
Omega-6		17							
	<Median		43	1.00	Referent	-	1.00	Referent	-
	≥Median		48	1.13	(0.71, 1.78)	0.606	1.22	(0.68, 2.18)	0.509
Selenium									
	<Median	9	39	1.00	Referent	-	1.00	Referent	-
	≥Median		52	1.37	(0.86, 2.17)	0.182	1.20	(0.74, 1.96)	0.458
Vitamin B12									
	<Median	6	42	1.00	Referent	-	1.00	Referent	-
	≥Median		49	1.17	(0.74, 1.84)	0.509	0.99	(0.56, 1.76)	0.981
Fat		44							
	<Median		37	1.00	Referent	-	1.00	Referent	-
	≥Median		54	1.29	(0.81, 2.05)	0.281	1.49	(0.92, 2.41)	0.107
Protein		18							
	<Median		42	1.00	Referent	-	1.00	Referent	-
	≥Median		49	0.89	(0.56, 1.41)	0.625	0.88	(0.55, 1.42)	0.609
Carbohydrate		38							
	<Median		50	1.00	Referent	-	1.00	Referent	-
	≥Median		41	0.77	(0.49, 1.22)	0.266	0.69	(0.43, 1.11)	0.127

** Adjusted for age, total energy intake, BMI, ever smoked, education and employment*

Table 4. Crude and adjusted odds ratios of endometriosis according to intake of vitamins/minerals

	Cases	Crude odds ratio	95% CI	p-value	Adjusted odds ratio*	95% CI	p-value
Lutein							
1	33	1.00	Referent	-	1.00	Referent	-
2	29	0.86	(0.49, 1.50)	0.59	0.820	(0.46, 1.45)	0.498
3	25	0.73	(0.41, 1.29)	0.280	0.570	(0.31, 1.06)	0.075
*P-t*rend		0.414					
Vitamin E							
1	35	1.00	Referent	-	1.00	Referent	-
2	29	0.79	(0.46, 1.34)	0.403	0.730	(0.41, 1.29)	0.279
3	27	0.74	(0.42, 1.29)	0.283	0.560	(0.31, 1.03)	0.064
*P-t*rend		0.427					
Folate							
1	25	1.00	Referent	-	1.00	Referent	-
2	41	1.91	(1.10, 3.33)	**0.022**	1.47	(0.79, 2.72)	0.222
3	25	1.08	(0.59, 1.97)	0.810	0.55	(0.24, 1.26)	0.156
*P-t*rend		0.784					

** Adjusted for age, total energy intake, BMI, ever smoked, education and employment*

Table 5. Frequencies and percentages of reproductive characteristics by endometriosis and control groups

	Endometriosis	Symptomatic Control	Asymptomatic control
Age at menarche			
≤12	200 (52.8%)	1,393 (50.3%)	1,913 (48.9%)
13-14	141 (37.2%)	1,070 (38.7%)	1,537 (39.3%)
≥15	38 (10.0%)	305 (11.0%)	466 (11.9%)
Menstrual cycle length			
<24	50 (17.4%)	369 (14.4%)	431 (15.2%)
24-31	210 (72.9%)	1,922 (75.2%)	2,150 (75.9%)
≥32	28 (9.7%)	266 (10.4%)	250 (8.8%)
Menstrual cycle irregularity			
Regular	265 (84.1%)	2,342 (86.9%)	2,618 (87.5%)
Irregular	50 (15.9%)	354 (13.1%)	374 (12.5%)
Duration of menstrual phase			
≤4 days	121 (39.8%)	965 (36.6%)	1.227 (42.0%)
5-6 days	122 (40.1%)	1,224 (46.4%)	1,324 (45.4%)
≥7 days	61 (20.1%)	448 (17.0%)	368 (12.6%)
Average intensity of menstrual flow			
Spotting/Light	85 (27.3%)	751 (28.1%)	991 (33.7%)
Moderate	195 (62.7%)	1,690 (63.1%)	1,789 (61.1%)
Heavy	31 (9.8%)	236 (8.8%)	154 (5.2%)

Table 6. Crude and adjusted odds ratios of menstrual characteristics in relation to endometriosis cases and control groups

	Endometriosis vs symptomatic control						Endometriosis vs asymptomatic control					
	Crude odds ratio	**(95% CIs)**	**p-value**	**Adjusted odds ratio***	**(95% CIs)**	**p-value**	**Crude odds ratio**	**(95% CIs)**	**p-value**	**Adjusted odds ratio**	**(95% CIs)**	**p-value**
Age at menarche												
≤12	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
13-14	0.92	(0.73, 1.15)	0.464	0.94	(0.75, 1.20)	0.640	0.88	(0.70, 1.10)	0.256	0.93	(0.74, 1.17)	0.525
≥15	0.87	(0.60, 1.25)	0.450	0.93	(0.64, 1.35)	0.699	0.78	(0.54, 1.12)	0.178	0.81	(0.56, 1.17)	0.258
Menstrual cycle length*												
<24	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
24-31	0.81	(0.58, 1.12)	0.198	0.89	(0.64, 1.24)	0.497	0.84	(0.61, 1.17)	0.300	0.84	(0.60, 1.16)	0.287
≥32	0.78	(0.48, 1.27)	0.311	0.90	(0.55, 1.48)	0.682	1.00	(0.59, 1.57)	0.888	0.93	(0.57, 1.53)	0.788
Menstrual cycle irregularity**												
Regular	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
Irregular	1.25	(0.90, 1.72)	0.177	1.20	(0.86, 1.67)	0.290	1.32	(0.96, 1.82)	0.089	1.45	(1.05, 2.01)	**0.025**
Duration of menstrual phase*												
≤4 days	1.26	(0.96, 1.64)	0.090	1.18	(0.90, 1.54)	0.233	1.07	(0.82, 1.39)	0.613	1.07	(0.82, 1.39)	0.623
5-6 days	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	**-**
≥7 days	1.37	(0.99, 1.89)	0.061	1.32	(0.94, 1.84)	0.105	1.80	(0.30, 2.50)	**<0.001**	1.94	(1.39, 2.70)	**<0.001**
Average intensity of menstrual flow*												
Spotting/Light	0.89	(0.75, 1.28)	0.888	1.07	(0.81, 1.40)	0.645	0.79	(0.61, 1.03)	0.084	0.79	(0.61, 1.03)	0.086
Moderate	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
Heavy	1.14	(0.76, 1.70)	0.528	1.10	(0.73, 1.66)	0.641	1.86	(1.23, 2.81)	**0.003**	1.92	(1.27, 2.91)	**0.002**

** Adjusted for age, ethnicity, employment, education, civil status*
95% CI, 95% Confidence Interval

Table 6. Crude and adjusted odds ratios of menstrual characteristics in relation to endometriosis cases and control groups. Analysis is restricted to women with regular menstrual cycles

	Endometriosis vs symptomatic control						Endometriosis vs asymptomatic control					
	Crude odds ratio	**(95% confidence intervals)**	**p-value**	**Adjusted odds ratio***	**(95% confidence intervals)**	**p-value**	**Crude odds ratio**	**(95% confidence intervals)**	**p-value**	**Adjusted odds ratio**	**(95% confidence intervals)**	**p-value**
Duration of menstrual phase*												
≤4 days	1.27	(0.95, 1.68)	0.102	1.16	(0.87, 1.54)	0.320	1.11	(0.84, 1.47)	0.471	1.10	(0.83, 1.47)	0.498
5-6 days	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
≥7 days	1.38	(0.96, 1.98)	0.079	1.33	(0.92, 1.93)	0.130	1.77	(1.23, 2.55)	**0.002**	1.92	(1.3, 2.78)	**<0.001**
Average intensity of menstrual flow*												
Spotting/Light	1.02	(0.77, 1.36)	0.880	1.13	(0.84, 1.51)	0.424	0.87	(0.65, 1.15)	0.324	0.86	(0.65, 1.16)	0.335
Moderate	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
Heavy	1.12	(0.70, 1.80)	0.637	1.09	(0.67, 1.76)	0.728	1.66	(1.02, 2.69)	**0.038**	1.69	(1.04, 2.73)	**0.034**

Only includes women with regular menstrual cycles

** Adjusted for age, ethnicity, employment, education, civil status*

Table 8. Frequencies and percentages of anthropometric characteristics by endometriosis and control groups

	Endometriosis (n=387)	Symptomatic pain controls (n=2,804)	Asymptomatic controls (n=3,978)
Family history			
BMI (kg/m^2)			
≤18.5	14 (3.7%)	148 (5.4%)	125 (3.3%)
>18.5 to ≤ 24.9	216 (57.6%)	1,578 (58.0%)	1,917 (50.2%)
>24.9 to ≤ 29.9	103 (27.5%)	627 (23.0%)	1,134 (29.7%)
>29.9	42 (11.2%)	370 (13.6%)	646 (16.9%)
Waist-to-hip-ratio (cm)			
≤80.41	43 (29.9%)	202 (22.4%)	246 (17.6%)
>80.41 to ≤84.91	35 (24.3%)	194 (21.5%)	261 (18.7%)
>84.91 to ≤88.12	21 (14.6%)	186 (20.6%)	283 (20.3%)
>88.12 to ≤92.23	22 (15.3%)	165 (18.3%)	300 (21.5%)
>92.23	23 (16.0%)	154 (17.1%)	307 (22.0%)
Height (m)			
≤1.56	34 (23.5%)	160 (17.8%)	329 (23.5%)
>1.56 to ≤1.60	30 (20.7%)	215 (23.9%)	347 (24.8%)
>1.60 to ≤1.63	27 (18.6%)	183 (20.3%)	243 (17.4%)
>1.63 to ≤1.67	21 (14.5%)	157 (17.4%)	212 (15.2%)
>1.67 to ≤1.82	33 (22.8%)	186 (20.6%)	168 (19.2%)

Table 9. Crude and adjusted odds ratios of anthropometric in relation to endometriosis cases and control groups

	Endometriosis vs symptomatic control						Endometriosis vs asymptomatic control					
	Crude odds ratio	**(95% confidence intervals)**	**p-value**	**Adjusted odds ratio***	**(95% confidence intervals)**	**p-value**	**Crude odds ratio**	**(95% confidence intervals)**	**p-value**	**Adjusted odds ratio**	**(95% confidence intervals)**	**p-value**
BMI (kg/m^2)												
≤18.5	0.69	(0.39, 1.22)	0.201	1.75	(0.63, 4.87)	0.282	0.99	(0.56, 1.76)	0.983	1.04	(0.39, 2.80)	0.940
>18.5 to ≤ 24.9	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
>24.9 to ≤ 29.9	1.20	(0.93, 1.54)	0.156	0.75	(0.48, 1.16)	0.192	0.81	(0.63, 1.03)	0.086	0.86	(0.57, 1.30)	0.475
>29.9	0.83	(0.58, 1.18)	0.294	0.73	(0.42, 1.26)	0.253	0.58	(0.41, 0.81)	0.002	0.80	(0.48, 1.34)	0.392
Waist-to-hip-ratio (cm)**												
≤80.41	1.89	(1.08, 3.30)	0.026	2.19	(1.21, 3.97)	**0.010**	2.36	(1.36, 4.08)	**0.002**	2.35	(1.32, 4.20)	**0.004**
>80.41 to ≤84.91	1.60	(0.90, 2.85)	0.111	1.79	(0.98, 3.29)	0.060	1.81	(1.03, 3.18)	**0.041**	1.85	(1.02, 3.34)	**0.041**
>84.91 to ≤88.12	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
>88.12 to ≤92.23	1.18	(0.63, 2.23)	0.607	1.24	(0.63, 2.43)	0.528	0.99	(0.53, 1.84)	0.970	1.13	(0.59, 2.16)	0.712
>92.23	1.32	(0.71, 2.48)	0.383	1.24	(0.62, 2.49)	0.538	1.01	(0.55, 1.86)	0.976	1.28	(0.66, 2.50)	0.462
Height (m)												
≤1.56	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
>1.56 to ≤1.60	0.66	(0.39, 1.12)	0.121	0.64	(0.37, 1.11)	0.11	0.84	(0.50, 1.40)	0.496	0.74	(0.44, 1.25)	0.264
>1.60 to ≤1.63	0.69	(0.40, 1.20)	0.192	0.73	(0.42, 1.28)	0.273	1.08	(0.63, 1.83)	0.789	0.94	(0.55, 1.61)	0.818
>1.63 to ≤1.67	0.63	(0.35, 1.13)	0.122	0.68	(0.37, 1.24)	0.206	0.96	(0.54, 1.70)	0.884	0.81	(0.45, 1.45)	0.472
>1.67 to ≤1.82	0.83	(0.49, 1.41)	0.499	0.85	(0.50, 1.46)	0.561	1.19	(0.72, 1.98)	0.497	0.94	(0.56, 1.58)	0.820

** Adjusted for age, ethnicity, employment, education, civil status*

***Adjusted for BMI, age, ethnicity, employment, education, civil status*

Table 10. Frequencies and percentages of family histories by endometriosis and control groups

	Endometriosis (n=387)	Symptomatic pain controls (n=2,804)	Asymptomatic controls (n=3,978)
Family history			
Endometriosis			
No	297 (76.7%)	2,657 (94.8%)	3,833 (96.4%)
Yes	90 (23.3%)	147 (5.2%)	145 (3.7%)
Chronic pelvic pain			
No	330 (85.3%)	2,612 (93.2%)	3,794 (95.4%)
Yes	57 (14.7%)	192 (6.9%)	184 (4.6%)
Heavy bleeding			
No	289 (74.7%)	2,296 (81.9%)	3,447 (86.7%)
Yes	98 (25.3%)	508 (18.2%)	531 (13.4%)
Uterine fibroids			
No	261 (67.4%)	2,185 (77.9%)	3,248 (81.7%)
Yes	126 (32.6%)	619 (22.1%)	730 (18.4%)
Polycystic ovary syndrome (PCOS)			
No	346 (89.4%)	2,614 (93.2%)	3,759 (94.5%)
Yes	41 (10.6%)	190 (6.8%)	219 (5.5%)

Table 11. Crude and adjusted odds ratios of family history in relation to endometriosis cases and control groups.

	Endometriosis vs symptomatic control						Endometriosis vs asymptomatic control					
Family history	**Crude odds ratio**	**(95% confidence intervals)**	**p-value**	**Adjusted odds ratio***	**(95% confidence intervals)**	**p-value**	**Crude odds ratio**	**(95% confidence intervals)**	**p-value**	**Adjusted odds ratio***	**(95% confidence intervals)**	**p-value**
Endometriosis												
No	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
Yes	5.48	(4.10, 7.31)	**<0.001**	6.14	(4.53, 8.34)	**<0.001**	8.01	(6.00, 10.69)	**<0.001**	7.79	(5.81, 10.43)	**<0.001**
Chronic pelvic pain												
No	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
Yes	2.35	(1.71, 3.23)	**<0.001**	2.53	(1.82, 3.52)	**<0.001**	3.56	(2.59, 4.89)	**<0.001**	3.61	(2.62, 4.98)	**<0.001**
Heavy bleeding												
No	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
Yes	1.53	(1.20, 1.96)	**0.001**	1.49	(1.16, 1.93)	**0.002**	2.20	(1.72, 2.82)	**<0.001**	2.15	(1.68, 2.76)	**<0.001**
Uterine fibroids												
No	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
Yes	1.70	(1.35, 2.15)	**<0.001**	1.54	(1.21, 1.95)	**<0.001**	2.15	(1.71, 2.70)	**<0.001**	2.05	(1.63, 2.58)	**<0.001**
Polycystic ovary syndrome (PCOS)												
No	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
Yes	1.63	(1.14, 2.33)	**0.007**	1.69	(1.17, 2.44)	**0.005**	2.03	(1.43, 2.89)	**<0.001**	1.87	(1.31, 2.67)	**0.001**

** Adjusted for age, ethnicity, employment, education, civil status*

Table 12. Frequencies and percentages of lifestyle factors by endometriosis and control groups

	Endometriosis (n=387)	Symptomatic pain controls (n=2,804)	Asymptomatic controls (n=3,978)
Ever smoked*			
No	236 (61.0%)	1,840 (65.6%)	2,789 (70.1%)
Yes	151 (39.0%)	964 (34.4%)	1,189 (29.9%)
Currently smokes			
No	38 (25.2%)	187 (19.4%)	311 (26.2%)
Yes	113 (74.8%)	777 (80.6%)	878 (73.8%)
Drinks alcohol			
No	240 (62.0%)	1,797 (64.1%)	3,049 (76.7%)
Yes	147 (38.0%)	1,007 (35.9%)	929 (23.4%)
Any exercise			
No	344 (88.9%)	2,449 (87.3%)	3,539 (89.0%)
Yes	43 (11.1%)	355 (12.7%)	439 (11.0%)

**Smoked at least 100 cigarettes*

Table 13. Crude and adjusted odds ratios of lifestyle factors in relation to endometriosis cases and control groups.

	Endometriosis vs symptomatic control						Endometriosis vs asymptomatic control					
	Crude odds ratio	**(95% confidence intervals)**	**p-value**	**Adjusted odds ratio***	**(95% confidence intervals)**	**p-value**	**Crude odds ratio**	**(95% confidence intervals)**	**p-value**	**Adjusted odds ratio***	**(95% confidence intervals)**	**p-value**
Ever smoked**												
No	1.00	Referent	-	1.00	-	1.00	Referent	-	1.00	Referent	-	
Yes	1.22	(0.98, 1.52)	**<0.001**	1.17	(0.93, 1.47)	0.170	1.50	(0.21, 1.86)	**<0.001**	1.54	(1.24, 1.92)	**<0.001**
Currently smokes												
No	1.00	Referent	-	1.00	-	1.00	Referent	-	1.00	Referent	-	
Yes	0.72	(0.48, 1.07)	0.102	0.82	(0.54, 1.24)	0.354	1.05	(0.71, 1.56)	0.794	1.06	(0.71, 1.58)	0.776
Drinks alcohol												
No	1.00	Referent	-	1.00	-	1.00	Referent	-	1.00	Referent	-	
Yes	1.09	(0.88, 1.36)	0.427	1.27	(1.00, 1.60)	**0.049**	2.01	(1.62, 2.50)	**<0.001**	1.73	(1.38, 2.16)	**<0.001**
Any exercise												
No	1.00	Referent	-	1.00	-	1.00	Referent	-	1.00	Referent	-	
Yes	0.86	(0.62, 1.21)	0.388	0.96	(0.68, 1.35)	0.808	1.01	(0.72, 1.40)	0.964	0.96	(0.68, 1.34)	0.791

** Adjusted for age, ethnicity, employment, education, civil status*
***Smoked at least 100 cigarettes*

Table 14. Frequencies and percentages of co-morbidities and deficiencies by endometriosis and control groups

	Endometriosis	Symptomatic Control	Asymptomatic control
Reproductive disorders			
No	222 (57.4%)	2,273 (81.1%)	3,326 (83.6%)
Yes	165 (42.6%)	531 (18.9%)	652 (16.4%)
Autoimmune			
No	316 (81.7%)	2,393 (85.3%)	3,343 (84.0%)
Yes	71 (18.4%)	411 (14.7%)	635 (16.0%)
Allergic			
No	332 (85.8%)	2,519 (89.8%)	3,689 (92.7%)
Yes	55 (14.2%)	285 (10.2%)	289 (7.3%)
Metabolic/Obesity related			
No	313 (80.9%)	2,435 (86.8%)	3,448 (86.7%)
Yes	74 (19.2%)	369 (13.2%)	530 (13.3%)
Cardiovascular			
No	310 (80.1%)	2,398 (85.5%)	3,394 (85.3%)
Yes	77 (19.9%)	406 (14.5%)	584 (14.7%)
Thalassaemia carrier			
No	360 (93.0%)	2,642 (94.2%)	3,760 (94.5%)
Yes	27 (7.0%)	162 (5.8%)	218 (5.5%)
Iron deficiency			
No	239 (61.8%)	1,867 (66.6%)	3,924 (73.5%)
Yes	148 (38.2%)	937 (33.4%)	1,054 (26.5%)
Vitamin D deficiency			
No	294 (76.0%)	2,265 (80.8%)	3,331 (83.7%)
Yes	93 (24.0%)	539 (19.2%)	647 (16.3%)

Reproductive - polycystic ovary syndrome, uterine fibroids, ovarian cysts; Autoimmune - thyroid disease, systemic lupus erythematosus, Sjogren's, rheumatoid arthritis, multiple sclerosis, irritable bowel disease, psoriasis type 1 diabetes,; Allergic - asthma, eczema; Metabolic/Obesity related - type 2 diabetes, Insulin resistance, hypoglycaemia, high cholesterol, obesity; Cardiac - cardiovascular disease, mitral valve prolapse, angina, arrythmia, congenital heart disease, high blood pressure, low blood pressure; Thalassaemia carriers - alpha thalassaemia carrier, beta thalassaemia carrier, unspecified carrier

Table 15. Crude and adjusted odds ratios of co-morbidities and deficiencies in relation to endometriosis cases and control groups.

	Endometriosis vs symptomatic control						Endometriosis vs asymptomatic control					
	Crude odds ratio	**(95% confidence intervals)**	**p-value**	**Adjusted odds ratio***	**(95% confidence intervals)**	**p-value**	**Crude odds ratio**	**(95% confidence intervals)**	**p-value**	**Adjusted odds ratio***	**(95% confidence intervals)**	**p-value**
Reproductive												
No	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
Yes	3.18	(2.55, 3.97)	**<0.001**	2.55	(2.02, 3.21)	**<0.001**	3.79	(3.05, 4.72)	**<0.001**	4.17	(3.33, 5.23)	**<0.001**
Autoimmune conditions												
No	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
Yes	1.31	(0.99, 1.73)	0.058	0.94	(0.71, 1.25)	0.677	1.18	(0.90, 1.55)	0.225	1.22	(0.93, 1.61)	0.149
Allergic												
No	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
Yes	1.46	(1.07, 2.00)	**0.016**	1.43	(1.04, 1.96)	**0.030**	2.11	(1.55, 2.88)	**<0.001**	2.00	(1.47, 2.74)	**<0.001**
Metabolic/Obesity related												
No	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
Yes	1.56	(1.18, 2.06)	**0.002**	1.20	(0.90, 1.59)	0.215	1.54	(1.17, 2.01)	**0.002**	1.71	(1.29, 2.24)	**<0.001**
Cardiovascular												
No												
Yes	1.47	(1.12, 1.92)	**0.006**	1.14	(0.86, 1.51)	0.358	1.44	(1.11, 1.88)	**0.007**	1.65	(1.26, 2.16)	**<0.001**

	Endometriosis vs symptomatic control						Endometriosis vs asymptomatic control					
	Crude odds ratio	**(95% confidence intervals)**	**p-value**	**Adjusted odds ratio***	**(95% confidence intervals)**	**p-value**	**Crude odds ratio**	**(95% confidence intervals)**	**p-value**	**Adjusted odds ratio***	**(95% confidence intervals)**	**p-value**
Thalassemia carrier												
No	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
Yes	1.22	(0.80, 1.87)	0.35	0.96	(0.62, 1.48)	0.849	1.29	(0.85, 1.96)	0.223	1.23	(0.81, 1.87)	0.334
Iron deficiency												
No	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
Yes	1.23	(0.99, 1.54)	0.061	1.15	(0.91, 1.43)	0.237	1.72	(1.38, 2.13)	**<0.001**	1.70	(1.37, 2.12)	**<0.001**
Vitamin D												
No	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
Yes	1.33	(1.03, 1.71)	**0.026**	1.11	(0.86, 1.44)	0.418	1.63	(1.27, 2.09)	**<0.001**	1.52	(1.18, 1.95)	**0.001**

Reproductive - polycystic ovary syndrome, uterine fibroids, ovarian cysts; Autoimmune - thyroid disease, systemic lupus erythematosus, Sjogren's, rheumatoid arthritis, multiple sclerosis, irritable bowel disease, psoriasis type 1 diabetes,; Allergic - asthma, eczema; Obesity related - type 2 diabetes, Insulin resistance, hypoglycaemia, high cholesterol, obesity; Cardiac - cardiovascular disease, mitral valve prolapse, angina, arrythmia, congenital heart disease, high blood pressure, low blood pressure; Thalassaemia carriers - alpha thalassaemia carrier, beta thalassaemia carrier, unspecified carrier

**Adjusted for age, ethnicity, education, employment, civil status*

Table 16. Frequencies and percentages of pigmentary traits and sun habits by endometriosis and control groups

	Endometriosis	Symptomatic Control	Asymptomatic control
Eye colour			
Brown, hazel	167 (87.3%)	1,450 (88.0%)	1,792 (88.2%)
Blue, green, grey	24 (12.6%)	198 (12.0%)	239 (11.8%)
Hair Colour			
Blonde/red	9 (4.7%)	84 (5.1%)	107 (5.3%)
Light brown	59 (30.9%)	454 (27.6%)	457 (22.6%)
Dark brown	99 (51.8%)	844 (51.2%)	1,041 (51.3%)
Black	24 (12.6%)	266 (16.1%)	424 (20.9%)
Skin colour			
Very light, light, light intermediate	163 (85.3%)	1,284 (77.9%)	1,590 (78.3%)
Dark intermediate, dark, very dark	28 (14.7%)	364 (22.1%)	441 (21.7%)
Number of moles			
None	10 (5.2%)	75 (4.6%)	101 (5.0%)
1 to 10	100 (52.4%)	927 (56.3%)	1,162 (57.2%)
11 to 50	59 (30.9%)	483 (29.3%)	605 (29.8%)
50 or more	22 (11.5%)	163 (9.9%)	163 (8.0%)
Time outside during summer <25 years			
Less than an hour per week	33 (17.3%)	261 (15.8%)	323 (15.9%)
2 to 4 hours per week	69 (36.1%)	610 (37.0%)	721 (35.5%)
5+ hours per week	89 (46.6%)	777 (47.2%)	987 (48.6%)
Time outside during winter <25 years			
Less than an hour per week	52 (27.2%)	415 (25.2%)	493 (24.3%)
2 to 4 hours per week	87 (45.6%)	751 (45.6%)	863 (42.5%)
5+ hours per week	52 (27.2%)	482 (29.3%)	675 (33.2%)
Sunscreen in summer			
No	70 (36.7%)	733 (44.5%)	1,063 (52.4%)
Yes	121 (63.4%)	914 (55.5%)	97 (47.6%)
Sunscreen in winter			
No	107 (56.3%)	1,133 (69.8%)	1.434 (71.2%)
Yes	83 (43.7%)	490 (30.2%)	579 (28.8%)

Table 17. Crude and adjusted odds ratios of pigmentary traits and sun habits in relation to endometriosis cases and control groups.

	Endometriosis vs symptomatic control						Endometriosis vs asymptomatic control					
	Crude odds ratio	**(95% confidence intervals)**	**p-value**	**Adjusted odds ratio***	**(95% confidence intervals)**	**p-value**	**Crude odds ratio**	**(95% confidence intervals)**	**p-value**	**Adjusted odds ratio***	**(95% confidence intervals)**	**p-value**
Eye colour												
Brown, hazel	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
Blue, green, grey	1.05	(0.67, 1.66)	0.825	1.00	(0.63, 1.59)	0.999	1.08	(0.69, 1.69)	0.744	1.02	(0.65, 1.61)	0.931
Hair Colour												
Blonde/red	0.91	(0.45, 1.87)	0.805	0.98	(0.47, 2.05)	0.966	0.88	(0.43, 1.80)	0.735	0.88	(0.43, 1.81)	0.735
Light brown	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
Dark brown	1.11	(0.79, 1.56)	0.557	1.09	(0.77, 1.55)	0.628	1.35	(0.96, 1.90)	0.083	1.32	(0.93, 1.86)	0.115
Black	0.77	(0.48, 1.23)	0.271	0.81	(0.50, 1.31)	0.392	0.6	(0.38, 0.94)	**0.027**	0.69	(0.43, 1.10)	0.120
Skin colour												
Very light, light, light intermediate	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
Dark intermediate, dark, very dark	0.61	(0.40, 0.92)	**0.019**	0.60	(0.39, 0.92)	**0.018**	0.62	(0.41, 0.94)	**0.024**	0.70	(0.46, 1.06)	0.094
Number of moles												
None	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
1 to 10	0.81	(0.41, 1.62)	0.548	0.81	(0.40, 1.66)	0.565	0.87	(1.44, 1.72)	0.687	0.89	(0.45, 1.77)	0.739
11 to 50	0.92	(0.45, 1.87)	0.810	0.85	(0.41, 1.77)	0.665	0.98	(0.49, 1.99)	0.966	0.98	(0.48, 1.99)	0.948
50 or more	1.01	(0.46, 2.24)	0.976	0.85	(0.37, 1.93)	0.693	1.36	(0.62, 3.00)	0.441	1.40	(0.63, 3.12)	0.412
Time outside during summer <25 years												
Less than an hour per week	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
2 to 4 hours per week	0.89	(0.58, 1.39)	0.619	0.90	(0.57, 1.41)	0.644	0.94	(0.61, 1.45)	0.768	0.90	(0.58, 1.40)	0.633
5+ hours per week	0.91	(0.59, 1.38)	0.647	0.88	(0.57, 1.36)	0.569	0.88	(0.58, 1.34)	0.559	0.87	(0.57, 1.34)	0.537
Time outside during winter <25 years												
Less than an hour per week	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
2 to 4 hours per week	0.92	(0.64, 1.33)	0.673	0.90	(0.62, 1.30)	0.571	0.96	(0.67, 1.37)	0.806	0.96	(0.67, 1.39)	0.836
5+ hours per week	0.86	(0.57, 1.29)	0.470	0.87	(0.57, 1.32)	0.519	0.73	(0.49, 1.09)	0.125	0.80	(0.53, 1.20)	0.273

	Endometriosis vs symptomatic control						Endometriosis vs asymptomatic control					
	Crude odds ratio	**(95% confidence intervals)**	**p-value**	**Adjusted odds ratio***	**(95% confidence intervals)**	**p-value**	**Crude odds ratio**	**(95% confidence intervals)**	**p-value**	**Adjusted odds ratio***	**(95% confidence intervals)**	**p-value**
Time outside during summer in the past 2 years												
Less than an hour per week	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
2 to 4 hours per week	0.80	(0.52, 1.22)	0.299	0.88	(0.57, 1.38)	0.586	1.01	(0.66, 1.53)	0.976	0.92	(0.60, 1.42)	0.716
5+ hours per week	0.62	(0.40, 0.98)	**0.040**	0.83	(0.52, 1.32)	0.427	0.80	(0.51, 1.24)	0.315	0.74	(0.47, 1.16)	0.190
Time outside during winter in the past 2 years												
Less than an hour per week	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
2 to 4 hours per week	0.92	(0.64, 1.33)	0.673	0.90	(0.62, 1.30)	0.571	0.96	(0.67, 1.37)	0.806	0.96	(0.67, 1.39)	0.836
5+ hours per week	0.86	(0.57, 1.29)	0.470	0.87	(0.57, 1.32)	0.519	0.73	(0.49, 1.09)	0.125	0.80	(0.53, 1.20)	0.273
Sunscreen in summer												
No	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
Yes	1.39	(1.02, 1.89)	**0.039**	1.12	(0.81, 1.55)	0.506	1.90	(1.40, 2.58)	**<0.001**	1.49	(1.08, 2.05)	**0.014**
Sunscreen in winter												
No	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
Yes	1.79	(1.32, 2.43)	**<0.001**	1.37	(0.99, 1.88)	0.055	1.92	(1.42, 2.60)	**<0.001**	1.72	(1.26, 2.36)	**0.001**

Table 18. Crude and adjusted odds ratios of vitamin D deficiency, pigmentary traits, and sun habits <25 years of age in relation to endometriosis cases symptomatic controls

	Model 1			Model 2			Model 3a			Model 3b		
	Crude odds ratio	**(95% confidence intervals)**	**p-value**	**Adjusted odds ratio**	**(95% confidence intervals)**	**p-value**	**Crude odds ratio**	**(95% confidence intervals)**	**p-value**	**Crude odds ratio**	**(95% confidence intervals)**	**p-value**
Vitamin D deficiency												
No	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
Yes	1.5	(1.05, 2.14)	0.027	1.28	(0.89, 1.86)	0.19	1.27	(0.87, 1.84)	0.216	1.29	(0.88, 1.88)	0.190
Age				1.05	(1.03, 1.08)	**<0.001**	1.05	(1.03, 1.08)	**<0.001**	1.05	(1.03, 1.08)	**<0.001**
Ethnicity												
Turkish Cypriot	-	-	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
Turkish	-	-	-	0.97	(0.65, 1.45)	0.88	1.00	(0.67, 1.49)	0.990	1.00	(0.67, 1.50)	0.998
Other/Mixed	-	-	-	0.81	(0.39, 1.68)	0.58	0.79	(0.38, 1.64)	0.527	0.80	(0.39, 1.67)	0.556
Employment												
Not in paid employment	-	-	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
In paid employment	-	-	-	1.05	(0.67, 1.65)	0.83	1.03	(0.65, 1.63)	0.891	1.02	(0.65, 1.61)	0.933
Education												
Primary school	-	-	-	1.00	Referent	-	1.00	Referent		1.00	Referent	-
High school/Post-secondary	-	-	-	1.73	(0.92, 3.26)	0.09	1.69	(0.89, 3.22)	0.110	1.62	(0.86, 3.08)	0.138
Undergraduate degree	-	-	-	2.84	(1.46, 5.54)	**0.002**	2.71	(1.38, 5.33)	**<0.001**	2.58	(1.32, .5.06)	**0.006**
Postgraduate degree	-	-	-	3.53	(1.75, 7.11)	**<0.001**	3.35	(1.63, 6.87)	**<0.001**	3.14	(1.54, 6.40)	**0.002**
Civil Status												
Married	-	-	-	1.00	Referent	-	1.00	Referent		1.00	Referent	-
Single	-	-	-	0.74	(0.48, 1.13)	0.163	0.74	(0.48, 1.14)	0.171	0.74	(0.48, 1.14)	0.171
Divorced/separated	-	-	-	1.45	(0.90, 2.35)	0.125	1.51	(0.93, 2.45)	0.097	1.51	(0.93, 2.46)	0.097

	Model 1			Model 2			Model 3a			Model 3b		
	Crude odds ratio	**(95% confidence intervals)**	**p-value**	**Adjusted odds ratio**	**(95% confidence intervals)**	**p-value**	**Crude odds ratio**	**(95% confidence intervals)**	**p-value**	**Crude odds ratio**	**(95% confidence intervals)**	**p-value**
Uses sunscreen*												
No	-	-	-	-	-	-	1.00	Referent	-	1.00	Referent	-
Yes	-	-	-	-	-	-	1.09	(0.78, 1.51)	0.626	1.31	(0.95, 1.82)	0.100
Average time spent under sunlight <25 years old**												
Less than an hour per week	-	-	-	-	-	-	1.00	Referent	-	1.00	Referent	-
2-4 hours a week	-	-	-	-	-	-	0.92	(0.58, 1.45)	0.705	0.95	(0.65, 1.39)	0.799
5+ hours a week	-	-	-	-	-	-	0.90	(0.57, 1.40)	0.635	0.92	(0.60, 1.41)	0.706
Eye colour												
Brown, hazel	-	-	-	-	-	-	1.00	Referent	-	1.00	Referent	-
Blue, green, grey	-	-	-	-	-	-	0.91	(0.55, 1.51)	0.725	0.93	(0.56, 1.54)	0.781
Hair colour												
Blonde, red	-	-	-	-	-	-	0.91	(0.41, 1.99)	0.807	0.88	(0.40, 1.93)	0.756
Light brown	-	-	-	-	-	-	1.00	Referent	-	1.00	Referent	-
Dark brown	-	-	-	-	-	-	1.02	(0.70, 1.46)	0.933	0.98	(0.68, 1.42)	0.918
Black							0.88	(0.54, 1.43)	0.593	0.85	(0.52, 1.38)	0.517
Skin tone												
Very light, light, light intermediate	-	-	-	-	-	-	1.00	Referent	-	1.00	Referent	-
Dark intermediate, dark, very dark	-	-	-	-	-	-	0.60	(0.39, 0.94)	**0.024**	0.61	(0.39, 0.95)	**0.030**
Number of moles												
None	-	-	-	-	-	-	1.21	(0.58, 2.51)	0.607	1.31	(0.63, 2.72)	0.476
1 to 10	-	-	-	-	-	-	1.00	Referent	-	1.00	Referent	-
11 to 50	-	-	-	-	-	-	1.02	(0.72, 1.45)	0.912	1.00	(0.70, 1.42)	0.991
50 or more	-	-	-	-	-	-	0.98	(0.59, 1.63)	0.943	0.97	(0.58, 1.62)	0.906

**Model 3a uses sunscreen in summer, Model 3b uses sunscreen in winter*

***Model 3a uses average time in the summer, Model 3b average time in the winter*

Table 19. Crude and adjusted odds ratios of vitamin D deficiency, pigmentary traits, and sun habits <25 years of age in relation to endometriosis cases asymptomatic controls

	Model 1			Model 2			Model 3a			Model 3b		
	Crude odds ratio	**(95% confidence intervals)**	**p-value**	**Adjusted odds ratio**	**(95% confidence intervals)**	**p-value**	**Crude odds ratio**	**(95% confidence intervals)**	**p-value**	**Crude odds ratio**	**(95% confidence intervals)**	**p-value**
Vitamin D deficiency												
No	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	Referent	-	-
Yes	2.03	(1.41 2.90)	**<0.001**	1.83	(1.27, 2.64)	**<0.001**	1.77	(1.23, 2.57)	**0.002**	1.87	(1.29, 2.71)	**0.001**
Age				0.98	(0.96, 1.00)	**0.020**	0.98	(0.96, 1.00)	**0.030**	0.97	(0.96, 0.99)	**0.011**
Ethnicity												
Turkish Cypriot	**-**	-	-	1.00	Referent	-	1.00	Referent	-	Referent	-	-
Turkish	**-**	-	-	1.07	(0.72, 1.58)	0.740	1.09	(0.73, 1.61)	0.682	1.12	(0.75, 1.66)	0.581
Other/Mixed	**-**	-	-	0.94	(0.46, 1.93)	0.870	0.90	(0.44, 1.85)	0.770	0.88	(0.42, 1.81)	0.719
Employment												
Not in paid employment	**-**	-	-	1.00	Referent	-	1.00	Referent	-	Referent	-	-
In paid employment	**-**	-	-	1.20	(0.77, 1.88)	0.420	1.13	(0.72, 1.77)	0.602	1.12	(0.71, 1.76)	0.638
Education												
Primary school	**-**	-	-	1.00	Referent	-	1.00	Referent	-	Referent	-	-
High school/Post-secondary	**-**	-	-	1.49	(0.81, 2.75)	0.200	1.36	(0.73, 2.53)	0.331	1.35	(0.73, 2.52)	0.336
Undergraduate degree	**-**	-	-	2.42	(1.28, 4.58)	**0.010**	2.11	(1.11, 4.04)	**0.024**	2.08	(1.09, 3.97)	**0.026**
Postgraduate degree	**-**	-	-	3.39	(1.72, 6.67)	**<0.001**	2.81	(1.41, 5.60)	**0.003**	2.74	(1.38, 5.46)	**0.004**
Civil Status												
Married	**-**	-	-	1.00	Referent	-	1.00	Referent	-	Referent	-	-
Single	**-**	-	-	1.12	(0.73, 1.71)	0.610	1.13	(0.73, 1.73)	0.592	1.13	(0.74, 1.75)	0.569
Divorced/separated	**-**	-	-	1.85	(1.17, 2.91)	**0.010**	1.78	(1.12, 2.82)	**0.014**	1.79	(1.13, 2.84)	**0.013**

	Model 1			Model 2			Model 3a			Model 3b		
	Crude odds ratio	**(95% confidence intervals)**	**p-value**	**Adjusted odds ratio**	**(95% confidence intervals)**	**p-value**	**Crude odds ratio**	**(95% confidence intervals)**	**p-value**	**Crude odds ratio**	**(95% confidence intervals)**	**p-value**
Uses sunscreen*												
No	-	-	-	-	-	-	1.00	Referent	-	Referent	-	-
Yes	-	-	-	-	-	-	1.44	(1.04, 1.98)	**0.029**	1.68	(1.22, 2.31)	**0.001**
Average time spent under sunlight <25 years old**												
Less than an hour per week		-	-	-	-	-	1.00	Referent	-	Referent	-	-
2-4 hours a week			-	-	-	-	0.92	(0.58, 1.43)	0.701	0.98	(0.67, 1.42)	0.904
5+ hours a week	-	-	-	-	-	-	0.94	(0.61, 1.45)	0.774	0.82	(0.54, 1.25)	0.357
Eye colour												
Brown, hazel	-	-	-	-	-	-	1.00	Referent	-	Referent	-	-
Blue, green, gray	-	-	-	-	-	-	0.97	(0.59, 1.58)	0.896	1.01	(0.62, 1.64)	0.980
Hair colour												
Blonde, red	-	-	-	-	-	-						
Light brown	-	-	-	-	-	-	1.00	Referent	-	Referent	-	-
Dark brown	-	-	-	-	-	-	0.80	(0.37, 1.73)	0.573	0.81	(0.38, 1.75)	0.599
Black	-	-	-	-	-	-	1.22	(0.85, 1.74)	0.286	1.20	(0.83, 1.72)	0.332
Skin tone												
Very light, light, light intermediate			-	-	-	-	1.00	Referent	-	Referent	-	-
Dark intermediate, dark, very dark			-	-	-	-	0.76	(0.49, 1.17)	0.210	0.79	(0.51, 1.23)	0.299
Number of moles												
None	-	-	-	-	-	-	1.02	(0.50, 2.05)	0.963	1.03	(0.51, 2.08)	0.942
1 to 10	-	-	-	-	-	-	1.00	Referent	-	Referent	-	-
11 to 50	-	-	-	-	-	-	1.05	(0.74, 1.49)	0.786	1.03	(0.73, 1.47)	0.849
50 or more	-	-	-	-	-	-	1.45	(0.87, 2.41)	0.153	1.41	(0.85, 2.35)	0.187

**Model 3a uses sunscreen in summer for Model 3b uses sunscreen in winter*

***Model 3a average time in the summer, for Model 3b average time in the winter*

Table 20. Crude and adjusted odds ratios of vitamin D deficiency, pigmentary traits and sun habits in the past 2 years in relation to endometriosis cases symptomatic controls

	Model 1			Model 2			Model 3a			Model 3b		
Deficiency	**Crude odds ratio**	**(95% confidence intervals)**	**p-value**	**Adjusted odds ratio**	**(95% confidence intervals)**	**p-value**	**Crude odds ratio**	**(95% confidence intervals)**	**p-value**	**Crude odds ratio**	**(95% confidence intervals)**	**p-value**
Vitamin D deficiency												
No	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
Yes	1.88	(1.28, 2.76)	**0.001**	1.54	(1.03, 2.31)	**0.034**	1.52	(1.01, 2.27)	**0.044**	1.48	(0.97, 2.23)	0.066
Age				1.06	(1.04, 1.09)	**<0.001**	1.06	(1.03, 1.08)	**<0.001**	1.05	(1.02, 1.08)	**<0.001**
Ethnicity												
Turkish Cypriot	**-**	-	-	1.00	Referent	-						
Turkish	**-**	-	-	1.12	(0.72, 1.73)	0.620	1.00	Referent	-	1.14	(0.73, 1.78)	0.566
Other/Mixed	**-**	-	-	0.89	(0.41, 1.94)	0.770	0.93	(0.42, 2.04)	0.854	0.97	(0.44, 2.14)	0.94
Employment												
Not in paid employment	**-**	-	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
In paid employment	**-**	-	-	1.00	(0.61, 1.66)	0.985	0.95	(0.57, 1.58)	0.837	0.98	(0.58, 1.66)	0.946
Education												
Primary school	**-**	-	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
High school/Post-secondary	**-**	-	-	1.54	(0.81, 2.95)	0.187	1.43	(0.74, 2.76)	0.283	1.34	(0.69, 2.58)	0.385
Undergraduate degree	**-**	-	-	2.65	(1.34, 5.25)	**0.005**	2.39	(1.19, 4.81)	0.015	2.18	(1.08, 4.37)	**0.029**
Postgraduate degree	**-**	-	-	3.35	(1.61, 6.98)	**0.001**	2.88	(1.35, 6.14)	0.006	2.77	(1.31, 5.83)	**0.008**
Civil Status												
Married	**-**	-	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
Single	**-**	-	-	0.78	(0.48, 1.28)	0.322	0.78	(0.47, 1.28)	0.322	0.79	(0.48, 1.31)	0.364
Divorced/separated	**-**	-	-	1.43	(0.86, 2.38)	0.165	1.47	(0.88, 2.46)	0.138	1.49	(0.89, 2.50)	0.132

	Model 1			Model 2			Model 3a			Model 3b		
	Crude odds ratio	**(95% confidence intervals)**	**p-value**	**Adjusted odds ratio**	**(95% confidence intervals)**	**p-value**	**Crude odds ratio**	**(95% confidence intervals)**	**p-value**	**Crude odds ratio**	**(95% confidence intervals)**	**p-value**
Uses sunscreen*												
No	-	-	-	-	-	-	1.00	Referent	-	1.00	Referent	-
Yes	-	-	-	-	-	-	1.29	(0.89, 1.88)	0.178	1.49	(1.04, 2.13)	**0.031**
Average time spent under sunlight in the last 2 years**												
Less than an hour per week	-	-	-	-	-	-	1.00	Referent	-	1.00	Referent	-
2-4 hours a week	-	-	-	-	-	-	0.86	(0.56, 1.32)	0.486	0.95	(0.64, 1.41)	0.796
5+ hours a week	-	-	-	-	-	-	0.82	(0.52, 1.29)	0.389	0.93	(0.58, 1.48)	0.750
Eye colour							1.00	Referent	-	1.00	Referent	-
Brown, hazel	-	-	-	-	-	-	1.12	(0.66, 1.91)	0.677	1.09	(0.63, 1.88)	0.763
Blue, green, gray	-	-	-	-	-	-						
Hair colour												
Blonde, red	-	-	-	-	-	-	0.49	(0.16, 1.50)	0.211	0.24	(0.06, 1.09)	0.064
Light brown	-	-	-	-	-	-	0.96	(0.64, 1.43)	0.828	0.93	(0.62, 1.40)	0.725
Dark brown	-	-	-	-	-	-	1.00	Referent	-	1.00	Referent	-
Black	-	-	-				0.74	(0.43, 1.27)	-	0.73	(0.42, 1.25)	0.251
Skin tone												
Very light, light, light intermediate	-	-	-	-	-	-	1.00	Referent	-	1.00	Referent	-
Dark intermediate, dark, very dark	-	-	-	-	-	-	0.73	0.46, 1.16)	0.178	0.70	(0.44, 1.13)	0.145
Number of moles												
None	-	-	-	-	-	-	1.49	(0.65, 3.43)	0.344	1.69	(0.73, 3.92)	0.220
1 to 10	-	-	-	-	-	-	1.00	Referent	-	1.00	Referent	-
11 to 50	-	-	-	-	-	-	1.01	(0.68, 1.50)	0.951	1.02	(0.68, 1.52)	0.924
50 or more	-	-	-	-	-	-	1.12	(0.66, 1.89)	0.675	1.12	(0.66, 1.91)	0.661

**Model 3a uses sunscreen in summer, Model 3b uses sunscreen in winter*
*** Model 3a average time in the summer, Model 3b average time in the winter*

Table 21. Crude and adjusted odds ratios of vitamin D deficiency, pigmentary traits, and sun habits in the past 2 years in relation to endometriosis cases asymptomatic controls

	Model 1			Model 2			Model 3a			Model 3b		
Deficiency	**Crude odds ratio**	**(95% confidence intervals)**	**p-value**	**Adjusted odds ratio**	**(95% confidence intervals)**	**p-value**	**Crude odds ratio**	**(95% confidence intervals)**	**p-value**	**Crude odds ratio**	**(95% confidence intervals)**	**p-value**
Vitamin D deficiency												
No	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
Yes	2.21	(1.51, 3.23)	**<0.001**	2.05	(1.39, 3.03)	**<0.001**	2.04	(1.37, 3.02)	**<0.001**	2.02	(1.35, 3.02)	**<0.001**
Age				0.98	(0.96, 1.00)	0.096	0.98	(0.96, 1.00)	0.124	0.98	(0.96, 1.00)	0.059
Ethnicity												
Turkish Cypriot	-	-	-	1.00	Referent		1.00	Referent		1.00	Referent	-
Turkish	-	-	-	1.20	(0.79, 1.82)	0.390	1.26	(0.82, 1.92)	0.291	1.25	(0.81, 1.92)	0.315
Other/Mixed	-	-	-	1.16	(0.54, 2.49)	0.700	1.11	(0.51, 2.40)	0.795	1.08	(0.49, 2.34)	0.852
Employment												
Not in paid employment	-	-	-	1.00	Referent		1.00	Referent		1.00	Referent	-
In paid employment	-	-	-	1.17	(0.71, 1.92)	0.534	1.04	(0.63, 1.72)	0.869	1.07	(0.64, 1.79)	0.795
Education												
Primary school	-	-	-	1.00	Referent		1.00	Referent		1.00	Referent	-
High school/Post-secondary	-	-	-	1.27	(0.68, 2.37)	0.444	1.12	(0.60, 2.10)	0.725	1.08	(0.57, 2.04)	0.817
Undergraduate degree	-	-	-	2.13	(1.11, 4.10)	**0.023**	1.78	(0.91, 3.46)	0.092	1.72	(0.88, 3.37)	0.113
Postgraduate degree	-	-	-	3.03	(1.50, 6.14)	**0.002**	2.28	(1.10, 4.69)	**0.026**	2.32	(1.12, 4.79)	**0.023**
Civil Status												
Married	-	-	-	1.00	Referent	-	1.00	Referent	-	1.00	Referent	-
Single	-	-	-	1.14	(0.70, 1.86)	0.598	1.19	(0.73, 1.96)	0.488	1.22	(0.74, 2.00)	0.435
Divorced/separated	-	-	-	1.76	(1.09, 2.84)	**0.021**	1.72	(1.06, 2.80)	**0.028**	1.86	(1.14, 3.03)	**0.013**

	Model 1			Model 2			Model 3a			Model 3b		
	Crude odds ratio	**(95% confidence intervals)**	**p-value**	**Adjusted odds ratio**	**(95% confidence intervals)**	**p-value**	**Crude odds ratio**	**(95% confidence intervals)**	**p-value**	**Crude odds ratio**	**(95% confidence intervals)**	**p-value**
Uses sunscreen*												
No	-	-	-	-	-	-	1.00	Referent	-	1.00	Referent	-
Yes	-	-	-	-	-	-	1.77	(1.23, 2.55)	**0.002**	1.90	(1.34, 2.71)	**<0.001**
Average time spent under sunlight in the last 2 years**												
Less than an hour per week	-	-	-	-	-	-	1.00	Referent	-	1.00	Referent	-
2-4 hours a week	-	-	-	-	-	-	0.91	(0.60, 1.38)	0.653	0.92	(0.63, 1.37)	0.692
5+ hours a week	-	-	-	-	-	-	0.82	(0.53, 1.28)	0.390	0.81	(0.51, 1.28)	0.368
Eye colour												
Brown, hazel	-	-	-	-	-	-	1.00	Referent	-	1.00	Referent	-
Blue, green, gray	-	-	-				1.22	(0.73, 2.04)	0.440	1.16	(0.68, 1.97)	0.579
Hair colour												
Blonde, red	-	-	-	-	-	-	0.39	(0.13, 1.15)	0.087	0.21	(0.05, 0.89)	**0.034**
Light brown	-	-	-	-	-	-	1.00	Referent	-	1.00	Referent	-
Dark brown	-	-	-	-	-	-	1.15	(0.77, 1.70)	0.498	1.14	(0.76, 1.69)	0.529
Black	-	-	-	-	-	-	0.68	(0.40, 1.14)	0.145	0.68	(0.40, 1.15)	0.150
Skin tone												
Very light, light, light intermediate	-	-	-	-	-	-	1.00	Referent	-	1.00	Referent	-
Dark intermediate, dark, very dark	-	-	-				0.88	(0.56, 1.40)	0.598	0.88	(0.55, 1.40)	0.585
Number of moles												
None	-	-	-	-	-	-	1.00	(0.45, 2.17)	0.976	1.03	(0.46, 2.28)	0.948
1 to 10	-	-	-	-	-	-	0.99	Referent	-	1	Referent	-
11 to 50	-	-	-	-	-	-	1.07	(0.73, 1.57)	0.732	1.05	(0.71, 1.56)	0.798
50 or more	-	-	-	-	-	-	1.67	(0.99, 2.81)	0.055	1.65	(0.97, 2.79)	0.063

**For Model 3a uses sunscreen in summer for Model 3b uses sunscreen in winter*

***For Model 3a average time in the summer, for Model 3b average time in the winter*

Table 22. Frequencies and percentages of sun exposure under the age of 25 compared to the past 2 years in endometriosis and control groups

	Summer			Winter		
Change in sun exposure from <25 years to in the past 2 years	Endometriosis	Symptomatic control	Asymptomatic control	Endometriosis	Symptomatic control	Asymptomatic control
Decreased	33 (21.6%)	236 (17.7%)	407 (21.9%)	28 (18.5%)	165 (12.5%)	283 (15.5%)
No change	114 (74.5%)	1,060 (79.7%)	1,411 (76.1%)	119 (78.8%)	1,131 (85.5%)	1,511 (82.7%)
Increased	6 (3.9%)	34 (3.6%)	37 (2.0%)	4 (2.7%)	27 (2.0%)	34 (1.9%)

**Only includes women aged 26 years and above at time of recruitment*

Chapter 7 – Conclusion

7.1 Overview

This thesis presents data on the epidemiology of endometriosis in Northern Cyprus for the first time. Using data from the COHERE Initiative[257], which recruited 7,646 women aged 18-55 living in Northern Cyprus, this thesis had the following aims:

i. To estimate the prevalence of endometriosis, diagnostic delay, symptom profile, and co-occurrence of migraines in this population of women.
ii. To investigate the impact endometriosis has on both physical and mental quality of life and prevalence of anxiety and depression.
iii. To describe the effect endometriosis has on work productivity and activity and to quantify the cost of endometriosis including healthcare and productivity costs.
iv. To investigate potential risk factors for endometriosis in this population of women including menstrual-related, anthropometric, lifestyle, pigmentary traits, sun exposure, vitamin D deficiency and investigate the prevalence of co-morbidities in this population of women.

7.2 Main findings

7.2.1 Prevalence, symptoms, and diagnostic delay of endometriosis

Overall, endometriosis prevalence was 5.4% (95%CI: 4.9%-5.9%, n=410) which included both self-reported cases (n=395) and incident endometrioma cases (n=15) picked up as part of the clinical visits offered as part of this study (*Chapter 3*). Only 12% of endometriosis cases reported to have been diagnosed laparoscopically, reflecting the fact that specialised endometriosis laparoscopy is not available in Northern Cyprus. Most cases (83%) reported to have been diagnosed by imaging techniques (ultrasound/MRI). There were no differences in demographics between endometriosis cases and incident endometrioma cases or laparoscopically diagnosed women. The average age reported for first endometriosis symptoms was 26 years and the mean age of endometriosis diagnosis was 28 years, despite the earliest age of reported pain symptoms being 16 years on average. This suggests that there is a low awareness of endometriosis symptoms in both the public and clinicians. It also demonstrates a mean diagnostic delay of 9 years which is similar to other studies in Western societies. Pain was the most common reported symptom prompting a healthcare appointment (in 50% of cases) and was experienced by women who said that pain was not a reason to seek healthcare. This again suggests that pain is not recognised as a symptom of endometriosis in this population of women. In addition to this, all but one (n=14) of the incident endometrioma cases reported to have experienced severe dysmenorrhea.

Misdiagnoses in women with endometriosis were high with reasons for pain received from a healthcare provider including IBS, ovarian cysts, PID and stress. Overall hormone use in this population was low (24%) and 48% of endometriosis cases reported to have ever used hormones, despite guidelines such as those from ESHRE[51,65] which state that hormonal treatment should be offered to women who are experiencing endometriosis-associated pain. This suggests there could be opportunities to improve access to pain-relieving medication.

Prevalence of dysmenorrhea, dyspareunia and non-cyclic pelvic pain was 48%, 6% and 13% in the endometriosis group and 38%, 4% and 6% in the control group. Due to the complex nature of endometriosis, difficulties in diagnosing and apparent low awareness of symptoms of endometriosis in this population, it is likely that there are undiagnosed endometriosis cases in the control group. Furthermore, endometriosis cases were on average older than the symptomatic control group. Since average age of endometriosis diagnosis was 28 years, it is probable that symptomatic control women younger than this had not received a diagnosis yet. Endometriosis cases were also more likely to have a higher educational attainment compared to the symptomatic control group, which may reflect socioeconomic bases in that more educated women have a higher level of knowledge on reproductive health and so receive a diagnosis quicker than those in the symptomatic control group.

Women with endometriosis were more likely to report bladder pain compared to the asymptomatic control group, but not the symptomatic control group, suggesting the presence of bladder pain is a co-occurrence in people with pain, rather than a function of endometriosis in this cohort. Endometriosis cases were more likely to fulfil the Rome IV criteria when considering IBS relating to pelvic pain compared to both control groups, but only had a significantly higher prevalence of IBS relating to menstrual pain compared to the asymptomatic control group. It is still unclear whether IBS is a true co-morbidity of endometriosis, but it is possible that some women in the case group are misclassified as endometriosis cases when they have IBS and some women in the control group are misclassified as controls with IBS when they have undiagnosed endometriosis. Odds of migraine as a co-morbidity of endometriosis were higher compared to controls, even after adjustment for pelvic pain, suggesting the central sensitisation theory is less likely to be involved here. Prevalence of difficulties in becoming pregnant within 6 months in women with endometriosis was 15%, which was double that of both control groups and odds remained high even after adjustment for demographic factors.

7.2.2 Endometriosis and quality of life

Chapter 4 investigated the impact of endometriosis on HRQoL. Women with endometriosis had significantly lower scores for all of the eight health domains and the two overall summary scores, PCS and MCS compared to the asymptomatic control group. However, compared to the symptomatic control

group, the only significant difference was for the role physical sub-scale, which asks questions on difficulties and time spent on performing work and other activities. This may be because all the symptomatic control group suffer from pain, whereas only 50% of the endometriosis cases reported pain, which would bias estimates towards the null. Mental health scores were significantly impaired in both the endometriosis and symptomatic control group and the symptomatic control group had slightly lower but non-significant scores compared to the endometriosis group. This may be because the symptomatic control group consists of a group of women who are experiencing severe pain, but do not have a diagnosis for the pain, which could take on toll on their mental health.

When stratifying HRQoL score by pain type, women with endometriosis who experienced dysmenorrhea had significantly lower physical health compared to symptomatic controls with the same symptom. This is likely because though both groups experience dysmenorrhea, severity was higher in the endometriosis group, as shown in *Chapter 3*. For all women, there was an inverse correlation between number of pain types experienced and HRQoL, but the small sample size means that these results need to be interpreted with caution. There were no differences in HRQoL between self-reported endometriosis cases and incident endometrioma cases picked up as part of the clinic visit in this study or any significant differences between diagnostic delay and HRQoL.

Women with endometriosis were significantly more likely to report to have anxiety compared to both symptomatic and asymptomatic controls, suggesting that the anxiety may not be due to the symptoms themselves, but due to other endometriosis-related factors such as an early age of symptom onset and long diagnostic delay. However, there were no significant differences between prevalence of depression and the two case groups, which may be due to perceived stigma surrounding mental health issues or a misclassification of the self-reported data.

7.2.3 Work Productivity impairment and economic burden

Chapter 5 examined work productivity loss and economic burden in women who reported to be employed. Women with endometriosis reported on average to lose 25.8% of their time at work due to reduced productivity, which was significantly more than women in the asymptomatic group (18.5%). Productivity losses were also high in the symptomatic control group (27.6%). Endometriosis cases had a significantly higher activity impairment (23.4%) compared to the asymptomatic control group (15.3%) but there was no significant difference when comparing activity losses of the symptomatic control group (15.4%). These results are suggestive of the hypothesis that it is the pain symptoms that are causing these losses of work productivity and activities, rather than the endometriosis *per se*. However, there is potential for misclassification of cases and controls as the data is self-reported which would bias estimates towards the null.

When considering direct healthcare costs and indirect costs due to absence from work and loss of productivity, the average cost associated with endometriosis cases was on average Int $9,864.35, which was not significantly different from the average associated with symptomatic control women (Int $10,429.68), but significantly higher than the average for asymptomatic control women, Int $6,587.63. Loss of productivity was the biggest component of this cost for all women and though the average healthcare cost was highest in women with endometriosis, the average total loss of productivity costs was highest in the symptomatic control group. Women with endometriosis have received a diagnosis and may be undergoing more specialised treatment which would expose them to high healthcare costs; women in the symptomatic control group do not have a diagnosis and presumably do not have a treatment plan, so may need to take more time off work or may be less productive at work due to the symptoms. With increasing age, the total average cost for women with endometriosis peaked between the ages of 26-35 whereas for the symptomatic control group, costs remained high across the life course. This may reflect the fact that the symptomatic control group are yet to receive their endometriosis diagnosis and will incur costs due to investigative procedures and loss of productivity from work. As reported period pain at its worst (NRS score) increased in all women, the total annual cost increased from Int $6,165.14 to Int $10,800.74, with the main contributing factor being loss of productivity. *Chapter 3* revealed that hormone use in this population was low – access to further treatment options for endometriosis and pain could be one avenue for

improvement in this population which would help to drive the high loss of productivity costs down.

The calculations above relied on several assumptions with regards to frequency of treatments, types of treatments used and assumed all participants earnt the national minimum wage, as this data were not collected, so estimated costs may not be accurate. Nevertheless, what is important is the magnitude of differences between case and control groups rather than the actual costs.

7.2.4 Co-morbidities of endometriosis and potential risk factors

Chapter 6 aimed to investigate the co-occurrence of self-reported co-morbidities with endometriosis and investigate potential risk factors for the disease, though the cross-sectional study design means that the analyses suffer from issues with temporality and therefore cannot be used to investigate causal associations.

There were no significant associations observed between age of menarche or menstrual cycle length and endometriosis, contrary to other studies[91,109,394]. Women with longer, heavier and more irregular menstrual cycles were more likely to be endometriosis cases, which would, in theory, increase exposure to menstruation and menstrual reflux and support Sampson's hypothesis of retrograde menstruation being the origin of endometriosis[18]. In terms of anthropometric characteristics, women with a lower WHR had a higher

likelihood of reporting to have endometriosis compared to both control groups, though the result was not linear, and the case group was small.

Women with a family history of endometriosis, chronic pelvic pain, heavy bleeding, uterine fibroids and PCOS were more likely to have a diagnosis of endometriosis compared to both control groups. This could be due to shared genetic susceptibilities between diseases, diseases having shared lifestyle factors that increase risk, or the fact that women with endometriosis may be more aware of family members having gynaecological conditions compared to women who do not have the disease.

There was an inverse relationship between fruit and vegetable intake and endometriosis, though no associations were seen between adherence to the Mediterranean diet and endometriosis. Women with endometriosis appeared to report to consume less folate, lutein and vitamin E compared to women without endometriosis. Since folate and lutein are found in dark leafy vegetables, these associations may be because of a higher intake of vegetables rather than because of the vitamins/minerals themselves.

Compared to the asymptomatic control group, women who reported to have ever smoked and were regular alcohol drinkers were at an increased risk of endometriosis in this study, compared to women who had never smoked and those who were not regular alcohol drinkers. Research on smoking and endometriosis risk is mixed[103,157,404], but as temporality cannot be accounted for

in cross-sectional studies, it may be that the associations seen between endometriosis and cigarette smoking and alcohol consumption are prone to reverse causality.

Women with endometriosis were significantly more likely to report having allergic, reproductive, and cardiovascular diseases compared to asymptomatic controls. It is unclear whether these are true co-morbidities in this population or whether women with endometriosis are more familiar with the healthcare system and so undergo more medical tests and screenings compared to the control groups. Women reporting to be iron deficient were more likely to be endometriosis cases, potentially due to this group of women also reporting higher rates of heavy bleeding and menstrual dysregulation. This finding however is interesting in this population, because in general, iron deficiency is common (estimated as 28.9% in whole cohort) as thalassemia carriers are prevalent in the region[218], which has also been associated with iron deficiency[219,417].

After adjustment for demographics, pigmentary traits and sun habits, endometriosis risk was higher in vitamin D deficient women compared to women who did not report a vitamin D deficiency. It has been suggested that vitamin D could act as an immunomodulator and an anti-inflammatory agent in the pathogenesis of endometriosis[420,421]. This finding is especially interesting because Cyprus is a warm country that receives a lot of sunlight, though this

may mean that vitamin D deficiency is prevalent (estimated as 17.3% in whole cohort) because people avoid direct sunlight and work in offices.

7.3 Strengths and limitations

The study recruited 7,646 women meaning it was sufficiently powered to undertake the majority of analyses. Using previously validated tools and questionnaires, standardised and comprehensive information was collected on endometriosis and its related symptoms, which had previously not been collected in this population of women. As recruitment of women into the study was from workplaces and homes rather than a clinical setting, the study population was broadly representative of the 2019 census projections[258] and the case population did not suffer from biases as seen in studies that recruited predominantly from hospitals. The use of two control groups meant associations were able to be tested to see if they were because of endometriosis or because of pain.

The data collected was self-reported and therefore may suffer from recall bias, but in the absence of systematically collected medical records, it provides a good estimation into the current situation in Northern Cyprus. Although controls were women who did not report to have endometriosis and had no evidence of an endometrioma on an ultrasound scan if they had one as part of this study, there are likely endometriosis cases in the control groups, resulting in misclassification bias. However, this would attenuate any effect estimates

towards the null rather than inflate them and create spurious associations. Symptomatic control groups usually feature women with pain and women with fertility issues, however, since the study did not collect accurate information on infertility, symptomatic controls were restricted to women who experienced pain only. The lack of diagnostic laparoscopy available for endometriosis in Northern Cyprus means that most cases were diagnosed via imaging so are likely to be stage III/IV. Although this study included several previously validated tools (see *Chapter 2* for full list), other more endometriosis-specific tools such as the Endometriosis Health Profile 30 (EPH-30) questionnaire[429] and the WERF EndoCost tool[378], would have been interesting additions to this data.

Cross-sectional studies are not appropriate to investigate risk factors due to issues with temporality as they cannot accurately assess whether or not the exposure definitely preceded the outcome and are therefore prone to reverse causation. However, the results from this study can offer some insight into potential risk factors and can form the basis for future studies. Prospective longitudinal cohort studies where the exposures are assessed before the outcome are best placed for risk factor analysis. The FFQ recruited 513 women in total, including 99 cases which meant it was most likely not sufficiently powered. In addition, dietary habits were taken as follow-up and so cannot act as a sufficient exposure for endometriosis because diets may have changed in response to symptoms or diagnosis. Since the data on co-morbidities and deficiencies was self-reported, it is prone to recall bias, however, the magnitude of this bias is likely to be equal in both the case and control groups. Although all

analyses were adjusted for potential confounders, it is likely that residual confounding may remain from unmeasured or incorrectly measured factors such as those relating to parity, infertility and medications.

7.4 Future directions

This is the first time that endometriosis has been investigated in this population and this research provides an excellent foundation to base follow-up studies on.

Large prospective studies with multiple points of follow-up are the most appropriate study types to investigate associations between endometriosis and outcomes and potential risk factors for endometriosis. Laparoscopically confirmed endometriosis cases would help to confirm whether the prevalence estimated in this study was accurate or more likely under-estimated. However, in the absence of diagnostic laparoscopy in Northern Cyprus, this would be near impossible. Therefore, endometriosis cases confirmed by imaging would be a good alternative and symptomatic controls could be women with pain or infertility but who did not have evidence of endometrioma on ultrasound scans with asymptomatic controls being women who had no symptoms and evidence of no endometriosis.

To investigate the association between endometriosis and vitamin D and iron deficiency further, blood measurements could be taken to verify whether participants were deficient. These measurements could be taken at several

different time points and across seasons, but, if they were collected prior to endometriosis onset, then it would allow for a robust analysis of these deficiencies as risk factors. This would allow for a longitudinal analysis of data. In addition to this, if FFQ data were collected at the same time, then information on vitamin D and iron from diet could supplement this analysis and help to elucidate potential mechanisms between these deficiencies and endometriosis.

The study collected saliva samples from 699 women, including 83 endometriosis cases, 234 symptomatic controls and 382 asymptomatic controls. Analysis of this genetic data was beyond the scope of this DPhil but is currently underway. The Turkish Cypriot genome is likely to be subject to admixture due to migration over the years and to date, there is no reference population for the region. The analysis of the genotyped data will aim to provide this and provide insight into potential genes that may be implicated in endometriosis in women from this ancestral background. This data will be combined with laparoscopically confirmed endometriosis cases from Turkey to ensure the study has sufficient power.

Finally, the results from this study clearly suggest that awareness of endometriosis and its symptoms is low in this population. Advancements must be made to ensure that younger women experiencing symptoms can quickly get the help that they need which would help to drive down diagnostic delay. This would not only increase the HRQoL of these women but would reduce the high economic costs associated with endometriosis and its symptoms. There are

opportunities to enhance treatment options for endometriosis patients and women suffering from chronic pain, such as hormones and over the counter and prescription painkillers as well as psychological and community-based support. Continued awareness campaigns in the region will help to ensure that young women suffering from endometriosis and pain get the help that they need and deserve.

Bibliography

1. Zondervan KT, Becker CM, Koga K, Missmer SA, Taylor RN, Viganò P. Endometriosis. *Nat Rev Dis Prim*. 2018;4(1):1-25. doi:10.1038/s41572-018-0008-5
2. Zondervan KT, Becker CM, Missmer SA. Endometriosis. *N Engl J Med*. 2020;382(13):1244-1256. doi:10.1056/NEJMra1810764
3. Eskenazi B, Warner ML. Epidemiology of endometriosis. *Obstet Gynecol Clin North Am*. 1997;24(2):235-258. doi:10.1016/S0889-8545(05)70302-8
4. Marsh EE, Laufer MR. Endometriosis in premenarcheal girls who do not have an associated obstructive anomaly. *Fertil Steril*. 2005;83(3):758-760. doi:10.1016/j.fertnstert.2004.08.025
5. Morotti M, Remorgida V, Venturini PL, Ferrero S. Endometriosis in menopause: A single institution experience. *Arch Gynecol Obstet*. 2012;286(6):1571-1575. doi:10.1007/s00404-012-2473-5
6. Schrodt GR, Alcorn MO, Ibanez J. Endometriosis of the male urinary system: A case report. *J Urol*. 1980;124(5):722-723. doi:10.1016/S0022-5347(17)55627-X
7. Canis M, Donnez JG, Guzick DS, et al. Revised American Society for Reproductive Medicine classification of endometriosis: 1996 American Society for Reproductive Medicine*t. *Fertil Steril*. 1997;67(5):817-821.
8. Schliep KC, Mumford SL, Peterson CM, et al. Pain typology and incident endometriosis. *Hum Reprod*. 2015;30(10):2427-2438. doi:10.1093/humrep/dev147
9. Roberts CP, Rock JA. The current staging system for endometriosis: Does it help? *Obstet Gynecol Clin North Am*. 2003;30(1):115-132. doi:10.1016/S0889-8545(02)00056-6
10. Koninckx PR, Oosterlynck D, D'Hooghe T, Meuleman C. Deeply Infiltrating Endometriosis Is a Disease Whereas Mild Endometriosis Could Be Considered a Non-Disease. *Ann N Y Acad Sci*. 1994;734(1):333-341. doi:10.1111/j.1749-6632.1994.tb21763.x
11. Sampson JA. Peritoneal endometriosis due to the menstrual dissemination of endometrial tissue into the peritoneal cavity. *Am J Obstet Gynecol*. 1927;14(4):422-469. doi:10.1016/s0002-9378(15)30003-x
12. Koninckx PR, Ide P, Vandenbroucke W, Brosens IA. New aspects of the pathophysiology of endometriosis and associated infertility. *J Reprod Med Obstet Gynecol*. 1980;24(6):257-260. https://pubmed.ncbi.nlm.nih.gov/7420327/. Accessed August 19, 2020.
13. Halme J, Hammond MG, Hulka JF, Raj SG, Talbert LM. Retrograde menstruation in healthy women and in patients with endometriosis. *Obstet Gynecol*. 1984;64(2):151-154. https://pubmed.ncbi.nlm.nih.gov/6234483/. Accessed August 19, 2020.
14. Lucidi RS, Witz CA, Chrisco M, Binkley PA, Shain SA, Schenken RS. A novel in vitro model of the early endometriotic lesion demonstrates that attachment of endometrial cells to mesothelial cells is dependent on the source of endometrial cells. *Fertil Steril*. 2005;84(1):16-21. doi:10.1016/j.fertnstert.2004.10.058
15. van der Linden PJQ. Theories on the Pathogenesis of Endometriosis. In:

Endometriosis: Science and Practice. ; 1996:42-53. doi:10.1002/9781444398519.ch5
16. Suginami H. A reappraisal of the coelomic metaplasia theory by reviewing endometriosis occurring in unusual sites and instances. *Am J Obstet Gynecol*. 1991;165(1):214-218. doi:10.1016/0002-9378(91)90254-O
17. Laganà AS, Garzon S, Götte M, et al. The pathogenesis of endometriosis: Molecular and cell biology insights. *Int J Mol Sci*. 2019;20(22):5615. doi:10.3390/ijms20225615
18. Sampson JA. Metastatic or Embolic Endometriosis, due to the Menstrual Dissemination of Endometrial Tissue into the Venous Circulation. *Am J Pathol*. 1927;3(2):93-110.43. https://pubmed.ncbi.nlm.nih.gov/19969738/. Accessed August 19, 2020.
19. Jubanyik KJ, Comite F. Extrapelvic endometriosis. *Obstet Gynecol Clin North Am*. 1997;24(2):411-440. doi:10.1016/S0889-8545(05)70311-9
20. Treloar SA, O'Connor DT, O'Connor VM, Martin NG. Genetic influences on endometriosis in an Australian twin sample. *Fertil Steril*. 1999;71(4):701-710. doi:10.1016/S0015-0282(98)00540-8
21. Saha R, Pettersson HJ, Svedberg P, et al. Heritability of endometriosis. *Fertil Steril*. 2015;104(4):947-952. doi:10.1016/j.fertnstert.2015.06.035
22. Lee SH, Harold D, Nyholt DR, et al. Estimation and partitioning of polygenic variation captured by common snps for alzheimer's disease, multiple sclerosis and endometriosis. *Hum Mol Genet*. 2013;22(4):832-841. doi:10.1093/hmg/dds491
23. Sapkota Y, Steinthorsdottir V, Morris AP, et al. Meta-analysis identifies five novel loci associated with endometriosis highlighting key genes involved in hormone metabolism. *Nat Commun*. 2017;8(1):1-12. doi:10.1038/ncomms15539
24. Nilufer R, Karina B, Paraskevi C, et al. Large-scale genome-wide association meta-analysis of endometriosis reveals 13 novel loci and genetically-associated comorbidity with other pain conditions. *bioRxiv*. September 2018:406967. doi:10.1101/406967
25. Zondervan KT, Rahmioglu N, Morris AP, et al. Beyond Endometriosis Genome-Wide Association Study: From Genomics to Phenomics to the Patient. *Semin Reprod Med*. 2016;34(4):242-254. doi:10.1055/s-0036-1585408
26. Giudice LC, Kao LC. Endometriosis. *Lancet*. 2004;364(9447):1789-1799. doi:10.1016/S0140-6736(04)17403-5
27. Tworoger SS, Sluss P, Hankinson SE. Association between plasma prolactin concentrations and risk of breast cancer among predominately premenopausal women. *Cancer Res*. 2006;66(4):2476-2482. doi:10.1158/0008-5472.CAN-05-3369
28. Lebovic DI, Mueller MD, Taylor RN. Immunobiology of endometriosis. *Fertil Steril*. 2001;75(1):1-10. doi:10.1016/S0015-0282(00)01630-7
29. Harada T, Iwabe T, Terakawa N. Role of cytokines in endometriosis. *Fertil Steril*. 2001;76(1):1-10. doi:10.1016/S0015-0282(01)01816-7
30. Shigesi N, Kvaskoff M, Kirtley S, et al. The association between endometriosis and autoimmune diseases: A systematic review and meta-analysis. *Hum Reprod Update*. 2019;25(4):486-503.

doi:10.1093/humupd/dmz014
31. Mu F, Harris HR, Rich-Edwards JW, et al. A Prospective Study of Inflammatory Markers and Risk of Endometriosis. *Am J Epidemiol*. 2018;187(3):515-522. doi:10.1093/aje/kwx272
32. Saunders PTK, Horne AW. Endometriosis: Etiology, pathobiology, and therapeutic prospects. *Cell*. 2021;184(11):2807-2824. doi:10.1016/j.cell.2021.04.041
33. Kitawaki J, Kado N, Ishihara H, Koshiba H, Kitaoka Y, Honjo H. Endometriosis: The pathophysiology as an estrogen-dependent disease. *J Steroid Biochem Mol Biol*. 2002;83(1-5):149-155. doi:10.1016/S0960-0760(02)00260-1
34. Bulun SE, Utsunomiya H, Lin Z, et al. Steroidogenic factor-1 and endometriosis. *Mol Cell Endocrinol*. 2009;300(1-2):104-108. doi:10.1016/j.mce.2008.12.012
35. McKinnon B, Mueller M, Montgomery G. Progesterone Resistance in Endometriosis: an Acquired Property? *Trends Endocrinol Metab*. 2018;29(8):535-548. doi:10.1016/j.tem.2018.05.006
36. Bulun SE. Endometriosis. *Yen Jaffe's Reprod Endocrinol Physiol Pathophysiol Clin Manag Eighth Ed*. 2018:609-642.e7. doi:10.1016/B978-0-323-47912-7.00025-1
37. Fauconnier A, Chapron C. Endometriosis and pelvic pain: Epidemiological evidence of the relationship and implications. *Hum Reprod Update*. 2005;11(6):595-606. doi:10.1093/humupd/dmi029
38. Shafrir AL, Farland L V., Shah DK, et al. Risk for and consequences of endometriosis: A critical epidemiologic review. *Best Pract Res Clin Obstet Gynaecol*. 2018;51:1-15. doi:10.1016/j.bpobgyn.2018.06.001
39. Asante A, Taylor RN. Endometriosis: The role of neuroangiogenesis. *Annu Rev Physiol*. 2011;73:163-182. doi:10.1146/annurev-physiol-012110-142158
40. As-Sanie S, Harris RE, Napadow V, et al. Changes in regional gray matter volume in women with chronic pelvic pain: A voxel-based morphometry study. *Pain*. 2012;153(5):1006-1014. doi:10.1016/j.pain.2012.01.032
41. Nijs J, George SZ, Clauw DJ, et al. Central sensitisation in chronic pain conditions: latest discoveries and their potential for precision medicine. *Lancet Rheumatol*. 2021;3(5):e383-e392. doi:10.1016/S2665-9913(21)00032-1
42. Coccia ME, Rizzello F, Palagiano A, Scarselli G. Long-term follow-up after laparoscopic treatment for endometriosis: Multivariate analysis of predictive factors for recurrence of endometriotic lesions and pain. *Eur J Obstet Gynecol Reprod Biol*. 2011;157(1):78-83. doi:10.1016/j.ejogrb.2011.02.008
43. Woolf CJ. Central sensitization: Implications for the diagnosis and treatment of pain. *Pain*. 2011;152(SUPPL.3):S2. doi:10.1016/j.pain.2010.09.030
44. Brawn J, Morotti M, Zondervan KT, Becker CM, Vincent K. Central changes associated with chronic pelvic pain and endometriosis. *Hum Reprod Update*. 2014;20(5):737-747. doi:10.1093/humupd/dmu025

45. Sutton CJG, Ewen SP, Whitelaw N, Haines P. Prospective, randomized, double-blind, controlled trial of laser laparoscopy in the treatment of pelvic pain associated with minimal, mild, and moderate endometriosis. *Fertil Steril*. 1994;62(4):696-700. doi:10.1016/S0015-0282(16)56990-8
46. Stratton P, Khachikyan I, Sinaii N, Ortiz R, Shah J. Association of chronic pelvic pain and endometriosis with signs of sensitization and myofascial pain. *Obstet Gynecol*. 2015;125(3):719-728. doi:10.1097/AOG.0000000000000663
47. Coxon L, Wiech K, Vincent K. Is There a Neuropathic-Like Component to Endometriosis-Associated Pain? Results From a Large Cohort Questionnaire Study. *Front Pain Res*. 2021;2:84. doi:10.3389/fpain.2021.743812
48. Lamvu G, Carrillo J, Ouyang C, Rapkin A. Chronic Pelvic Pain in Women: A Review. *JAMA - J Am Med Assoc*. 2021;325(23):2381-2391. doi:10.1001/jama.2021.2631
49. Cohen SP, Vase L, Hooten WM. Chronic pain: an update on burden, best practices, and new advances. *Lancet*. 2021;397(10289):2082-2097. doi:10.1016/S0140-6736(21)00393-7
50. Yong PJ, Williams C, Bedaiwy MA, Allaire C. A Proposed Platform for Phenotyping Endometriosis-Associated Pain: Unifying Peripheral and Central Pain Mechanisms. *Curr Obstet Gynecol Reports 2020 93*. 2020;9(3):89-97. doi:10.1007/S13669-020-00288-8
51. Becker CM, Bokor A, Heikinheimo O, et al. ESHRE guideline: endometriosis. *Hum Reprod Open*. 2022;2022(2):1-26. doi:10.1093/HROPEN/HOAC009
52. Kuznetsov L, Dworzynski K, Davies M, Overton C. Diagnosis and management of endometriosis: Summary of NICE guidance. *BMJ*. 2017;358. doi:10.1136/bmj.j3935
53. Bafort C, Beebeejaun Y, Tomassetti C, Bosteels J, Duffy JMN. Laparoscopic surgery for endometriosis. *Cochrane Database Syst Rev*. 2020;2020(10). doi:10.1002/14651858.CD011031.pub3
54. Stewart EA, Missmer SA, Rocca WA. Moving Beyond Reflexive and Prophylactic Gynecologic Surgery. *Mayo Clin Proc*. 2021;96(2):291-294. doi:10.1016/j.mayocp.2020.05.012
55. Mu F, Rich-Edwards J, Rimm EB, Spiegelman D, Missmer SA. Endometriosis and risk of coronary heart disease. *Circ Cardiovasc Qual Outcomes*. 2016;9(3):257-264. doi:10.1161/CIRCOUTCOMES.115.002224
56. Horne AW, Missmer SA. Pathophysiology, diagnosis, and management of endometriosis. *BMJ*. 2022:e070750. doi:10.1136/bmj-2022-070750
57. Prescott J, Farland L V., Tobias DK, et al. A prospective cohort study of endometriosis and subsequent risk of infertility. *Hum Reprod*. 2016;31(7):1475-1482. doi:10.1093/humrep/dew085
58. Counseller VS, Crenshaw JL. A clinical and surgical review of endometriosis. *Am J Obstet Gynecol*. 1951;62(4):930-942. doi:10.1016/0002-9378(51)90180-9
59. Muzii L, Di Tucci C, Di Feliciantonio M, et al. Antimüllerian hormone is reduced in the presence of ovarian endometriomas: a systematic review

and meta-analysis. *Fertil Steril*. 2018;110(5):932-940.e1. doi:10.1016/j.fertnstert.2018.06.025
60. Senapati S, Sammel MD, Morse C, Barnhart KT. Impact of endometriosis on in vitro fertilization outcomes: an evaluation of the Society for Assisted Reproductive Technologies Database. *Fertil Steril*. 2016;106(1):164-171.e1. doi:10.1016/j.fertnstert.2016.03.037
61. Macer ML, Taylor HS. Endometriosis and Infertility. A Review of the Pathogenesis and Treatment of Endometriosis-associated Infertility. *Obstet Gynecol Clin North Am*. 2012;39(4):535-549. doi:10.1016/j.ogc.2012.10.002
62. Adamson GD, Pasta DJ. Endometriosis fertility index: The new, validated endometriosis staging system. *Fertil Steril*. 2010;94(5):1609-1615. doi:10.1016/j.fertnstert.2009.09.035
63. Nisenblat V, Bossuyt PMM, Shaikh R, et al. Blood biomarkers for the non-invasive diagnosis of endometriosis. *Cochrane Database Syst Rev*. 2016;2016(5). doi:10.1002/14651858.CD012179
64. Kennedy S, Bergqvist A, Chapron C, et al. ESHRE guideline for the diagnosis and treatment of endometriosis. *Hum Reprod*. 2005;20(10):2698-2704. doi:10.1093/humrep/dei135
65. Dunselman GAJ, Vermeulen N, Becker C, et al. ESHRE guideline: Management of women with endometriosis. *Hum Reprod*. 2014;29(3):400-412. doi:10.1093/humrep/det457
66. Chapron C, Querleu D, Bruhat MA, et al. Surgical complications of diagnostic and operative gynaecological laparoscopy: A series of 29,966 cases. *Hum Reprod*. 1998;13(4):867-872. doi:10.1093/humrep/13.4.867
67. Byrne D, Curnow T, Smith P, Cutner A, Saridogan E, Clark TJ. Laparoscopic excision of deep rectovaginal endometriosis in BSGE endometriosis centres: A multicentre prospective cohort study. *BMJ Open*. 2018;8(4). doi:10.1136/bmjopen-2017-018924
68. Pascoal E, Wessels JM, Aas-Eng MK, et al. Strengths and limitations of diagnostic tools for endometriosis and relevance in diagnostic test accuracy research. *Ultrasound Obstet Gynecol*. March 2022. doi:10.1002/uog.24892
69. Arruda MS, Petta CA, Abrão MS, Benetti-Pinto CL. Time elapsed from onset of symptoms to diagnosis of endometriosis in a cohort study of Brazilian women. *Hum Reprod*. 2003;18(4):756-759. doi:10.1093/HUMREP/DEG136
70. Dmowski WP, Pepping P, Lesniewicz R, Noursalehi M, Rana N. Changing trends in the diagnosis of endometriosis: A comparative study of women with pelvic endometriosis presenting with chronic pelvic pain or infertility. *Fertil Steril*. 1997;67(2):238-243. doi:10.1016/S0015-0282(97)81904-8
71. Hudelist G, Fritzer N, Thomas A, et al. Diagnostic delay for endometriosis in Austria and Germany: Causes and possible consequences. *Hum Reprod*. 2012;27(12):3412-3416. doi:10.1093/humrep/des316
72. Nnoaham KE, Hummelshoj L, Webster P, et al. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. *Fertil Steril*. 2019;112(4):e137-e152.

doi:10.1016/j.fertnstert.2019.08.082
73. Youngster M, Laufer MR, Divasta AD. Endometriosis for the primary care physician. *Curr Opin Pediatr*. 2013;25(4):454-462. doi:10.1097/MOP.0b013e3283628092
74. Y Weintraub A. Think Endometriosis: Delay in Diagnosis or Delay in Referral to Adequate Treatment? Journal of Fertilization: In Vitro - IVF-Worldwide, Reproductive Medicine, Genetics & Stem Cell Biology. doi:10.4172/2375-4508.1000127
75. As-Sanie S, Black R, Giudice LC, et al. Assessing research gaps and unmet needs in endometriosis. *Am J Obstet Gynecol*. 2019;221(2):86-94. doi:10.1016/j.ajog.2019.02.033
76. Gupta J, Cardoso LF, Harris CS, et al. How do adolescent girls and boys perceive symptoms suggestive of endometriosis among their peers? Findings from focus group discussions in New York City. *BMJ Open*. 2018;8(6):e020657. doi:10.1136/bmjopen-2017-020657
77. The Practice Committee of the American Society for Reproductive Medicine. Treatment of pelvic pain associated with endometriosis: A committee opinion. *Fertil Steril*. 2014;101(4):927-935. doi:10.1016/j.fertnstert.2014.02.012
78. Quibel A, Puscasiu L, Marpeau L, Roman H. General practitioners and the challenge of endometriosis screening and care: Results of a survey. *Gynecol Obstet Fertil*. 2013;41(6):372-380. doi:10.1016/j.gyobfe.2012.02.024
79. Zondervan KT, Cardon LR, Kennedy SH. What makes a good case-control study? Design issues for complex traits such as endometriosis. *Hum Reprod*. 2002;17(6):1415-1423. doi:10.1093/humrep/17.6.1415
80. Strathy JH, Molgaard CA, Coulam CB, Melton LJ. Endometriosis and infertility: A laparoscopic study of endometriosis among fertile and infertile women. *Fertil Steril*. 1982;38(6):667-672. doi:10.1016/S0015-0282(16)46691-4
81. Flores I, Abreu S, Abac S, Fourquet J, Laboy J, Ríos-Bedoya C. Self-reported prevalence of endometriosis and its symptoms among Puerto Rican women. *Int J Gynecol Obstet*. 2008;100(3):257-261. doi:10.1016/j.ijgo.2007.08.010
82. Buck Louis GM, Hediger ML, Peterson CM, et al. Incidence of endometriosis by study population and diagnostic method: The ENDO study. *Fertil Steril*. 2011;96(2):360-365. doi:10.1016/j.fertnstert.2011.05.087
83. Duignan NM, Jordan JA, Coughlan BM, Logan-Edwards R. ONE THOUSAND CONSECUTIVE CASES OF DIAGNOSTIC LAPAROSCOPY. *BJOG An Int J Obstet Gynaecol*. 1972;79(11):1016-1024. doi:10.1111/j.1471-0528.1972.tb11880.x
84. Meuleman C, Vandenabeele B, Fieuws S, Spiessens C, Timmerman D, D'Hooghe T. High prevalence of endometriosis in infertile women with normal ovulation and normospermic partners. *Fertil Steril*. 2009;92(1):68-74. doi:10.1016/j.fertnstert.2008.04.056
85. Farland L V., Horne AW. Disparity in endometriosis diagnoses between racial/ethnic groups. *BJOG An Int J Obstet Gynaecol*. 2019;126(9):1115-

1116. doi:10.1111/1471-0528.15805
86. Culley L, Law C, Hudson N, et al. The social and psychological impact of endometriosis on women's lives: a critical narrative review. *Hum Reprod Update*. 2013;19(6):625-639. doi:10.1093/HUMUPD/DMT027
87. Moradi M, Parker M, Sneddon A, Lopez V, Ellwood D. Impact of endometriosis on women's lives: A qualitative study. *BMC Womens Health*. 2014;14(1):1-12. doi:10.1186/1472-6874-14-123
88. De Graaff AA, D'hooghe TM, Dunselman GAJ, et al. The significant effect of endometriosis on physical, mental and social wellbeing: Results from an international cross-sectional survey. *Hum Reprod*. 2013;28(10):2677-2685. doi:10.1093/humrep/det284
89. Fourquet J, Báez L, Figueroa M, Iriarte RI, Flores I. Quantification of the impact of endometriosis symptoms on health-related quality of life and work productivity. *Fertil Steril*. 2011;96(1):107-112. doi:10.1016/j.fertnstert.2011.04.095
90. Friedl F, Riedl D, Fessler S, et al. Impact of endometriosis on quality of life, anxiety, and depression: an Austrian perspective. *Arch Gynecol Obstet*. 2015;292(6):1393-1399. doi:10.1007/s00404-015-3789-8
91. Mousa M, Al-Jefout M, Alsafar H, Becker CM, Zondervan KT, Rahmioglu N. Impact of Endometriosis in Women of Arab Ancestry on: Health-Related Quality of Life, Work Productivity, and Diagnostic Delay. *Front Glob Women's Heal*. 2021;2:66. doi:10.3389/fgwh.2021.708410
92. Dubernard G, Piketty M, Rouzier R, Houry S, Bazot M, Darai E. Quality of life after laparoscopic colorectal resection for endometriosis. *Hum Reprod*. 2006;21(5):1243-1247. doi:10.1093/humrep/dei491
93. Dubernard G, Rouzier R, David-Montefiore E, Bazot M, Darai E. Use of the SF-36 questionnaire to predict quality-of-life improvement after laparoscopic colorectal resection for endometriosis. *Hum Reprod*. 2008;23(4):846-851. doi:10.1093/humrep/den026
94. Soliman AM, Coyne KS, Gries KS, Castelli-Haley J, Snabes MC, Surrey ES. The effect of endometriosis symptoms on absenteeism and presenteeism in the workplace and at home. *J Manag Care Spec Pharm*. 2017;23(7):745-754. doi:10.18553/jmcp.2017.23.7.745
95. Langley P, Mller-Schwefe G, Nicolaou A, Liedgens H, Pergolizzi J, Varrassi G. The impact of pain on labor force participation, absenteeism and presenteeism in the European Union. *J Med Econ*. 2010;13(4):662-672. doi:10.3111/13696998.2010.529379
96. Zhang W, Bansback N, Boonen A, Young A, Singh A, Anis AH. Validity of the work productivity and activity impairment questionnaire - general health version in patients with rheumatoid arthritis. *Arthritis Res Ther*. 2010;12(5):1-7. doi:10.1186/ar3141
97. Armour M, Lawson K, Wood A, Smith CA, Abbott J. The cost of illness and economic burden of endometriosis and chronic pelvic pain in Australia: A national online survey. *PLoS One*. 2019;14(10). doi:10.1371/journal.pone.0223316
98. Greene R, Stratton P, Cleary SD, Ballweg M Lou, Sinaii N. Diagnostic experience among 4,334 women reporting surgically diagnosed endometriosis. *Fertil Steril*. 2009;91(1):32-39.

doi:10.1016/j.fertnstert.2007.11.020
99. Tirlapur SA, Kuhrt K, Chaliha C, Ball E, Meads C, Khan KS. The “evil twin syndrome” in chronic pelvic pain: A systematic review of prevalence studies of bladder pain syndrome and endometriosis. *Int J Surg*. 2013;11(3):233-237. doi:10.1016/j.ijsu.2013.02.003
100. Gao X, Outley J, Botteman M, Spalding J, Simon JA, Pashos CL. Economic burden of endometriosis. *Fertil Steril*. 2006;86(6):1561-1572. doi:10.1016/j.fertnstert.2006.06.015
101. Parazzini F, Viganò P, Candiani M, Fedele L. Diet and endometriosis risk: A literature review. *Reprod Biomed Online*. 2013;26(4):323-336. doi:10.1016/j.rbmo.2012.12.011
102. Eisenberg VH, Weil C, Chodick G, Shalev V. Epidemiology of endometriosis: a large population-based database study from a healthcare provider with 2 million members. *BJOG An Int J Obstet Gynaecol*. 2018;125(1):55-62. doi:10.1111/1471-0528.14711
103. Missmer SA, Hankinson SE, Spiegelman D, Barbieri RL, Marshall LM, Hunter DJ. Incidence of laparoscopically confirmed endometriosis by demographic, anthropometric, and lifestyle factors. *Am J Epidemiol*. 2004;160(8):784-796. doi:10.1093/AJE/KWH275
104. Reid R, Steel A, Wardle J, et al. The prevalence of self-reported diagnosed endometriosis in the Australian population: Results from a nationally-representative survey. *BMC Res Notes*. 2019;12(1). doi:10.1186/s13104-019-4114-6
105. Robert CA, Caraballo-Rivera EJ, Isola S, et al. Demographics and Hospital Outcomes in American Women With Endometriosis and Psychiatric Comorbidities. *Cureus*. 2020;12(8). doi:10.7759/cureus.9935
106. Bougie O, Yap MI, Sikora L, Flaxman T, Singh S. Influence of race/ethnicity on prevalence and presentation of endometriosis: a systematic review and meta-analysis. *BJOG An Int J Obstet Gynaecol*. 2019;126(9):1104-1115. doi:10.1111/1471-0528.15692
107. Schulman KA, Berlin JA, Harless W, et al. The Effect of Race and Sex on Physicians’ Recommendations for Cardiac Catheterization. *N Engl J Med*. 1999;340(8):618-626. doi:10.1056/nejm199902253400806
108. Williams C, Long AJ, Noga H, et al. East and South East Asian Ethnicity and Moderate-to-Severe Endometriosis. *J Minim Invasive Gynecol*. 2019;26(3):507-515. doi:10.1016/j.jmig.2018.06.009
109. Barbieri RL. Reproductive history and endometriosis among premenopausal women. *Obstet Gynecol*. 2004;104(5):965-974. doi:10.1097/01.AOG.0000142714.54857.f8
110. Nnoaham KE, Webster P, Kumbang J, Kennedy SH, Zondervan KT. Is early age at menarche a risk factor for endometriosis? A systematic review and meta-analysis of case-control studies. *Fertil Steril*. 2012;98(3). doi:10.1016/j.fertnstert.2012.05.035
111. Cramer DW, Wilson E, Stillman RJ, et al. The Relation of Endometriosis to Menstrual Characteristics, Smoking, and Exercise. *JAMA J Am Med Assoc*. 1986;255(14):1904-1908. doi:10.1001/jama.1986.03370140102032
112. Parazzini F, Ferraroni M, Fedele L, Bocciolone L, Rubessa S, Riccardi A.

Pelvic endometriosis: Reproductive and menstrual risk factors at different stages in Lombardy, northern Italy. *J Epidemiol Community Health*. 1995;49(1):61-64. doi:10.1136/jech.49.1.61
113. Shah DK, Correia KF, Vitonis AF, Missmer SA. Body size and endometriosis: results from 20 years of follow-up within the Nurses' Health Study II prospective cohort. *Hum Reprod*. 2013;28(7):1783-1792. doi:10.1093/humrep/det120
114. Farland L V., Missmer SA, Bijon A, et al. Associations among body size across the life course, adult height and endometriosis. *Hum Reprod*. 2017;32(8):1732-1742. doi:10.1093/humrep/dex207
115. McCann SE, Freudenheim JL, Darrow SL, Batt RE, Zielezny MA. Endometriosis and body fat distribution. *Obstet Gynecol*. 1993;82(4):545-549. doi:10.1097/00006250-199310000-00014
116. Rahmioglu N, MacGregor S, Drong AW, et al. Genome-wide enrichment analysis between endometriosis and obesity-related traits reveals novel susceptibility loci. *Hum Mol Genet*. 2015;24(4):1185-1199. doi:10.1093/hmg/ddu516
117. De Ridder CM, Bruning PF, Zonderland ML, et al. Body fat mass, body fat distribution, and plasma hormones in early puberty in females. *J Clin Endocrinol Metab*. 1990;70(4):888-893. doi:10.1210/jcem-70-4-888
118. Masala G, Assedi M, Bendinelli B, et al. Fruit and vegetables consumption and breast cancer risk: The EPIC italy study. *Breast Cancer Res Treat*. 2012;132(3):1127-1136. doi:10.1007/s10549-011-1939-7
119. Pala V, Sieri S, Masala G, et al. Associations between dietary pattern and lifestyle, anthropometry and other health indicators in the elderly participants of the EPIC-Italy cohort. *Nutr Metab Cardiovasc Dis*. 2006;16(3):186-201. doi:10.1016/j.numecd.2005.05.009
120. Kyprianidou M, Panagiotakos D, Faka A, Kambanaros M, Makris KC, Christophi CA. Adherence to the Mediterranean diet in Cyprus and its relationship to multi-morbidity: An epidemiological study. *Public Health Nutr*. 2021;24(14):4546-4555. doi:10.1017/S1368980020004267
121. Davis C, Bryan J, Hodgson J, Murphy K. Definition of the mediterranean diet: A literature review. *Nutrients*. 2015;7(11):9139-9153. doi:10.3390/nu7115459
122. Parazzini F, Chiaffarino F, Surace M, et al. Selected food intake and risk of endometriosis. *Hum Reprod*. 2004;19(8):1755-1759. doi:10.1093/humrep/deh395
123. Trabert B, Peters U, De Roos AJ, Scholes D, Holt VL. Diet and risk of endometriosis in a population-based case-control study. *Br J Nutr*. 2011;105(3):459-467. doi:10.1017/S0007114510003661
124. Harris HR, Eke AC, Chavarro JE, Missmer SA. Fruit and vegetable consumption and risk of endometriosis. *Hum Reprod*. 2018;33(4):715-727. doi:10.1093/humrep/dey014
125. Arab A, Karimi E, Vingrys K, Kelishadi MR, Mehrabani S, Askari G. Food groups and nutrients consumption and risk of endometriosis: a systematic review and meta-analysis of observational studies. *Nutr J*. 2022;21(1):1-14. doi:10.1186/s12937-022-00812-x
126. Darling AM, Chavarro JE, Malspeis S, Harris HR, Missmer SA. A

prospective cohort study of vitamins B, C, E, and multivitamin intake and endometriosis. *J Endometr Pelvic Pain Disord*. 2013;5(1):17-26. doi:10.5301/je.5000151
127. Trabert B, Peters U, De Roos AJ, Scholes D, Holt VL. Diet and risk of endometriosis in a population-based case-control study. *Br J Nutr*. 2011;105(3):459-467. doi:10.1017/S0007114510003661
128. Britton JA, Westhoff C, Howe G, Gammon MD. Diet and benign ovarian tumors (United States). *Cancer Causes Control*. 2000;11(5):389-401. doi:10.1023/A:1008921710400
129. Mier-Cabrera J, Aburto-Soto T, Burrola-Méndez S, et al. Women with endometriosis improved their peripheral antioxidant markers after the application of a high antioxidant diet. *Reprod Biol Endocrinol*. 2009;7. doi:10.1186/1477-7827-7-54
130. Savaris AL, Do Amaral VF. Nutrient intake, anthropometric data and correlations with the systemic antioxidant capacity of women with pelvic endometriosis. *Eur J Obstet Gynecol Reprod Biol*. 2011;158(2):314-318. doi:10.1016/j.ejogrb.2011.05.014
131. Traber MG, Stevens JF. Vitamins C and E: Beneficial effects from a mechanistic perspective. *Free Radic Biol Med*. 2011;51(5):1000-1013. doi:10.1016/j.freeradbiomed.2011.05.017
132. Lambrinoudaki I V., Augoulea A, Christodoulakos GE, et al. Measurable serum markers of oxidative stress response in women with endometriosis. *Fertil Steril*. 2009;91(1):46-50. doi:10.1016/j.fertnstert.2007.11.021
133. Mier-Cabrera J, Jiménez-Zamudio L, García-Latorre E, Cruz-Orozco O, Hernández-Guerrero C. Quantitative and qualitative peritoneal immune profiles, T-cell apoptosis and oxidative stress-associated characteristics in women with minimal and mild endometriosis. *BJOG An Int J Obstet Gynaecol*. 2011;118(1):6-16. doi:10.1111/j.1471-0528.2010.02777.x
134. Harris HR, Chavarro JE, Malspeis S, Willett WC, Missmer SA. Dairy-Food, Calcium, Magnesium, and Vitamin D Intake and Endometriosis: A Prospective Cohort Study. *Am J Epidemiol*. 2013;177(5):420-430. doi:10.1093/AJE/KWS247
135. Zemel MB, Sun X. Dietary calcium and dairy products modulate oxidative and inflammatory stress in mice and humans. *J Nutr*. 2008;138(6):1047-1052. doi:10.1093/jn/138.6.1047
136. Yamamoto A, Harris HR, Vitonis AF, Chavarro JE, Missmer SA. A prospective cohort study of meat and fish consumption and endometriosis risk. *Am J Obstet Gynecol*. 2018;219(2):178.e1-178.e10. doi:10.1016/j.ajog.2018.05.034
137. Cramer DW, Missmer SA. The Epidemiology of Endometriosis. *Ann N Y Acad Sci*. 2002;955(1):11-22. doi:10.1111/J.1749-6632.2002.TB02761.X
138. Missmer SA, Chavarro JE, Malspeis S, et al. A prospective study of dietary fat consumption and endometriosis risk. *Hum Reprod*. 2010;25(6):1528-1535. doi:10.1093/humrep/deq044
139. Li J, Wu B, Selbæk G, Krokstad S, Helvik AS. Factors associated with consumption of alcohol in older adults - A comparison between two cultures, China and Norway: The CLHLS and the HUNT-study. *BMC Geriatr*. 2017;17(1):10-12. doi:10.1186/s12877-017-0562-9

140. Prentice R, Thompson D, Clifford C, Gorbach S, Goldwin B, Byar D. Dietary fat reduction and plasma estradiol concentration in healthy postmenopausal women. *J Natl Cancer Inst*. 1990;82(2):129-134. doi:10.1093/jnci/82.2.129
141. Barnard ND, Scialli AR, Hurlock D, Bertron P. Diet and sex-hormone binding globulin, dysmenorrhea, and premenstrual symptoms. *Obstet Gynecol*. 2000;95(2):245-250. doi:10.1016/S0029-7844(99)00525-6
142. Missmer SA, Chavarro JE, Malspeis S, et al. A prospective study of dietary fat consumption and endometriosis risk. *Hum Reprod*. 2010;25(6):1528-1535. doi:10.1093/humrep/deq044
143. Gazvani MR, Smith L, Haggarty P, Fowler PA, Templeton A. High ω-3:ω-6 fatty acid ratios in culture medium reduce endometrial-cell survival in combined endometrial gland and stromal cell cultures from women with and without endometriosis. *Fertil Steril*. 2001;76(4):717-722. doi:10.1016/S0015-0282(01)01991-4
144. Sørensen LB, Raben A, Stender S, Astrup A. Effect of sucrose on inflammatory markers in overweight humans. *Am J Clin Nutr*. 2005;82(2):421-427. doi:10.1093/ajcn/82.2.421
145. Qi L, Rimm E, Liu S, Rifai N, Hu FB. Dietary glycemic index, glycemic load, cereal fiber, and plasma adiponectin concentration in diabetic men. *Diabetes Care*. 2005;28(5):1022-1028. doi:10.2337/diacare.28.5.1022
146. Esposito K, Nappo F, Giugliano F, et al. Meal modulation of circulating interleukin 18 and adiponectin concentrations in healthy subjects and in patients with type 2 diabetes mellitus. *Am J Clin Nutr*. 2003;78(6):1135-1140. doi:10.1093/ajcn/78.6.1135
147. Ajani UA, Ford ES, Mokdad AH. Dietary Fiber and C-Reactive Protein: Findings from National Health and Nutrition Examination Survey Data. *J Nutr*. 2004;134(5):1181-1185. doi:10.1093/jn/134.5.1181
148. King DE, Egan BM, Geesey ME. Relation of dietary fat and fiber to elevation of C-reactive protein. *Am J Cardiol*. 2003;92(11):1335-1339. doi:10.1016/j.amjcard.2003.08.020
149. Sowers MFR, Crawford S, McConnell DS, et al. Selected diet and lifestyle factors are associated with estrogen metabolites in a multiracial/ethnic population of women. *J Nutr*. 2006;136(6):1588-1595. doi:10.1093/jn/136.6.1588
150. Kaneda N, Nagata C, Kabuto M, Shimizu H. Fat and fiber intakes in relation to serum estrogen concentration in premenopausal Japanese women. *Nutr Cancer*. 1997;27(3):279-283. doi:10.1080/01635589709514538
151. Schwartz NRM, Afeiche MC, Terry KL, et al. Glycemic Index, Glycemic Load, Fiber, and Gluten Intake and Risk of Laparoscopically Confirmed Endometriosis in Premenopausal Women. *J Nutr*. 2022;152(9):2088-2096. doi:10.1093/jn/nxac107
152. Ashrafi M, Jahangiri N, Sadatmahalleh SJ, Aliani F, Akhoond M. Diet and the risk of endometriosis in Iranian women: A case-control study. *Int J Fertil Steril*. 2020;14(3):193-200. doi:10.22074/ijfs.2020.44378
153. Vidal JD, VandeVoort CA, Marcus CB, Lazarewicz NR, Conley AJ. In vitro exposure to environmental tobacco smoke induces CYP1B1 expression

in human luteinized granulosa cells. *Reprod Toxicol*. 2006;22(4):731-737. doi:10.1016/j.reprotox.2006.06.001
154. Sanders SR, Cuneo SP, Turzillo AM. Effects of nicotine and cotinine on bovine theca intema and granulosa cells. *Reprod Toxicol*. 2002;16(6):795-800. doi:10.1016/S0890-6238(02)00049-7
155. Miceli F, Minici F, Tropea A, et al. Effects of nicotine on human luteal cells in vitro: A possible role on reproductive outcome for smoking women. *Biol Reprod*. 2005;72(3). doi:10.1095/biolreprod.104.032318
156. MacMahon B, Trichopoulos D, Cole P, Brown J. Cigarette Smoking and Urinary Estrogens. *N Engl J Med*. 1982;307(17):1062-1065. doi:10.1056/nejm198210213071707
157. Bravi F, Parazzini F, Cipriani S, et al. Tobacco smoking and risk of endometriosis: a systematic review and meta-analysis. *BMJ Open*. 2014;4:6325. doi:10.1136/bmjopen-2014
158. Seitz HK, Pelucchi C, Bagnardi V, La Vecchia C. Epidemiology and pathophysiology of alcohol and breast cancer: Update 2012. *Alcohol Alcohol*. 2012;47(3):204-212. doi:10.1093/alcalc/ags011
159. Singletary KW, Gapstur SM. Alcohol and breast cancer: Review of epidemiologic and experimental evidence and potential mechanisms. *J Am Med Assoc*. 2001;286(17):2143-2151. doi:10.1001/jama.286.17.2143
160. Cassano N, Vestita M, Apruzzi D, Vena GA. Alcohol, psoriasis, liver disease, and anti-psoriasis drugs. *Int J Dermatol*. 2011;50(11):1323-1331. doi:10.1111/j.1365-4632.2011.05100.x
161. Grodstein F, Goldman MB, Cramer DW. Infertility in women and moderate alcohol use. *Am J Public Health*. 1994;84(9):1429-1432. doi:10.2105/AJPH.84.9.1429
162. Perper MM, Breitkopf LJ, Breitstein R, Cody RP, Manowitz P. MAST Scores, Alcohol Consumption, and Gynecological Symptoms in Endometriosis Patients. *Alcohol Clin Exp Res*. 1993;17(2):272-278. doi:10.1111/j.1530-0277.1993.tb00762.x
163. Parazzini F, Cipriani S, Bravi F, et al. A metaanalysis on alcohol consumption and risk of endometriosis. *Am J Obstet Gynecol*. 2013;209(2):106.e1-106.e10. doi:10.1016/j.ajog.2013.05.039
164. Signorello LB, Harlow BL, Cramer DW, Spiegelman D, Hill JA. Epidemiologic determinants of endometriosis: A hospital-based case-control study. *Ann Epidemiol*. 1997;7(4):267-274. doi:10.1016/S1047-2797(97)00017-3
165. Dhillon PK, Holt VL. Recreational physical activity and endometrioma risk. *Am J Epidemiol*. 2003;158(2):156-164. doi:10.1093/aje/kwg122
166. Tworoger SS, Missmer SA, Eliassen AH, Barbieri RL, Dowsett M, Hankinson SE. Physical activity and inactivity in relation to sex hormone, prolactin, and insulin-like growth factor concentrations in premenopausal women: Exercise and premenopausal hormones. *Cancer Causes Control*. 2007;18(7):743-752. doi:10.1007/s10552-007-9017-5
167. Warren MP, Perlroth NE. The effects of intense exercise on the female reproductive system. *J Endocrinol*. 2001;170(1):3-11. doi:10.1677/joe.0.1700003
168. Ricci E, Viganò P, Cipriani S, et al. Physical activity and endometriosis

risk in women with infertility or pain: Systematic review and meta-analysis. *Med (United States)*. 2016;95(40). doi:10.1097/MD.0000000000004957
169. Vitonis AF, Hankinson SE, Hornstein MD, Missmer SA. Adult physical activity and endometriosis risk. *Epidemiology*. 2010;21(1):16-23. doi:10.1097/EDE.0b013e3181c15d40
170. Vitonis AF, Baer HJ, Hankinson SE, Laufer MR, Missmer SA. A prospective study of body size during childhood and early adulthood and the incidence of endometriosis. *Hum Reprod*. 2010;25(5):1325-1334. doi:10.1093/humrep/deq039
171. Kvaskoff M, Bijon A, Clavel-Chapelon F, Mesrine S, Boutron-Ruault MC. Childhood and adolescent exposures and the risk of endometriosis. *Epidemiology*. 2013;24(2):261-269. doi:10.1097/EDE.0b013e3182806445
172. Kennedy S, Mardon H, Barlow D. Familial endometriosis. *J Assist Reprod Genet*. 1995;12(1):32-34. doi:10.1007/BF02214126
173. Stefansson H, Geirsson RT, Steinthorsdottir V, et al. Genetic factors contribute to the risk of developing endometriosis. *Hum Reprod*. 2002;17(3):555-559. doi:10.1093/humrep/17.3.555
174. Zondervan KT, Cardon LR, Kennedy SH. The genetic basis of endometriosis. *Curr Opin Obstet Gynecol*. 2001;13(3):309-314. doi:10.1097/00001703-200106000-00011
175. Matalliotakis M, Goulielmos GN, Zervou MI, Matalliotaki C, Koumantakis G, Matalliotakis I. The familial risk of endometriosis among the female relatives of patients with endometriosis in Greece. *J Endometr Pelvic Pain Disord*. 2017;9(3):184-187. doi:10.5301/JEPPD.5000290/FORMAT/EPUB
176. Gallagher CS, Mäkinen N, Harris HR, et al. Genome-wide association and epidemiological analyses reveal common genetic origins between uterine leiomyomata and endometriosis. *Nat Commun*. 2019;10(1):1-11. doi:10.1038/s41467-019-12536-4
177. Kori M, Gov E, Arga KY. Molecular signatures of ovarian diseases: Insights from network medicine perspective. *Syst Biol Reprod Med*. 2016;62(4):266-282. doi:10.1080/19396368.2016.1197982
178. Matalliotakis IM, Cakmak H, Krasonikolakis GD, et al. Endometriosis related to family history of malignancies in the Yale series. *Surg Oncol*. 2010;19(1):33-37. doi:10.1016/j.suronc.2009.02.012
179. Matalliotakis IM, Cakmak H, Mahutte N, Goumenou AG, Koumantakis G, Arici A. The familial risk of breast cancer in women with endometriosis from Yale series. *Surg Oncol*. 2008;17(4):289-293. doi:10.1016/j.suronc.2008.01.002
180. Kvaskoff M, Mu F, Terry KL, et al. Endometriosis: A high-risk population for major chronic diseases? *Hum Reprod Update*. 2014;21(4):500-516. doi:10.1093/humupd/dmv013
181. Jenabi E, Khazaei S. Endometriosis and migraine headache risk: a meta-analysis. *Women Heal*. 2020;60(8):939-945. doi:10.1080/03630242.2020.1779905
182. Miller JA, Missmer SA, Vitonis AF, Sarda V, Laufer MR, DiVasta AD. Prevalence of migraines in adolescents with endometriosis. doi:10.1016/j.fertnstert.2017.12.016
183. Nyholt DR, Gillespie NG, Merikangas KR, Treloar SA, Martin NG,

Montgomery GW. Common genetic influences underlie comorbidity of migraine and endometriosis. *Genet Epidemiol*. 2009;33(2):105-113. doi:10.1002/gepi.20361
184. Stirparo G, Zicari A, Favilla M, Lipari M, Martelletti P. Linked activation of nitric oxide synthase and cyclooxygenase in peripheral monocytes of asymptomatic migraine without aura patients. *Cephalalgia*. 2000;20(2):100-106. doi:10.1046/j.1468-2982.2000.00025.x
185. Sarchielli P, Alberti A, Codini M, Floridi A, Gallai V. Nitric oxide metabolites, prostaglandins and trigeminal vasoactive peptides in internal jugular vein blood during spontaneous migraine attacks. *Cephalalgia*. 2000;20(10):907-918. doi:10.1046/j.1468-2982.2000.00146.x
186. Karck U, Reister F, Schäfer W, Zahradnik HP, Breckwoldt M. PGE2 and PGF2α Release by Human Peritoneal Macrophages in Endometriosis. *Prostaglandins Other Lipid Mediat*. 1996;51(1):49-60. doi:10.1016/0090-6980(95)00159-X
187. Schenken RS, Asch RH. Surgical induction of endometriosis in the rabbit: Effects on fertility and concentrations of peritoneal fluid prostaglandins. *Fertil Steril*. 1980;34(6):581-587. doi:10.1016/s0015-0282(16)45199-x
188. Ferrero S, Pretta S, Bertoldi S, et al. Increased frequency of migraine among women with endometriosis. *Hum Reprod*. 2004;19(12):2927-2932. doi:10.1093/humrep/deh537
189. Wu CC, Chung SD, Lin HC. Endometriosis increased the risk of bladder pain syndrome/interstitial cystitis: A population-based study. *Neurourol Urodyn*. 2018;37(4):1413-1418. doi:10.1002/nau.23462
190. Lamale LM, Lutgendorf SK, Zimmerman MB, Kreder KJ. Interleukin-6, histamine, and methylhistamine as diagnostic markers for interstitial cystitis. *Urology*. 2006;68(4):702-706. doi:10.1016/j.urology.2006.04.033
191. Ogawa T, Homma T, Igawa Y, et al. CXCR3 Binding Chemokine and TNFSF14 Over Expression in Bladder Urothelium of Patients With Ulcerative Interstitial Cystitis. *J Urol*. 2010;183(3):1206-1212. doi:10.1016/j.juro.2009.11.007
192. Saidi K, Sharma S, Ohlsson B. A systematic review and meta-analysis of the associations between endometriosis and irritable bowel syndrome. *Eur J Obstet Gynecol Reprod Biol*. 2020;246:99-105. doi:10.1016/j.ejogrb.2020.01.031
193. Ek M, Roth B, Ekström P, Valentin L, Bengtsson M, Ohlsson B. Gastrointestinal symptoms among endometriosis patients-A case-cohort study. *BMC Womens Health*. 2015;15(1):1-10. doi:10.1186/s12905-015-0213-2
194. Ek M, Roth B, Nilsson PM, Ohlsson B. Characteristics of endometriosis: A case-cohort study showing elevated IgG titers against the TSH receptor (TRAb) and mental comorbidity. *Eur J Obstet Gynecol Reprod Biol*. 2018;231:8-14. doi:10.1016/J.EJOGRB.2018.09.034
195. Azizi Z, Anbardan SJ, Daryani NE. A Review of the Clinical Manifestations, Pathophysiology and Management of Opioid Bowel Dysfunction and Narcotic Bowel Syndrome. *Middle East J Dig Dis*. 2014;6(1):5. /pmc/articles/PMC4005483/. Accessed November 25, 2022.
196. Hammar O, Roth B, Bengtsson M, Mandl T, Ohlsson B. Autoantibodies

and gastrointestinal symptoms in infertile women in relation to in vitro fertilization. *BMC Pregnancy Childbirth*. 2013;13(1):1-9. doi:10.1186/1471-2393-13-201
197. Moore J, Barlow D, Jewell D, Kennedy S. Do gastrointestinal symptoms vary with the menstrual cycle? *BJOG An Int J Obstet Gynaecol*. 1998;105(12):1322-1325. doi:10.1111/j.1471-0528.1998.tb10014.x
198. Shah E, Rezaie A, Riddle M, Pimentel M. Psychological disorders in gastrointestinal disease: Epiphenomenon, cause or consequence? *Ann Gastroenterol*. 2014;27(3):224-230. /pmc/articles/PMC4073018/. Accessed November 25, 2022.
199. Barrier BF. Immunology of endometriosis. *Clin Obstet Gynecol*. 2010;53(2):397-402. doi:10.1097/GRF.0b013e3181db7c33
200. Eisenberg VH, Zolti M, Soriano D. Is there an association between autoimmunity and endometriosis? *Autoimmun Rev*. 2012;11(11):806-814. doi:10.1016/j.autrev.2012.01.005
201. de Barros IBL, Malvezzi H, Gueuvoghlanian-Silva BY, Piccinato CA, Rizzo LV, Podgaec S. "What do we know about regulatory T cells and endometriosis? A systematic review." *J Reprod Immunol*. 2017;120:48-55. doi:10.1016/j.jri.2017.04.003
202. Izumi G, Koga K, Takamura M, et al. Involvement of immune cells in the pathogenesis of endometriosis. *J Obstet Gynaecol Res*. 2018;44(2):191-198. doi:10.1111/jog.13559
203. Matalliotakis I, Cakmak H, Matalliotakis M, Kappou D, Arici A. High rate of allergies among women with endometriosis. *J Obstet Gynaecol (Lahore)*. 2012;32(3):291-293. doi:10.3109/01443615.2011.644358
204. Harris HR, Korkes KMN, Li T, et al. Endometriosis, Psoriasis, and Psoriatic Arthritis: A Prospective Cohort Study. *Am J Epidemiol*. 2022;191(6):1050-1060. doi:10.1093/AJE/KWAC009
205. Ferrero S, Petrera P, Colombo BM, et al. Asthma in women with endometriosis. *Hum Reprod*. 2005;20(12):3514-3517. doi:10.1093/humrep/dei263
206. Rahmioglu N, Nyholt DR, Morris AP, Missmer SA, Montgomery GW, Zondervan KT. Genetic variants underlying risk of endometriosis: Insights from meta-analysis of eight genome-wide association and replication datasets. *Hum Reprod Update*. 2014;20(5):702-716. doi:10.1093/humupd/dmu015
207. Uno S, Zembutsu H, Hirasawa A, et al. A genome-wide association study identifies genetic variants in the CDKN2BAS locus associated with endometriosis in Japanese. *Nat Genet*. 2010;42(8):707-710. doi:10.1038/ng.612
208. Samani NJ, Erdmann J, Hall AS, et al. Genomewide Association Analysis of Coronary Artery Disease. *N Engl J Med*. 2007;357(5):443-453. doi:10.1056/nejmoa072366
209. Helgadottir A, Thorleifsson G, Manolescu A, et al. A common variant on chromosome 9p21 affects the risk of myocardial infarction. *Science (80-)*. 2007;316(5830):1491-1493. doi:10.1126/science.1142842
210. McPherson R, Pertsemlidis A, Kavaslar N, et al. A common allele on chromosome 9 associated with coronary heart disease. *Science (80-)*.

2007;316(5830):1488-1491. doi:10.1126/science.1142447
211. Farland L V., Degnan WJ, Harris HR, Tobias DK, Missmer SA. A prospective study of endometriosis and risk of type 2 diabetes. *Diabetologia*. 2021;64(3):552-560. doi:10.1007/s00125-020-05347-6
212. Tobias DK, Gaskins AJ, Missmer SA, et al. History of infertility and risk of type 2 diabetes mellitus: a prospective cohort study. *Diabetologia*. 2015;58(4):707-715. doi:10.1007/s00125-015-3493-z
213. Reaven GM. Role of insulin resistance in human disease. *Diabetes*. 1988;37(12):1595-1607. doi:10.2337/diab.37.12.1595
214. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. *Nature*. 2006;444(7121):840-846. doi:10.1038/nature05482
215. Ross R. Malaria in Cyprus and, Greece. *Proc R Soc Med*. 1914;7(Epidem_State_Me):107-118. doi:10.1177/003591571400701505
216. Weatherall DJ, Williams TN, Allen SJ, O'Donnell A. The population genetics and dynamics of the thalassemias. *Hematol Oncol Clin North Am*. 2010;24(6):1021-1031. doi:10.1016/j.hoc.2010.08.010
217. Bozkurt G. Results from the North Cyprus Thalassemia Prevention Program. *Hemoglobin*. 2007;31(2):257-264. doi:10.1080/03630260701297204
218. Kyrri AR, Kalogerou E, Loizidou D, et al. The changing epidemiology of β-Thalassemia in the greek-cypriot population. *Hemoglobin*. 2013;37(5):435-443. doi:10.3109/03630269.2013.801851
219. Dolai TK, Nataraj KS, Sinha N, Mishra S, Bhattacharya M, Ghosh MK. Prevalance of iron deficiency in thalassemia minor: A study from tertiary hospital. *Indian J Hematol Blood Transfus*. 2012;28(1):7-9. doi:10.1007/s12288-011-0088-9
220. Atkins HM, Appt SE, Taylor RN, et al. Systemic Iron Deficiency in a Nonhuman Primate Model of Endometriosis. *Comp Med*. 2018;68(4):298. doi:10.30802/AALAS-CM-17-000082
221. Kassebaum NJ, Jasrasaria R, Naghavi M, et al. A systematic analysis of global anemia burden from 1990 to 2010. *Blood*. 2014;123(5):615-624. doi:10.1182/blood-2013-06-508325
222. Cooke AG, McCavit TL, Buchanan GR, Powers JM. Iron Deficiency Anemia in Adolescents Who Present with Heavy Menstrual Bleeding. *J Pediatr Adolesc Gynecol*. 2017;30(2):247-250. doi:10.1016/j.jpag.2016.10.010
223. Kvaskoff M, Mesrine S, Clavel-Chapelon F, Boutron-Ruault M-C. Endometriosis risk in relation to naevi, freckles and skin sensitivity to sun exposure: the French E3N cohort. *Int J Epidemiol*. 2009;38:1143-1153. doi:10.1093/ije/dyp175
224. Kvaskoff M, Han J, Qureshi AA, Missmer SA. Pigmentary traits, family history of melanoma and the risk of endometriosis: A cohort study of US women. *Int J Epidemiol*. 2014;43(1):255-263. doi:10.1093/ije/dyt235
225. FRISCH RE, WYSHAK G, ALBERT LS, SOBER AJ. Dysplastic Nevi, Cutaneous Melanoma, and Gynecologic Disorders. *Int J Dermatol*. 1992;31(5):331-335. doi:10.1111/j.1365-4362.1992.tb03948.x
226. Hornstein MD, Thomas PP, Sober AJ, Wyshak G, Albright NL, Frisch RE.

Association between endometriosis, dysplastic naevi and history of melanoma in women of reproductive age. *Hum Reprod*. 1997;12(1):143-145. doi:10.1093/humrep/12.1.143
227. Vercellini P, Buggio L, Somigliana E, Dridi D, Marchese MA, Viganò P. 'Behind blue eyes'†: The association between eye colour and deep in filtrating endometriosis. *Hum Reprod*. 2014;29(10):2171-2175. doi:10.1093/humrep/deu169
228. Somigliana E, Vigan P, Abbiati A, et al. "Here comes the sun": Pigmentary traits and sun habits in women with endometriosis. *Hum Reprod*. 2010;25(3):728-733. doi:10.1093/humrep/dep453
229. Salmeri N, Ottolina J, Bartiromo L, et al. 'Guess who'? An Italian multicentric study on pigmentation traits prevalence in endometriosis localizations. *Eur J Obstet Gynecol Reprod Biol*. 2022;274:5-12. doi:10.1016/j.ejogrb.2022.05.001
230. Missmer SA, Spiegelman D, Hankinson SE, Malspeis S, Barbieri RL, Hunter DJ. Natural hair color and the incidence of endometriosis. *Fertil Steril*. 2006;85(4):866-870. doi:10.1016/j.fertnstert.2005.12.008
231. Wyshak G, Frisch RE. Red hair color, melanoma, and endometriosis: Suggestive associations. *Int J Dermatol*. 2000;39(10):795-800. doi:10.1046/j.1365-4362.2000.00051-2.x
232. Viganò P, Somigliana E, Panina P, Rabellotti E, Vercellini P, Candiani M. Principles of phenomics in endometriosis. *Hum Reprod Update*. 2012;18(3):248-259. doi:10.1093/humupd/dms001
233. Sturm RA. Skin colour and skin cancer - MC1R, the genetic link. *Melanoma Res*. 2002;12(5):405-416. doi:10.1097/00008390-200209000-00001
234. Olsen CM, Pandeya N, Thompson BS, et al. Association between Phenotypic Characteristics and Melanoma in a Large Prospective Cohort Study. *J Invest Dermatol*. 2019;139(3):665-672. doi:10.1016/j.jid.2018.09.022
235. Saraswat L, Ayansina D, Cooper KG, Bhattacharya S. Risk of melanoma in women with endometriosis: A Scottish national cohort study. *Eur J Obstet Gynecol Reprod Biol*. 2021;257:144-148. doi:10.1016/j.ejogrb.2020.12.033
236. Farland L V., Lorrain S, Missmer SA, et al. Endometriosis and the risk of skin cancer: a prospective cohort study. *Cancer Causes Control*. 2017;28(10):1011-1019. doi:10.1007/s10552-017-0939-2
237. Kvaskoff M, Mesrine S, Fournier A, Boutron-Ruault MC, Clavel-Chapelon F. Personal history of endometriosis and risk of cutaneous melanoma in a large prospective cohort of French women. *Arch Intern Med*. 2007;167(19):2061-2065. doi:10.1001/archinte.167.19.2061
238. Yang F, Mortlock S, MacGregor S, et al. Genetic Relationship Between Endometriosis and Melanoma. *Front Reprod Heal*. 2021;3:50. doi:10.3389/frph.2021.711123
239. Farland L V., Degnan WJ, Harris HR, et al. Recreational and residential sun exposure and risk of endometriosis: A prospective cohort study. *Hum Reprod*. 2021;36(1):199-210. doi:10.1093/humrep/deaa280
240. Møller P, Wallin H, Holst E, Knudsen LE. Sunlight-induced DNA damage

in human mononuclear cells. *FASEB J*. 2002;16(1):45-53. doi:10.1096/fj.01-0386com
241. Narbutt J, Cebula B, Lesiak A, et al. The effect of repeated exposures to low-dose UV radiation on the apoptosis of peripheral blood mononuclear cells. *Arch Dermatol*. 2009;145(2):133-138. doi:10.1001/archdermatol.2008.574
242. Muthusamy V, Piva TJ. The UV response of the skin: A review of the MAPK, NFκB and TNFα signal transduction pathways. *Arch Dermatol Res*. 2010;302(1):5-17. doi:10.1007/S00403-009-0994-Y/FIGURES/4
243. Arnson Y, Amital H, Shoenfeld Y. Vitamin D and autoimmunity: New aetiological and therapeutic considerations. *Ann Rheum Dis*. 2007;66(9):1137-1142. doi:10.1136/ard.2007.069831
244. Kalaitzopoulos DR, Lempesis IG, Athanasaki F, et al. Association between vitamin D and endometriosis: a systematic review. *Hormones*. 2020;19(2):109-121. doi:10.1007/s42000-019-00166-w
245. Anastasi E, Fuggetta E, De Vito C, et al. Low levels of 25-OH Vitamin D in women with endometriosis and associated pelvic pain. *Clin Chem Lab Med*. 2017;55(12):e282-e284. doi:10.1515/CCLM-2017-0016/MACHINEREADABLECITATION/RIS
246. Baek JC, Jo JY, Lee SM, et al. Differences in 25-hydroxy vitamin D and vitamin D-binding protein concentrations according to the severity of endometriosis. *Clin Exp Reprod Med*. 2019;46(3):125-131. doi:10.5653/cerm.2018.00416
247. Almassinokiani F, Khodaverdi S, Solaymani-Dodaran M, Akbari P, Pazouki A. Effects of vitamin D on endometriosis-related pain: A double-blind clinical trial. *Med Sci Monit*. 2016;22:4960-4966. doi:10.12659/MSM.901838
248. Nodler JL, Divasta AD, Vitonis AF, et al. Supplementation with vitamin D or ω-3 fatty acids in adolescent girls and young women with endometriosis (SAGE): A double-blind, randomized, placebo-controlled trial. *Am J Clin Nutr*. 2020;112(1):229-236. doi:10.1093/ajcn/nqaa096
249. Lee S-Y, Koo Y-J, Lee D-H. Classification of endometriosis. *Yeungnam Univ J Med*. 2021;38(1):10. doi:10.12701/YUJM.2020.00444
250. Farland L V., Collier ARY, Correia KF, et al. Who receives a medical evaluation for infertility in the United States? *Fertil Steril*. 2016;105(5):1274-1280. doi:10.1016/j.fertnstert.2015.12.132
251. Zondervan KT, Cardon LR, Kennedy SH. What makes a good case-control study? Design issues for complex traits such as endometriosis. *Hum Reprod*. 2002;17(6):1415-1423. doi:10.1093/humrep/17.6.1415
252. Farland L V., Missmer SA, Rich-Edwards J, Chavarro JE, Barbieri RL, Grodstein F. Use of fertility treatment modalities in a large United States cohort of professional women. *Fertil Steril*. 2014;101(6):1705-1710. doi:10.1016/j.fertnstert.2014.03.016
253. Rahmioglu N, Naci H, Cylus J. Improving health care services in Northern Cyprus: A call for research and action. *Eur J Public Health*. 2012;22(6):754-755. doi:10.1093/eurpub/cks145
254. Bryant R. History's remainders: On time and objects after conflict in Cyprus. *Am Ethnol*. 2014;41(4):681-697. doi:10.1111/amet.12105

255. Colditz GA, Philpott SE, Hankinson SE. The impact of the nurses' health study on population health: Prevention, translation, and control. *Am J Public Health*. 2016;106(9):1540-1545. doi:10.2105/AJPH.2016.303343
256. Banks E, Richardson A, Beral V, et al. Effect on attendance at breast cancer screening of adding a self administered questionnaire to the usual invitation to breast screening in southern England. *J Epidemiol Community Health*. 1998;52(2):116-119. doi:10.1136/jech.52.2.116
257. Hocaoglu MB, Gurkas S, Karaderi T, et al. Cyprus Women's Health Research (COHERE) initiative: Determining the relative burden of women's health conditions and related co-morbidities in an Eastern Mediterranean population. *BMC Womens Health*. 2019;19(1):1-7. doi:10.1186/s12905-019-0750-1
258. Swift B, Naci H, Taneri B, Becker CM, Zondervan KT, Rahmioglu N. The Cyprus Women's Health Research (COHERE) initiative: normative data from the SF-36v2 questionnaire for reproductive aged women from the Eastern Mediterranean. *Qual Life Res*. 2022;31(7):2011-2022. doi:10.1007/s11136-022-03100-7
259. Vitonis AF, Vincent K, Rahmioglu N, et al. World Endometriosis Research Foundation Endometriosis Phenome and biobanking harmonization project: II. Clinical and covariate phenotype data collection in endometriosis research. *Fertil Steril*. 2014;102(5):1223-1232. doi:10.1016/j.fertnstert.2014.07.1244
260. Boonstra AM, Stewart RE, Albère AJ, et al. Cut-offpoints for mild, moderate, and severe pain on the numeric rating scale for pain in patients with chronic musculoskeletal pain: Variability and influence of sex and catastrophizing. *Front Psychol*. 2016;7(SEP):1466. doi:10.3389/fpsyg.2016.01466
261. Sullivan M, Bishop S, Pivik J. *The Pain Catastrophizing Scale: User Manual*. Vol 7.; 1995. http://sullivan-painresearch.mcgill.ca/pdf/pcs/PCSManual_English.pdf%5Cnhttp://psycnet.apa.org/journals/pas/7/4/524/. Accessed April 8, 2020.
262. Melzack R. The McGill Pain Questionnaire: Major properties and scoring methods. *Pain*. 1975;1:277-299.
263. Lacy BE, Patel NK. Rome criteria and a diagnostic approach to irritable bowel syndrome. *J Clin Med*. 2017;6(11):99. doi:10.3390/jcm6110099
264. Tom T, Brody M, Valabhji A, Turner L, Molgaard C, Rothrock J. Validation of a new instrument for determining migraine prevalence: The UCSD migraine questionnaire. *Neurology*. 1994;44(5):925-928. doi:10.1212/wnl.44.5.925
265. Ware Jr JE, Kosinski M, Turner-Bowker DM, Gandek B. *How to Score Version 2 of the SF-36 Health Survey. Lincoln, RI: QualityMetric*.; 2000.
266. Reilly MC, Zbrozek AS, Dukes EM. The Validity and Reproducibility of a Work Productivity and Activity Impairment Instrument. *Pharmacoeconomics*. 1993;4(5):353-365. doi:10.2165/00019053-199304050-00006
267. Chasan-Taber S, Rimm EB, Stampfer MJ, et al. Reproducibility and validity of a self-administered physical activity questionnaire for male health professionals. *Epidemiology*. 1996;7(1):81-86.

doi:10.1097/00001648-199601000-00014
268. Chen CX, Kwekkeboom KL, Ward SE. Self-report pain and symptom measures for primary dysmenorrhoea: A critical review. *Eur J Pain*. 2015;19(3):377-391. doi:10.1002/ejp.556
269. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF. *Arthritis Care Res*. 2011;63(SUPPL. 11):S240-S252. doi:10.1002/acr.20543
270. Quartana PJ, Campbell CM, Edwards RR. Pain catastrophizing a critical review. *Expert Rev Neurother*. 2009;9(5):745-758. doi:10.1586/ern.09.34
271. Ugurlu M, Karakas Ugurlu G, Erten S, Caykoylu A. Validity of Turkish form of pain catastrophizing scale and modeling of the relationship between pain-related disability with pain intensity, cognitive, and emotional factors. *Psychiatry Clin Psychopharmacol*. 2017;27(2):189-196. doi:10.1080/24750573.2017.1322672
272. Burckhardt CS. The use of the McGill Pain Questionnaire in assessing arthritis pain. *Pain*. 1984;19(3):305-314. doi:10.1016/0304-3959(84)90007-1
273. International Headache Society. Migraine - ICHD-3. https://ichd-3.org/1-migraine/1-1-migraine-without-aura/. Accessed August 11, 2020.
274. Menken M. The Little Black Book of Neurology: A Manual for Neurological House Officers. *Neurology*. 1987;37(9):1573-1573. doi:10.1212/wnl.37.9.1573-a
275. Demiral Y, Ergor G, Unal B, et al. Normative data and discriminative properties of short form 36 (SF-36) in Turkish urban population. *BMC Public Health*. 2006;6. doi:10.1186/1471-2458-6-247
276. Mis C, Kofali G, Swift B, et al. Protocol for the Cultural Translation and Adaptation of the World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonization Project Endometriosis Participant Questionnaire (EPHect). *Front Glob Women's Heal*. 2021;0:11. doi:10.3389/FGWH.2021.644609
277. WHO. *Waist Circumference and Waist–Hip Ratio*. Vol 64.; 2011. http://www.nature.com/doifinder/10.1038/ejcn.2009.139. Accessed September 2, 2020.
278. Gunes FE, Imeryuz N, Akalin A, et al. Development and validation of a semi-quantitative food frequency questionnaire to assess dietary intake in Turkish adults. *J Pakistan Med Assoc*. 2015;65(7):756-763. https://jpma.org.pk/article-details/7407?article_id=7407. Accessed March 2, 2020.
279. Yusuf S, Islam S, Chow CK, et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): A prospective epidemiological survey. *Lancet*. 2011;378(9798):1231-1243. doi:10.1016/S0140-6736(11)61215-4
280. Teo K, Chow CK, Vaz M, et al. The Prospective Urban Rural Epidemiology (PURE) study: Examining the impact of societal influences

on chronic noncommunicable diseases in low-, middle-, and high-income countries. *Am Heart J*. 2009;158(1):7.e1. doi:10.1016/j.ahj.2009.04.019
281. Hu FB, Bronner L, Willett WC, et al. Fish and Omega-3 Fatty Acid Intake and Risk of Coronary Heart Disease in Women. *JAMA*. 2002;287(14):1815-1821. doi:10.1001/JAMA.287.14.1815
282. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean Diet and Survival in a Greek Population. *N Engl J Med*. 2003;348(26):2599-2608. doi:10.1056/nejmoa025039
283. Trichopoulou A, Kouris-Blazos A, Wahlqvist ML, et al. Diet and overall survival in elderly people. *BMJ*. 1995;311(7018):1457. doi:10.1136/bmj.311.7018.1457
284. Buckland G, Agudo A, Luján L, et al. Adherence to a Mediterranean diet and risk of gastric adenocarcinoma within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. *Am J Clin Nutr*. 2010;91(2):381-390. doi:10.3945/AJCN.2009.28209
285. International Standard Classification of Occupations (ISCO). In: *Encyclopedia of Quality of Life and Well-Being Research*. Springer Netherlands; 2014:3336-3336. doi:10.1007/978-94-007-0753-5_102084
286. Hawthorne G, Osborne RH, Taylor A, Sansoni J. The SF36 Version 2: Critical analyses of population weights, scoring algorithms and population norms. *Qual Life Res*. 2007;16(4):661-673. doi:10.1007/s11136-006-9154-4
287. Çelik D, Çoban Ö. Short Form Health Survey version-2.0 Turkish (SF-36v2) is an efficient outcome parameter in musculoskeletal research. *Acta Orthop Traumatol Turc*. 2016;50(5):558-561. doi:10.1016/j.aott.2016.08.013
288. Acock AC. Working with missing values. *J Marriage Fam*. 2005;67(4):1012-1028. doi:10.1111/j.1741-3737.2005.00191.x
289. Jenkinson C, Stewart-Brown S, Petersen S, Paice C. Assessment of the SF-36 version 2 in the United Kingdom. *J Epidemiol Community Health*. 1999;53(1):46-50. doi:10.1136/jech.53.1.46
290. Caetano R, Ramisetty-Mikler S, McGrath C. Characteristics of non-respondents in a US national longitudinal survey on drinking and intimate partner violence. *Addiction*. 2003;98(6):791-797. doi:10.1046/j.1360-0443.2003.00407.x
291. Korkeila K, Suominen S, Ahvenainen J, et al. Non-response and related factors in a nation-wide health survey. *Eur J Epidemiol*. 2001;17(11):991-999. doi:10.1023/A:1020016922473
292. Reinikainen J, Tolonen H, Borodulin K, et al. Participation rates by educational levels have diverged during 25 years in Finnish health examination surveys. *Eur J Public Health*. 2018;28(2):237-243. doi:10.1093/eurpub/ckx151
293. Reitsma MB, Kendrick PJ, Ababneh E, et al. Spatial, temporal, and demographic patterns in prevalence of smoking tobacco use and attributable disease burden in 204 countries and territories, 1990–2019: a systematic analysis from the Global Burden of Disease Study 2019. *Lancet*. 2021;397(10292):2337-2360. doi:10.1016/S0140-6736(21)01169-7

294. Çebi Karaaslan K, Karaaslan A. A study of factors affecting the alcohol consumption in Turkey. *J Subst Use*. 2022;27(4):422-427. doi:10.1080/14659891.2021.1953168
295. Watt RG, Heilmann A, Sabbah W, et al. Social relationships and health related behaviors among older US adults. *BMC Public Health*. 2014;14(1):1-11. doi:10.1186/1471-2458-14-533/TABLES/5
296. Lee S, Cho E, Grodstein F, Kawachi I, Hu FB, Colditz GA. Effects of marital transitions on changes in dietary and other health behaviours in US women. *Int J Epidemiol*. 2005;34(1):69-78. doi:10.1093/ije/dyh258
297. Li J, Powdthavee N. Does more education lead to better health habits? Evidence from the school reforms in Australia. *Soc Sci Med*. 2015;127:83-91. doi:10.1016/j.socscimed.2014.07.021
298. Public Health England. *Government Dietary Recommendations: Government Recommendations for Energy and Nutrients for Males and Females Aged 1 – 18 Years and 19+ Years.*; 2016. www.gov.uk/phe. Accessed September 15, 2020.
299. Delaney Burke J. *Dietary Guidelines for Americans*. Vol 50.; 2015. doi:10.1097/nt.0000000000000104
300. Buckland G, Agudo A, Luján L, et al. Adherence to a Mediterranean diet and risk of gastric adenocarcinoma within the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. *Am J Clin Nutr*. 2010;91(2):381-390. doi:10.3945/ajcn.2009.28209
301. Freedman LS, Midthune D, Arab L, et al. Combining a Food Frequency Questionnaire with 24-Hour Recalls to Increase the Precision of Estimation of Usual Dietary Intakes-Evidence from the Validation Studies Pooling Project. *Am J Epidemiol*. 2018;187(10):2227-2232. doi:10.1093/aje/kwy126
302. EuroStat. Eurostat Data Browser - Breast cancer and cervical cancer screenings. https://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=hlth_ps_scre&lang=en. Published 2021. Accessed April 20, 2020.
303. UK Health Security Agency. *Human Papillomavirus (HPV) Vaccination Coverage in Adolescent Females and Males in England: 2020 to 2021*.; 2021.
304. Nguyen-Huu NH, Thilly N, Derrough T, et al. Human papillomavirus vaccination coverage, policies, and practical implementation across Europe. *Vaccine*. 2020;38(6):1315-1331. doi:10.1016/j.vaccine.2019.11.081
305. Office of National Statistics. Breast screening programme. *BMJ*. 2021;298(6665). doi:10.1136/bmj.298.6665.48-c
306. Kallner HK, Thunell L, Brynhildsen J, Lindeberg M, Danielsson KG. Use of contraception and attitudes towards contraceptive use in Swedish women - A nationwide survey. *PLoS One*. 2015;10(5):e0125990. doi:10.1371/journal.pone.0125990
307. Office of National Statistics. Statistics on Sexual and Reproductive Health Services (Contraception). 2018;(April). www.statisticsauthority.gov.uk/assessment/code-of-. Accessed April 20, 2020.

308. Roser K, Mader L, Baenziger J, Sommer G, Kuehni CE, Michel G. Health-related quality of life in Switzerland: normative data for the SF-36v2 questionnaire. *Qual Life Res*. 2019;28:1963-1977. doi:10.1007/s11136-019-02161-5
309. Ware, J.E., Kosinski, M., Keller SD. *SF-36 Physical and Mental Health Summary Scales: A User's Manual*. Boston: The Health Assessment Lab, New England Medical Centre; 1994. https://www.researchgate.net/publication/292390260_SF-36_Physical_and_Mental_Health_Summary_Scales_a_User's_Manual. Accessed March 2, 2020.
310. Pappa E, Kontodimopoulos N, Niakas D. Validating and norming of the Greek SF-36 Health Survey. *Qual Life Res 2005 145*. 2005;14(5):1433-1438. doi:10.1007/S11136-004-6014-Y
311. Morawa E, Erim Y. Health-related quality of life and sense of coherence among Polish immigrants in Germany and indigenous Poles. *Transcult Psychiatry*. 2015;52(3):376-395. doi:10.1177/1363461514565851
312. Wiking E, Johansson SE, Sundquist J. Ethnicity, acculturation, and self reported health. A population based study among immigrants from Poland, Turkey, and Iran in Sweden. *J Epidemiol Community Health*. 2004;58(7):574-582. doi:10.1136/jech.2003.011387
313. Lindström M, Sundquist J, Östergren PO. Ethnic differences in self reported health in Malmö in southern Sweden. *J Epidemiol Community Health*. 2001;55(2):97-103. doi:10.1136/jech.55.2.97
314. USDA. 2015-2020 Dietary Guidelines for Americans. 2015. http://health.gov/dietaryguidelines/2015/guidelines/. Accessed December 7, 2022.
315. U.S. Food and Drug Administration (FDA). Food Labeling: Revision of the Nutrition and Supplement Facts Labels (Docket No. FDA- 2012-N-1210; RIN 0910-AF22). 2016;9(c):1-29. https://s3.amazonaws.com/public-inspection.federalregister.gov/2016-11867.pdf%0Ahttp://www.regulations.gov/#!documentDetail%5CnD=FDA-2012-N-1210-0499.
316. SACN. Salt and Health Scientific Advisory Committee on Nutrition 2003 The Stationery Office. 2003:1-134. www.sacn.gov.uk. Accessed December 7, 2022.
317. Public Health England. *Nutrient Intakes*.; 2014.
318. US Department for Agriculture, Services, Human UD for H and. *Dietary Guidelines For Americans*.; 2010. doi:10.1249/01.mss.0000517749.27083.df
319. Trumbo P, Schlicker S, Yates AA, Poos M. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids. *J Am Diet Assoc*. 2002;102(11):1621-1630. doi:10.1016/S0002-8223(02)90346-9
320. Agarwal SK, Chapron C, Giudice LC, et al. Clinical diagnosis of endometriosis: a call to action. *Am J Obstet Gynecol*. 2019;220(4):354.e1-354.e12. doi:10.1016/j.ajog.2018.12.039
321. Shafrir AL, Farland L V., Shah DK, et al. Risk for and consequences of endometriosis: A critical epidemiologic review. *Best Pract Res Clin Obstet*

Gynaecol. 2018;51:1-15. doi:10.1016/j.bpobgyn.2018.06.001
322. Ballard KD, Seaman HE, De Vries CS, Wright JT. Can symptomatology help in the diagnosis of endometriosis? Findings from a national case-control study - Part 1. *BJOG An Int J Obstet Gynaecol*. 2008;115(11):1382-1391. doi:10.1111/j.1471-0528.2008.01878.x
323. Ballard K, Lowton K, Wright J. What's the delay? A qualitative study of women's experiences of reaching a diagnosis of endometriosis. *Fertil Steril*. 2006;86(5):1296-1301. doi:10.1016/j.fertnstert.2006.04.054
324. Shafrir AL, Wise LA, Palmer JR, et al. Validity of self-reported endometriosis: a comparison across four cohorts. *Hum Reprod*. 2021;36(5):1268-1278. doi:10.1093/HUMREP/DEAB012
325. World Health Organization. ICD-11. https://icd.who.int/en. Accessed August 26, 2020.
326. Fisher C, Adams J, Hickman L, Sibbritt D. The use of complementary and alternative medicine by 7427 Australian women with cyclic perimenstrual pain and discomfort: A cross-sectional study. *BMC Complement Altern Med*. 2016;16(1):1-11. doi:10.1186/s12906-016-1119-8
327. Vos T, Barber RM, Bell B, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015;386(9995):743-800. doi:10.1016/S0140-6736(15)60692-4
328. Rosefort A, Huchon C, Estrade S, Paternostre A, Bernard JP, Fauconnier A. Is training sufficient for ultrasound operators to diagnose deep infiltrating endometriosis and bowel involvement by transvaginal ultrasound? *J Gynecol Obstet Hum Reprod*. 2019;48(2):109-114. doi:10.1016/j.jogoh.2018.04.004
329. Tammaa A, Fritzer N, Strunk G, Krell A, Salzer H, Hudelist G. Learning curve for the detection of pouch of Douglas obliteration and deep infiltrating endometriosis of the rectum. *Hum Reprod*. 2014;29(6):1199-1204. doi:10.1093/humrep/deu078
330. Holland TK, Cutner A, Saridogan E, Mavrelos D, Pateman K, Jurkovic D. Ultrasound mapping of pelvic endometriosis: Does the location and number of lesions affect the diagnostic accuracy? A multicentre diagnostic accuracy study. *BMC Womens Health*. 2013;13(1). doi:10.1186/1472-6874-13-43
331. Faber J, Fonseca LM. How sample size influences research outcomes. *Dental Press J Orthod*. 2014;19(4):27-29. doi:10.1590/2176-9451.19.4.027-029.ebo
332. Tewhaiti-Smith J, Semprini A, Bush D, et al. An Aotearoa New Zealand survey of the impact and diagnostic delay for endometriosis and chronic pelvic pain Chronic pelvic pain (CPP) causes important negative effects on quality of life. 123AD. doi:10.1038/s41598-022-08464-x
333. Staal AHJ, Van Der Zanden M, Nap AW. Diagnostic Delay of Endometriosis in the Netherlands. *Gynecol Obstet Invest*. 2016;81(4):321-324. doi:10.1159/000441911
334. Mathias SD, Kuppermann M, Liberman RF, Lipschutz RC, Steege JF. Chronic pelvic pain: Prevalence, health-related quality of life, and

economic correlates. *Obstet Gynecol*. 1996;87(3):321-327. doi:10.1016/0029-7844(95)00458-0
335. Viganò P, Parazzini F, Somigliana E, Vercellini P. Endometriosis: Epidemiology and aetiological factors. *Best Pract Res Clin Obstet Gynaecol*. 2004;18(2):177-200. doi:10.1016/j.bpobgyn.2004.01.007
336. Cyprus Women's Health Research Society (CoHERS). *Measuring Awareness on Menstruation and Endometriosis (S-0160; Supported by Grow Civic Project Funded by the EU)*.; 2020.
337. Randhawa AE, Tufte-Hewett AD, Weckesser AM, Jones GL, Hewett FG. Secondary School Girls' Experiences of Menstruation and Awareness of Endometriosis: A Cross-Sectional Study. *J Pediatr Adolesc Gynecol*. 2021;34(5):643-648. doi:10.1016/j.jpag.2021.01.021
338. Asut O, Ozenli O, Gur G, et al. The knowledge and perceptions of the first year medical students of an International University on family planning and emergency contraception in Nicosia (TRNC) 11 Medical and Health Sciences 1117 Public Health and Health Services. *BMC Womens Health*. 2018;18(1). doi:10.1186/s12905-018-0641-x
339. Flores-Caldera I, Ramos-Echevarría PM, Oliveras-Torres JA, et al. Ibero-American Endometriosis Patient Phenome: Demographics, Obstetric-Gynecologic Traits, and Symptomatology. *Front Reprod Heal*. 2021;3:15. doi:10.3389/frph.2021.667345
340. Cobellis L, Razzi S, De Simone S, et al. The treatment with a COX-2 specific inhibitor is effective in the management of pain related to endometriosis. *Eur J Obstet Gynecol Reprod Biol*. 2004;116(1):100-102. doi:10.1016/j.ejogrb.2004.02.007
341. Zondervan KT, Yudkin PL, Vessey MP, et al. The community prevalence of chronic pelvic pain in women and associated illness behaviour. *Br J Gen Pract*. 2001;51(468):541-547. /pmc/articles/PMC1314045/?report=abstract. Accessed August 25, 2020.
342. Grace VM, Zondervan KT. Chronic pelvic pain in New Zealand: Prevalence, pain severity, diagnoses and use of the health services. *Aust N Z J Public Health*. 2004;28(4):369-375. doi:10.1111/j.1467-842X.2004.tb00446.x
343. Moradi Y, Shams-Beyranvand M, Khateri S, et al. A systematic review on the prevalence of endometriosis in women. *Indian J Med Res*. 2021;154(3):446-454. doi:10.4103/ijmr.IJMR_817_18
344. Nunnink S, Meana M. Remembering the pain: Accuracy of pain recall in endometriosis. *J Psychosom Obstet Gynecol*. 2007;28(4):201-208. doi:10.1080/01674820701388781
345. Kennedy S. Should a diagnosis of endometriosis be sought in all symptomatic women? doi:10.1016/j.fertnstert.2006.06.047
346. Schomacker ML, Hansen KE, Ramlau-Hansen CH, Forman A. Is endometriosis associated with irritable bowel syndrome? A cross-sectional study. *Eur J Obstet Gynecol Reprod Biol*. 2018;231:65-69. doi:10.1016/j.ejogrb.2018.10.023
347. Viganò D, Zara F, Usai P. Irritable bowel syndrome and endometriosis: New insights for old diseases. *Dig Liver Dis*. 2018;50(3):213-219. doi:10.1016/j.dld.2017.12.017

348. Maroun P, Cooper MJW, Reid GD, Keirse MJNC. Relevance of gastrointestinal symptoms in endometriosis. *Aust New Zeal J Obstet Gynaecol*. 2009;49(4):411-414. doi:10.1111/j.1479-828X.2009.01030.x
349. Carey ET, Martin CE, Siedhoff MT, Bair ED, As-Sanie S. Biopsychosocial correlates of persistent postsurgical pain in women with endometriosis. *Int J Gynecol Obstet*. 2014;124(2):169-173. doi:10.1016/j.ijgo.2013.07.033
350. Martin CE, Johnson E, Wechter ME, Leserman J, Zolnoun DA. Catastrophizing: A predictor of persistent pain among women with endometriosis at 1 year. *Hum Reprod*. 2011;26(11):3078-3084. doi:10.1093/humrep/der292
351. Yang MH, Wang PH, Wang SJ, Sun WZ, Oyang YJ, Fuh JL. Women with endometriosis are more likely to suffer from migraines: A population-based study. *PLoS One*. 2012;7(3):e33941. doi:10.1371/journal.pone.0033941
352. Karp BI, Sinaii N, Nieman LK, Silberstein SD, Stratton P. Migraine in women with chronic pelvic pain with and without endometriosis. *Fertil Steril*. 2011;95(3):895-899. doi:10.1016/j.fertnstert.2010.11.037
353. Saha R, Kuja-Halkola R, Tornvall P, Marions L. Reproductive and lifestyle factors associated with endometriosis in a large cross-sectional population sample. *J Women's Heal*. 2017;26(2):152-158. doi:10.1089/jwh.2016.5795
354. Abd El-Kader AI, Gonied AS, Lotfy Mohamed M, Lotfy Mohamed S. Impact of endometriosis-related adhesions on quality of life among infertile women. *Int J Fertil Steril*. 2019;13(1):72-76. doi:10.22074/ijfs.2019.5572
355. Patrick DL, Bergner M. Measurement of health status in the 1990s. *Annu Rev Public Health*. 1990;11:165-183. doi:10.1146/annurev.pu.11.050190.001121
356. Health-Related Quality of Life (HRQOL) | CDC. https://www.cdc.gov/hrqol/index.htm. Published 2000. Accessed December 15, 2020.
357. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (Sf-36): I. conceptual framework and item selection. *Med Care*. 1992;30(6):473-483. doi:10.1097/00005650-199206000-00002
358. Kiykac Altinbas S, Bayoglu Tekin Y, Dilbaz B, Dilbaz S. Evaluation of quality of life in fertile Turkish women with severe endometriosis. *J Obstet Gynaecol (Lahore)*. 2015;35(1):49-52. doi:10.3109/01443615.2014.930110
359. Simoens S, Dunselman G, Dirksen C, et al. The burden of endometriosis: costs and quality of life of women with endometriosis and treated in referral centres. *Hum Reprod*. 2012;27(5):1292-1299. doi:10.1093/HUMREP/DES073
360. Marinho MCP, Magalhaes TF, Fernandes LFC, Augusto KL, Brilhante AVM, Bezerra LRPS. Quality of Life in Women with Endometriosis: An Integrative Review. *J Women's Heal*. 2018;27(3):399-408. doi:10.1089/jwh.2017.6397
361. Soliman AM, Coyne KS, Zaiser E, Castelli-Haley J, Fuldeore MJ. The burden of endometriosis symptoms on health-related quality of life in

women in the United States: a cross-sectional study. *J Psychosom Obstet Gynecol*. 2017;38(4):238-248. doi:10.1080/0167482X.2017.1289512
362. Souza CA, Oliveira LM, Scheffel C, et al. Quality of life associated to chronic pelvic pain is independent of endometriosis diagnosis-a cross-sectional survey. *Health Qual Life Outcomes*. 2011;9(1):1-5. doi:10.1186/1477-7525-9-41
363. Bazett-Jones DM, Rathleff MS, Holden S. Associations between number of pain sites and sleep, sports participation, and quality of life: A cross-sectional survey of 1021 youth from the Midwestern United States. *BMC Pediatr*. 2019;19(1):1-8. doi:10.1186/s12887-019-1576-6
364. Vercellini P, Fedele L, Aimi G, Pietropaolo G, Consonni D, Crosignani PG. Association between endometriosis stage, lesion type, patient characteristics and severity of pelvic pain symptoms: A multivariate analysis of over 1000 patients. *Hum Reprod*. 2007;22(1):266-271. doi:10.1093/humrep/del339
365. Sullivan-Myers C, Sherman KA, Beath AP, Duckworth TJ, Cooper MJW. Delineating sociodemographic, medical and quality of life factors associated with psychological distress in individuals with endometriosis. *Hum Reprod*. 2021;36(8):2170-2180. doi:10.1093/humrep/deab138
366. Estes SJ, Huisingh CE, Chiuve SE, Petruski-Ivleva N, Missmer SA. Depression, anxiety, and self-directed violence in women with endometriosis: A retrospective matched-cohort study. In: *American Journal of Epidemiology*. Vol 190. Oxford Academic; 2021:843-852. doi:10.1093/aje/kwaa249
367. Sokratous S, Merkouris A, Middleton N, Karanikola M. The prevalence and socio-demographic correlates of depressive symptoms among Cypriot university students: A cross-sectional descriptive co-relational study. *BMC Psychiatry*. 2014;14(1):1-15. doi:10.1186/s12888-014-0235-6
368. Çakici M, Gökçe Ö, Babayiğit A, Çakici E, Eş A. Depression: Point-prevalence and risk factors in a North Cyprus household adult cross-sectional study. *BMC Psychiatry*. 2017;17(1):1-11. doi:10.1186/s12888-017-1548-z
369. Papadopoulos C, Leavey G, Vincent C. Factors influencing stigma. A comparison of Greek-Cypriot and English attitudes towards mental illness in north London. *Soc Psychiatry Psychiatr Epidemiol*. 2002;37(9):430-434. doi:10.1007/s00127-002-0560-9
370. Chen L-C, Hsu J-W, Huang K-L, et al. Methods: Using the Taiwan National Health Insurance Research Database. 2015;10:439. doi:10.1016/j.jad.2015.10.030
371. Pope CJ, Sharma V, Sharma S, Mazmanian D. A Systematic Review of the Association Between Psychiatric Disturbances and Endometriosis. *J Obstet Gynaecol Canada*. 2015;37(11):1006-1015. doi:10.1016/S1701-2163(16)30050-0
372. Sepulcri R de P, Amaral VF d. Depressive symptoms, anxiety, and quality of life in women with pelvic endometriosis. *Eur J Obstet Gynecol Reprod Biol*. 2009;142(1):53-56. doi:10.1016/j.ejogrb.2008.09.003
373. Evans-Lacko S, Knapp M. Global patterns of workplace productivity for people with depression: absenteeism and presenteeism costs across

eight diverse countries. *Soc Psychiatry Psychiatr Epidemiol*. 2016;51(11):1525-1537. doi:10.1007/s00127-016-1278-4
374. Simoens S, Hummelshoj L, D'Hooghe T. Endometriosis: Cost estimates and methodological perspective. *Hum Reprod Update*. 2007;13(4):395-404. doi:10.1093/humupd/dmm010
375. The World Bank. PPP conversion factor, GDP (LCU per international $) | Data | Table. The World Bank. http://data.worldbank.org/indicator/PA.NUS.PPP. Published 2012. Accessed October 10, 2022.
376. Cyprus Turkish Medical Association. Obstetrics and Gynecology - Cyprus Turkish Medical Association. https://www.kttb.org/tarifeler/kadin-hastaliklari/. Published 2022. Accessed October 10, 2022.
377. Soliman AM, Surrey E, Bonafede M, Nelson JK, Castelli-Haley J. Real-World Evaluation of Direct and Indirect Economic Burden Among Endometriosis Patients in the United States. *Adv Ther*. 2018;35(3):408-423. doi:10.1007/s12325-018-0667-3
378. Simoens S, Hummelshoj L, Dunselman G, Brandes I, Dirksen C, D'Hooghe T. Endometriosis cost assessment (the EndoCost Study): A cost-of-illness study protocol. *Gynecol Obstet Invest*. 2011;71(3):170-176. doi:10.1159/000316055
379. Strömberg C, Aboagye E, Hagberg J, Bergström G, Lohela-Karlsson M. Estimating the Effect and Economic Impact of Absenteeism, Presenteeism, and Work Environment–Related Problems on Reductions in Productivity from a Managerial Perspective. *Value Heal*. 2017;20(8):1058-1064. doi:10.1016/j.jval.2017.05.008
380. Chalmers KJ, Catley MJ, Evans SF, Moseley GL. Clinical assessment of the impact of pelvic pain on women. *Pain*. 2017;158(3):498-504. doi:10.1097/j.pain.0000000000000789
381. Missmer SA, Tu F, Soliman AM, et al. Impact of endometriosis on women's life decisions and goal attainment: A cross-sectional survey of members of an online patient community. *BMJ Open*. 2022;12(4):e052765. doi:10.1136/bmjopen-2021-052765
382. Gerlinger C, Schumacher U, Faustmann T, Colligs A, Schmitz H, Seitz C. Defining a minimal clinically important difference for endometriosis-associated pelvic pain measured on a visual analog scale: Analyses of two placebo-controlled, randomized trials. *Health Qual Life Outcomes*. 2010;8(1):1-7. doi:10.1186/1477-7525-8-138
383. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials: IMMPACT Recommendations. *J Pain*. 2008;9(2):105-121. doi:10.1016/j.jpain.2007.09.005
384. Matalliotakis IM, Cakmak H, Fragouli YG, Goumenou AG, Mahutte NG, Arici A. Epidemiological characteristics in women with and without endometriosis in the Yale series. *Arch Gynecol Obstet*. 2008;277(5):389-393. doi:10.1007/s00404-007-0479-1
385. Boucher A, Mourad W, Mailloux J, Lemay A, Akoum A. Ovarian hormones modulate monocyte chemotactic protein-1 expression in endometrial cells of women with endometriosis. *Mol Hum Reprod*. 2000;6(7):618-626.

doi:10.1093/molehr/6.7.618
386. Fernandez S V. Estrogen, Alcohol Consumption, and Breast Cancer. *Alcohol Clin Exp Res*. 2011;35(3):389-391. doi:10.1111/j.1530-0277.2010.01355.x
387. Parazzini F, Esposito G, Tozzi L, Noli S, Bianchi S. Epidemiology of endometriosis and its comorbidities. *Eur J Obstet Gynecol Reprod Biol*. 2017;209:3-7. doi:10.1016/j.ejogrb.2016.04.021
388. Sinaii N, Cleary SD, Ballweg ML, Nieman LK, Stratton P. High rates of autoimmune and endocrine disorders, fibromyalgia, chronic fatigue syndrome and atopic diseases among women with endometriosis: A survey analysis. *Hum Reprod*. 2002;17(10):2715-2724. doi:10.1093/humrep/17.10.2715
389. Ammendola M, Pietropolli A, Saccucci P, Piccione E, Bottini E, Gloria-Bottini F. Acid phosphatase locus 1 genetic polymorphism, endometriosis, and allergy. *Fertil Steril*. 2008;90(4):1203-1205. doi:10.1016/j.fertnstert.2007.10.014
390. Peng YH, Su SY, Liao WC, et al. Asthma is associated with endometriosis: A retrospective population-based cohort study. *Respir Med*. 2017;132:112-116. doi:10.1016/j.rmed.2017.10.004
391. Sayegh L, Fuleihan GEH, Nassar AH. Vitamin D in endometriosis: A causative or confounding factor? *Metabolism*. 2014;63(1):32-41. doi:10.1016/j.metabol.2013.09.012
392. Woodworth SH, Singh M, Yussman MA, Sanfilippo JS, Cook CL, Lincoln SR. A prospective study on the association between red hair color and endometriosis in infertile patients. *Fertil Steril*. 1995;64(3):651-652. doi:10.1016/S0015-0282(16)57809-1
393. Emdin CA, Khera A V., Natarajan P, et al. Genetic association of waist-to-hip ratio with cardiometabolic traits, type 2 diabetes, and coronary heart disease. *JAMA - J Am Med Assoc*. 2017;317(6):626-634. doi:10.1001/jama.2016.21042
394. Treloar SA, Bell TA, Nagle CM, Purdie DM, Green AC. Early menstrual characteristics associated with subsequent diagnosis of endometriosis. *Am J Obstet Gynecol*. 2010;202(6):534.e1-534.e6. doi:10.1016/j.ajog.2009.10.857
395. Cooper R, Blell M, Hardy R, et al. Validity of age at menarche self-reported in adulthood. *J Epidemiol Community Health*. 2006;60(11):993-997. doi:10.1136/jech.2005.043182
396. Wei M, Cheng Y, Bu H, Zhao Y, Zhao W. Length of menstrual cycle and risk of endometriosis a meta-analysis of 11 case-control studies. *Med (United States)*. 2016;95(9). doi:10.1097/MD.0000000000002922
397. Bull JR, Rowland SP, Scherwitzl EB, Scherwitzl R, Danielsson KG, Harper J. Real-world menstrual cycle characteristics of more than 600,000 menstrual cycles. *npj Digit Med*. 2019;2(1). doi:10.1038/s41746-019-0152-7
398. Sangi-Haghpeykar H, Poindexter AN. Epidemiology of endometriosis among parous women. *Obstet Gynecol*. 1995;85(6):983-992. doi:10.1016/0029-7844(95)00074-2
399. Martire FG, Lazzeri L, Conway F, et al. Adolescence and endometriosis:

symptoms, ultrasound signs and early diagnosis. *Fertil Steril*. 2020;114(5):1049-1057. doi:10.1016/j.fertnstert.2020.06.012
400. Becker K, Heinemann K, Imthurn B, et al. Real world data on symptomology and diagnostic approaches of 27,840 women living with endometriosis. *Sci Rep*. 2021;11(1). doi:10.1038/S41598-021-99681-3
401. Kuan KKW, Gibson DA, Whitaker LHR, Horne AW. Menstruation Dysregulation and Endometriosis Development. *Front Reprod Heal*. 2021;3:68. doi:10.3389/frph.2021.756704
402. Yumiceba V, López-Cortés A, Pérez-Villa A, et al. Oncology and Pharmacogenomics Insights in Polycystic Ovary Syndrome: An Integrative Analysis. *Front Endocrinol (Lausanne)*. 2020;11:840. doi:10.3389/fendo.2020.585130
403. Throwba HPK, Unnikrishnan L, Pangath M, et al. The epigenetic correlation among ovarian cancer, endometriosis and PCOS: A review. *Crit Rev Oncol Hematol*. 2022;180:103852. doi:10.1016/j.critrevonc.2022.103852
404. Hemmert R, Schliep KC, Willis S, et al. Modifiable life style factors and risk for incident endometriosis. *Paediatr Perinat Epidemiol*. 2019;33(1):19-25. doi:10.1111/ppe.12516
405. Osteen KG, Bruner KL, Sharpe-Timms KL. Steroid and Growth Factor Regulation of Matrix Metalloproteinase Expression and Endometriosis. *Semin Reprod Endocrinol*. 1996;14(3):247-255. doi:10.1055/s-2007-1016334
406. An P, Rice T, Gagnon J, et al. A genetic study of sex hormone-binding globulin measured before and after a 20-week endurance exercise training program: The HERITAGE Family Study. *Metabolism*. 2000;49(8):1014-1020. doi:10.1053/meta.2000.7737
407. Davis L, Uezato A, Newell JM, Frazier E. Major depression and comorbid substance use disorders. *Curr Opin Psychiatry*. 2008;21(1):14-18. doi:10.1097/YCO.0b013e3282f32408
408. Patrick DL, Cheadle A, Thompson DC, Diehr P, Koepsell T, Kinne S. The validity of self-reported smoking: A review and meta-analysis. *Am J Public Health*. 1994;84(7):1086-1093. doi:10.2105/AJPH.84.7.1086
409. Lee MM, Whittemore AS, Jung DL. Reliability of recalled physical activity, cigarette smoking, and alcohol consumption. *Ann Epidemiol*. 1992;2(5):705-714. doi:10.1016/1047-2797(92)90015-I
410. D'Avanzo B, La Vecchia C, Katsouyanni K, Negri E, Trichopoulos D. Reliability of information on cigarette smoking and beverage consumption provided by hospital controls. *Epidemiology*. 1996;7(3):312-315. doi:10.1097/00001648-199605000-00018
411. Dinsdale NL, Crespi BJ. Endometriosis and polycystic ovary syndrome are diametric disorders. *Evol Appl*. 2021;14(7):1693-1715. doi:10.1111/eva.13244
412. Crain DA, Janssen SJ, Edwards TM, et al. Female reproductive disorders: the roles of endocrine-disrupting compounds and developmental timing. *Fertil Steril*. 2008;90(4):911-940. doi:10.1016/j.fertnstert.2008.08.067
413. Uimari O, Järvelä I, Ryynänen M. Do symptomatic endometriosis and uterine fibroids appear together? *J Hum Reprod Sci*. 2011;4(1):34.

doi:10.4103/0974-1208.82358
414. Hemmings R, Rivard M, Olive DL, et al. Evaluation of risk factors associated with endometriosis. *Fertil Steril*. 2004;81(6):1513-1521. doi:10.1016/j.fertnstert.2003.10.038
415. Santoro L, Donofrio F, Campo S, et al. Endothelial dysfunction but not increased carotid intima-media thickness in young European women with endometriosis. *Hum Reprod*. 2012;27(5):1320-1326. doi:10.1093/humrep/des062
416. Kinugasa S, Shinohara K, Wakatsuki A. Increased asymmetric dimethylarginine and enhanced inflammation are associated with impaired vascular reactivity in women with endometriosis. *Atherosclerosis*. 2011;219(2):784-788. doi:10.1016/j.atherosclerosis.2011.08.005
417. Verma S, Gupta R, Kudesia M, Mathur A, Krishan G, Singh S. Coexisting Iron Deficiency Anemia and Beta Thalassemia Trait: Effect of Iron Therapy on Red Cell Parameters and Hemoglobin Subtypes. *ISRN Hematol*. 2014;2014:1-5. doi:10.1155/2014/293216
418. Kvaskoff M, Bijon A, Mesrine S, Clavel-Chapelon F, Boutron-Ruault MC. Pigmentary traits and risk of endometriosis. *Hum Reprod*. 2010;25(12):3157-3158. doi:10.1093/humrep/deq250
419. Giampaolino P, Corte LD, Foreste V, Bifulco G. Is there a Relationship Between Vitamin D and Endometriosis? An Overview of the Literature. *Curr Pharm Des*. 2019;25(22):2421-2427. doi:10.2174/1381612825666190722095401
420. Van Etten E, Mathieu C. Immunoregulation by 1,25-dihydroxyvitamin D3: Basic concepts. *J Steroid Biochem Mol Biol*. 2005;97(1-2):93-101. doi:10.1016/j.jsbmb.2005.06.002
421. Boonstra A, Barrat FJ, Crain C, Heath VL, Savelkoul HFJ, O'Garra A. 1α,25-Dihydroxyvitamin D3 Has a Direct Effect on Naive CD4 + T Cells to Enhance the Development of Th2 Cells . *J Immunol*. 2001;167(9):4974-4980. doi:10.4049/jimmunol.167.9.4974
422. Autier P. Sunscreen abuse for intentional sun exposure. *Br J Dermatol*. 2009;161(SUPPL. 3):40-45. doi:10.1111/j.1365-2133.2009.09448.x
423. Krause M, Klit A, Blomberg Jensen M, et al. Sunscreens: Are they beneficial for health? An overview of endocrine disrupting properties of UV-filters. *Int J Androl*. 2012;35(3):424-436. doi:10.1111/j.1365-2605.2012.01280.x
424. Kunisue T, Chen Z, Buck Louis GM, et al. Urinary concentrations of benzophenone-type UV filters in U.S. women and their association with endometriosis. *Environ Sci Technol*. 2012;46(8):4624-4632. doi:10.1021/es204415a
425. Sanderson E, Glymour MM, Holmes M V., et al. Mendelian randomization. *Nat Rev Methods Prim*. 2022;2(1):1-21. doi:10.1038/s43586-021-00092-5
426. Xyda SE, Kotsa K, Doumas A, Papanastasiou E, Garyfallos AA, Samoutis G. Could the Majority of the Greek and Cypriot Population Be Vitamin D Deficient? *Nutrients*. 2022;14(18):3778. doi:10.3390/nu14183778
427. Borges MC, Martini LA, Rogero MM. Current perspectives on vitamin D,

immune system, and chronic diseases. *Nutrition*. 2011;27(4):399-404. doi:10.1016/j.nut.2010.07.022
428. Mithal A, Wahl DA, Bonjour JP, et al. Global vitamin D status and determinants of hypovitaminosis D. *Osteoporos Int*. 2009;20(11):1807-1820. doi:10.1007/s00198-009-0954-6
429. Jones G, Kennedy S, Barnard A, Wong J, Jenkinson C. Development of an endometriosis quality-of-life instrument: The Endometriosis Health Profile-30. *Obstet Gynecol*. 2001;98(2):258-264. doi:10.1016/S0029-7844(01)01433-8

Appendices

Appendix I

Participant information sheet and questionnaire in the English language

Appendix II

Supplementary Table 1. Frequency of co-morbidities by endometriosis cases, symptomatic and asymptomatic control groups

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Participant Information Sheet
Cyprus Women's Health Research (COHERE) Initiative

Dear Participant,

You are 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 undertaken and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish. Please feel free to 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 taking the time to read this information sheet.

1. What's the study about?
Disease can occur more commonly or rarely in different populations. This can be due to multiple reasons such as inherited (genetic) factors that are passed on to us from our parents as well as various environmental exposures or life style factors. In Northern Cyprus, we do not know the rates of women's health conditions therefore we cannot define the most burdensome and common health problems of women living in this community. In this study, we aim to determine the frequency and the distribution of women's health conditions and related symptomatology, such as pelvic pain, to define the health profiles of women living in Northern Cyprus. Moreover, we aim to investigate how various life-style factors and inherited factors (genetics) affect women's health in the population. In addition, we will quantify women's access to health care and estimate economic burden of women's health conditions in Northern Cyprus. The study is conducted by University of Oxford. A collaboration has been established between University of Oxford and Eastern Mediterranean University for the local data collection part of the study. More information on other sponsors of the study please visit our project website (www.cohereinitiative.org or www.kisaainisiyatifi.org).

2. Why have I been invited to take part?
You are between the ages of 18 and 55 and a citizen of Northern Cyprus or resident of Northern Cyprus for more than five years.

3. What's involved for me?
We will ask you to complete two questionnaires. The main study questionnaire is regarding your menstrual cycle, any medication you may be taking, and any symptoms you have (with particular regard to pelvic pain, bleeding or fertility), medical history, family history and lifestyle related information. The second questionnaire is the food frequency questionnaire, which is about your dietary intake in the past year. We will measure your weight, height, waist and hips circumference, and blood pressure.
We will ask you to give a saliva sample to be used for genetic studies, to investigate the role of inherited factors making women more susceptible to disease. The results from your genetic tests will not be fed back to you, and will only be used for research purposes. All data including the genetic data will be anynomised before analysis so that researchers will not be able to link research results to individuals. These anynomised genetic and biological data generated as part of our studies will be deposited in dedicated public scientific databases to ensure the greatest benefit to scientific research.

We will invite you to take part in a pelvic ultrasound scan (a transvaginal or a transabdominal) at a project gynaecology clinic (British Cyprus IVF Hospital, Gunes Dogum Klinigi, Jinomer). The pelvic ultrasound is an imaging test to look at women's reproductive organs and pelvic area. There are two types; (1) Transvaginal, where a probe that sends out sound waves is placed into the vagina and the pelvic cavity is screened internally. (2) Transabdominal, where the probe is placed on the abdomen and pelvic cavity is screened externally. Both methods are risk-free and painless standard gynaecological tests to examine for wide range of gynaecological conditions.

To take part in the study, the minimum requirement is to complete the study questionnaire. You may choose not to provide saliva samples for genetic testing and/or participate in the pelvic ultrasound scan.

In order to ensure quality control of the study, or to facilitate future studies that are also approved by an independent ethics committee, a key to enable linking anonymous biological and genetic data to individuals will be kept on a high compliance server at the University of Oxford, with access limited to few researchers. You will be asked if you are happy to be re-contacted for future research studies.

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4. What will happen to my data/samples?
The questionnaire data, the physical body measurements and ultrasound scan results will be stored in a secure cloud-based server space and transfer to high-compliance server space at University of Oxford. The paper-records will be stored in locked secure cabinets in Eastern Mediterranean University (EMU) until the end of the data collection phase and then transferred to Oxford University and stored there in locked secure cabinets until the end of the study.

The saliva samples will be shipped to the University of Oxford and used to extract genetic data that will be used in defining the ancestral background of this population and investigation of inherited factors for disease. The samples are considered a gift to the Oxford University and will be kept until they are all used up, which may take up to several years. Samples may be moved to a Research Tissue Bank in an anonymised fashion, or stored and used in other future ethically approved studies.
All the questionnaires, samples collected and ultrasound scan results will be kept confidential and anonymous with only your unique participant identification number.

5. Are there any risks in taking part?
You will be asked to recall medical problems, which may cause some discomfort. There are no medical risks in taking part in the study. The pelvic ultrasound scan is risk-free and it is a daily routine conducted in the gynaecological clinics. All the research data will be stored anonymously and therefore, there is no risk for a confidentiality bridge.

6. What are the benefits of taking part?
We are offering a free pelvic ultrasound scan to screen for pelvic gynaecological conditions. You will receive the findings report from the scan, which you can forward to your gynaecologist to seek advice if necessary. The study will promote evidence-based medicine in the region benefiting the local population but also providing a basis for an Eastern-Mediterranean women's health resource.

7. 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 will be asked to sign a consent form. You are still free to withdraw at any time and without giving any reason. Please feel fee to ask us if there is anything that is not clear or if you would like to have more information. If you do withdraw from the study, no more data will be collected about you. We would ask your permission to keep your samples and data collected up to that point; however, it will be possible to destroy any samples present at the time of withdrawal if you asked us to do this.

8. Has the study been reviewed by an ethics committee?
This research has been reviewed and given favourable opinion by the OxTREC Research Ethics Committee (37-17) and Eastern Mediterranean Ethics Committee (ETK00-2017-0240).

9. What if I have any questions or want to raise a concern?
Thank you for taking the time to read and consider this information sheet. You may ask questions/raise concerns at any time. Before, during or after the study if you have any questions please contact Dr. Nilufer Rahmioglu, Study Chief Investigator, or the research assistants during office hours at 0548 860 1483 or 0542 888 5020. If you have concerns regarding the ethical issues you can also contact the secretary of the local ethics committee at 0392 630 2021.

Overall Health

The following questions ask for your views about your health and how you feel about life in general. If you are unsure about how to answer any question, try and think about your overall health and give the best answer you can. Do not spend too much time answering, as your immediate response is likely to be the most accurate.

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
(a) Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐	☐	☐
(b) Moderate activities, such as moving a table, pushing a vacuum, bowling or playing golf	☐	☐	☐
(c) Lifting or carrying groceries	☐	☐	☐
(d) Climbing several flights of stairs	☐	☐	☐
(e) Climbing one flight of stairs	☐	☐	☐
(f) Bending, kneeling or stooping	☐	☐	☐
(g) Walking more than a mile	☐	☐	☐
(h) Walking half a mile	☐	☐	☐
(i) Walking 100 yards	☐	☐	☐
(j) 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?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
(a) Cut down on the amount of time you spent on work and other activities	☐	☐	☐	☐	☐
(b) Accomplished less than you would like	☐	☐	☐	☐	☐
(c) Were limited in the kind of work or other activities	☐	☐	☐	☐	☐
(d) 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)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
(a) Cut down on the amount of time you spent on work and other activities	☐	☐	☐	☐	☐
(b) Accomplished less than you would like	☐	☐	☐	☐	☐
(c) Did work or other activities 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. During the past 4 weeks, how much did pain interfere with your normal work (including both outside the home and housework)?

☐ Not at all
☐ Slightly
☐ Moderately
☐ Quite a bit
☐ Extremely

A9. 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.

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
(a) Did you feel full of life?	☐	☐	☐	☐	☐
(b) Have you been very nervous?	☐	☐	☐	☐	☐
(c) Have you felt so down in the dumps that nothing would cheer you up?	☐	☐	☐	☐	☐
(d) Have you felt calm and peaceful?	☐	☐	☐	☐	☐
(e) Did you have a lot of energy?	☐	☐	☐	☐	☐
(f) Have you felt downhearted and low?	☐	☐	☐	☐	☐
(g) Did you feel worn out?	☐	☐	☐	☐	☐
(h) Have you been happy?	☐	☐	☐	☐	☐
(i) Did you feel tired?	☐	☐	☐	☐	☐

A10. During the **past 4 weeks**, how much of the time has your **physical health** or **emotional problems** interfered with your social activities (like visiting friends, relatives, etc.)?

☐ All of the time
☐ Most of the time
☐ Some of the time
☐ A little of the time
☐ None of the time

A11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Not sure	Mostly false	Definitely false
(a) I seem to get ill more easily than other people	☐	☐	☐	☐	☐
(b) I am as healthy as anybody I know	☐	☐	☐	☐	☐
(c) I expect my health to get worse	☐	☐	☐	☐	☐
(d) My health is excellent	☐	☐	☐	☐	☐

Menstrual history and hormones

B1. How old were you when you had your first menstrual period?

☐ 8 years or younger ☐ 11 ☐ 14 ☐ 17 years or older
☐ 9 ☐ 12 ☐ 15 ☐ uncertain
☐ 10 ☐ 13 ☐ 16

B2. Have you had any periods **in the last 3 months**? *(We mean bleeding for which you needed a tampon or sanitary pad, NOT discharge (spotting) for which you needed a panty liner only)*

☐ No → **continue with question B2.1**
☐ Yes → **Skip to question B2.4**

If you have NOT had periods in the last 3 months:

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) → **If yes**: B2.1.1. Which of the following symptoms apply to you at this time? (Please ✓ the appropriate box for each symptom)

Symptoms	None	Mild	Moderate	Severe	Very Severe
(a) Hot flushes, sweating (episodes of sweating)	☐	☐	☐	☐	☐
(b) Heart discomfort (unusual awareness of heart beat, heart skipping, heart racing, tightness)	☐	☐	☐	☐	☐
(c) Sleep problems (difficulty in falling asleep, difficulty in sleeping through, waking up early)	☐	☐	☐	☐	☐
(d) Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings)	☐	☐	☐	☐	☐
(e) Irritability (feeling nervous, inner tension, feeling aggressive)	☐	☐	☐	☐	☐
(f) Anxiety (inner restlessness, feeling panicky).	☐	☐	☐	☐	☐
(g) Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness)	☐	☐	☐	☐	☐
(h) Sexual problems (change in sexual desire, in sexual activity and satisfaction)	☐	☐	☐	☐	☐
(i) Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence)	☐	☐	☐	☐	☐
(j) Dryness of vagina (sensation of dryness or burning in the vagina, difficulty with sexual intercourse)	☐	☐	☐	☐	☐
(k) Joint and muscular discomfort (pain in the joints, rheumatoid complaints)	☐	☐	☐	☐	☐

☐ Unsure
☐ Other (*Please describe*) _____

B2.2. Approximately how many periods have you had **over the last 12 months**? _____

B2.3. When was your last period?

☐ 3-6 months ☐ 7-12 months ☐ Over 12 months

→ **Please now continue with question B3.**

If you have had periods in the last 3 months, please answer the following questions about your recent periods.

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)

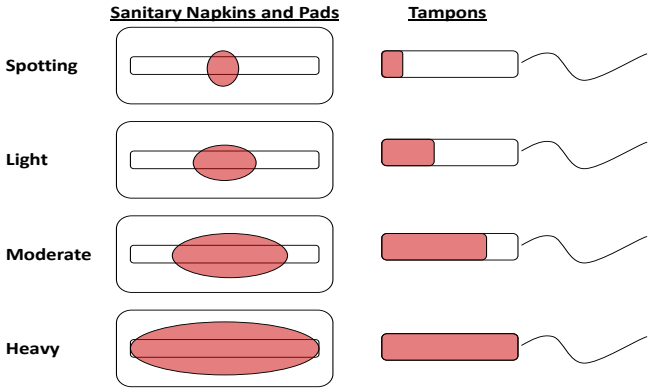
B2.7. How many days of bleeding did you usually have each period in the last 3 months? *(Not counting discharge/spotting for which you need a panty liner only)*

_____ 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



B2.9. In the last 3 months, how many days were there between the first day of one period and the first day of the next **on average**? *(Not including spotting)*

☐ < 24 days
☐ 24-31 days
☐ 32-38 days
☐ 39-50 days
☐ 51+ days
☐ Too irregular to estimate

B3. Please list below all hormones you have **ever** used for any reason (acne, bad cramping, irregular periods, birth control, fertility treatments). For each hormone used, please indicate what type of hormone it was using the number indicated for the categories below. Please also tell us the age you first used them and total time of use. If you cannot remember the name of the hormone you used, please write "unknown" in the first column. **If you have never used hormones** before, please tick ☐ and proceed to **B5**.

1=Combined birth control pill (e.g. Marvelon, Yasmin, Microgynon)
2=Progestin only birth control pill ("mini-pill", e.g. Cerazette, Micronor)
3=Unsure of which type of oral birth control pill
4=Progestin injection/shot (e.g. Depo provera)
5=Transdermals: patches (e.g. OrthoEvra, Climara), dots (Vivelle dot)
6=Vaginal ring (NuvaRing)
7=Progesterone containing coil/IUD (Mirena)
8=Hormonalimplant (Implanon/Nexplanon)
9=Oral progestins to regulate the cycle (e.g. medroxyprogesterone acetate [Provera], dydrogesterone [Duphaston],dienogest [Visanne], Norethisterone)
10=GnRH agonist injection/shot (e.g.leuprolilide (leuproline) acetate [Prostap], goserelin [Zoladex])
11=Norethindrone acetate (Aygestin)
12=Danazol (please specify if used vaginally or orally)
13=Hormone replacement therapy (e.g. Premarin, Provera)
14=Other
15=Don't know what type of hormone

Name of hormone	Type of hormone (Please enter the number associated with the category above.)	Age started	Used within the last 3 months?	Total time used
For example: Yasmin	*1*	*18*	✓ *No* ☐ *Yes*	*…… months* *2 years*
1.	.....	.....	☐ No ☐ Yes	…… months …… years
2.	.....	.....	☐ No ☐ Yes	…… months …… years
3.	.....	.....	☐ No ☐ Yes	…… months …… years
4.	.....	.....	☐ No ☐ Yes	…… months …… years
5.	.....	.....	☐ No ☐ Yes	…… months …… years

B4. What are/were your reasons for using hormones? *(Please tick ✓ all that apply)*

☐ Birth control / pregnancy prevention
☐ Irregular periods
☐ Heavy periods
☐ Acne
☐ Polycystic ovarian syndrome (PCOS)
☐ Ovarian cyst
☐ Pelvic pain or pain with periods
If yes: B4.1. Did hormones help with the pain? ☐ Yes ☐ No
B4.2. Did you ever discontinue or change hormones because they were not effective enough at controlling pain? ☐ Yes ☐ No
☐ Other (Please specify): _____

B5. Have you ever used a non-hormonal coil/IUD?

☐ No
☐ Yes → **If yes: B5.1.** At what age did you first use a non-hormonal coil/IUD? ____

B6. Have you ever used emergency contraception?

☐ No ☐ Yes → **If yes: B6.1.** How many times have you used emergency contraception? _____

Medical Screening and Resource Use

C1. Do you need a carer to assist you with your daily activities? (for basic hygiene, to help you move, administration of drugs, performing treatments, etc.)

☐ No → **Skip to C2**

☐ Yes → **If yes:** C1.1. Who is your main carer?

☐ Family member

☐ Another non-contracted person (e.g. friend)

☐ Professional carer → **If yes:**

C1.1.1. How many hours of care do you receive a week? ____

C1.1.2. What is the cost per hour/day? ____

C1.1.3. Who pays for the service and how much? ____

C2.1. At what age did you first visit a gynaecologist? ____ years old.

C2.2. Do you visit a gynaecologist at least once a year?

☐ No ☐ Yes

C3. Have you ever had a pap-smear test?

☐ No → **Skip to C4**

☐ Yes → **If yes: C3.1**. At what age did you have your first pap-smear test? ____ years old

C3.2. How often do you have a pap-smear test?

☐ Once a year

☐ Every other year

☐ Every three years

☐ Every five years

☐ Not regularly

C4. Have you had the Human Papillomavirus (HPV) vaccination?

☐ No ☐ Yes

C5. Do you self-exam your breasts for lumps, changes or discharge regularly?

☐ No ☐ Yes

C6. Have you ever had a clinical breast screening (ultra-sound, mammogram, MRI)?

☐ No → **Skip to C7**

☐ Yes → **If yes: C6.1.** How old were you when you had the first clinical breast screening?

____ years old

C6.2. How often do you get clinical breast screening (ultra-sound, mammogram, MRI)?

☐ Once a year

☐ Every other year

☐ Every three years

☐ Every five years

☐ Not regularly

C7. Have you had the below medical tests or screenings (prescribed by a doctor) in the last 6 months?

	Please ✓all the apply	**How was this funded?**
Blood Tests	☐	☐ State insurance ☐ Private insurance ☐ Out-of pocket
Ultra-sound (e.g. vaginal, thyroid, abdominal, breast)	☐	☐ State insurance ☐ Private insurance ☐ Out-of pocket
MRI/CT Scan	☐	☐ State insurance ☐ Private insurance ☐ Out-of pocket
Other (*Please Specify*)_____	☐	☐ State insurance ☐ Private insurance ☐ Out-of pocket

C8. How many visits to specialists have you had to undergo in the last 6 months? Please list them below.

Specialist	**Number of Visits**
1._____	_____
2._____	_____
3._____	_____
4._____	_____
5_____	_____

C9. How many visits to the emergency service have you made in the last 6 months?

_____ ☐ By myself or ☐ Ambulance

C10. Have you been admitted to hospital in the last 12 months?

☐ No → **Skip to D1**

☐ Yes→ **If yes:**

C10.1. How many times have you been admitted to hospital in the last 12 months? ____ times

C10.2. How many days have you spent as an inpatient in the hospital in the last 12 months? ___ days

C10.3. During the hospital admissions in the last 12 months, have you undergone any procedures?

☐ No → **Skip to C10.4**

☐ Yes→ **If yes:** Please list them below:

1. _____
2. _____
3. _____

C10.4. Please rate how satisfied you were with the health care received using a scale from 0 to 10 where 0= Not satisfied at all and 10= Very satisfied.

Not satisfied at all **Very satisfied**

0 1 2 3 4 5 6 7 8 9 10

C11. How many times have you used the following means of transport in the last 6 months for disease related travel to the health clinic, hospital, etc.?

☐ Private car: ____ times
☐ Bus: ____ times
☐ Aeroplane (if visiting another country) ____ times
☐ Ambulance ____ times

Pregnancy and fertility

D1. Have you ever been pregnant (confirmed by a positive pregnancy test, including miscarriages, ectopic pregnancies or terminations)?

☐ No → **Skip to D3**
☐ 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	☐	☐	☐	☐	☐	☐	☐	☐
Termination (abortion)	☐	☐	☐	☐	☐	☐	☐	☐
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 (using tablets, 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 or breast feeding?								
Gestational diabetes	☐	☐	☐	☐	☐	☐	☐	☐
Pregnancy-related high blood pressure	☐	☐	☐	☐	☐	☐	☐	☐
Pre-eclampsia Toxemia	☐	☐	☐	☐	☐	☐	☐	☐
Mastitis/breast infection	☐	☐	☐	☐	☐	☐	☐	☐
HELLP syndrome	☐	☐	☐	☐	☐	☐	☐	☐
Hyperemesis gravidarum	☐	☐	☐	☐	☐	☐	☐	☐
Pre-term birth (birth before 37 weeks)	☐	☐	☐	☐	☐	☐	☐	☐
Other:	☐	☐	☐	☐	☐	☐	☐	☐
Other:	☐	☐	☐	☐	☐	☐	☐	☐

D1. (continued)

	Pregnancy							
	1st	2nd	3rd	4th	5th	6th	7th	8th
If this pregnancy resulted in a birth, for how long did you breastfeed?								
(Please write the number of months you breastfed or write 0 if you did not breastfeed.);if you breastfed for less than 1 month, please write'1'	.....	.....	.....	.....	.....	.....	.....	.....
What was the birth weight and gender of the baby?								
Weight in kg	.....	.....	.....	.....	.....	.....	.....	.....
Height in cm	.....	.....	.....	.....	.....	.....	.....	.....
Girl	.....	.....	.....	.....	.....	.....	.....	.....
Boy	.....	.....	.....	.....	.....	.....	.....	.....
If more than one baby please continue below:								
Weight in kg	.....	.....	.....	.....	.....	.....	.....	.....
Height in cm	.....	.....	.....	.....	.....	.....	.....	.....
Girl	.....	.....	.....	.....	.....	.....	.....	.....
Boy	.....	.....	.....	.....	.....	.....	.....	.....

D2. After the birth of your **last** child and **after you stopped breastfeeding**, how were your menstrual cycles different compared to before you became pregnant with your first child? (*Please tick ✓all that apply*)

☐ No change
☐ Periods more regular
☐ Periods less regular
☐ Periods more painful
☐ Periods less painful

D3. Have you ever tried to get pregnant for more than 6 months in a row without succeeding?

☐ No → Skip to E1
☐ Yes → **If yes:** D3.1. What was the longest amount of time that you tried, whether or not you actually got pregnant? _____ months

D4. Have you or your partner ever had any tests/investigations to find out why you were not getting pregnant?

☐ No
☐ Yes → **If yes:** D4.1. What were the results of these tests? (*Please tick ✓all that apply*)

☐ Endometriosis (Chocolate cyst)
☐ 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……

D5. Did you ever seek treatment for infertility in any clinic?

☐ No

☐ Yes → **If yes: D5.1.** Please tell us about any fertility treatment you have used.

	Never used	**Used within 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	☐	☐	☐	……..
Intrauterine insemination with a donor's semen	☐	☐	☐	……..
In vitro fertilization (IVF)	☐	☐	☐	……..
In vitro fertilization with intracytoplasmic sperm injection (ICSI)	☐	☐	☐	……..
In vitro fertilization with eggs from a donor	☐	☐	☐	……..

D6. If you ever had **IVF, ICSI, or IVF with donor egg(s):** After what step did your IVF cycle(s) end?

(Please tick ✓ all that apply)

☐ Ovarian stimulation (did not have eggs retrieved)

☐ Egg retrieval (did not have embryos transferred)

☐ Embryo transfer (did not have a positive pregnancy test)

☐ Chemical pregnancy (had a positive pregnancy test but no heartbeat on ultrasound)

☐ Clinical pregnancy (heartbeat detected, but had a pregnancy loss before the end of 12 weeks)

☐ Pregnancy loss or stillbirth after 12 weeks

☐ Live birth

Pain

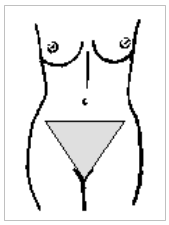
E1. Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint, back or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures, or surgery.

We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. 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 <u>with</u> 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:



E2. Have you **ever** had pain during your periods?

- ☐ No pain
- ☐ Mild cramps (medication never or rarely needed)
- ☐ Moderate cramps (medication usually needed)
- ☐ Severe cramps (medication and bed rest needed)

→ **E2.1.** 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 E12.

E3. How much pain did you have **during your last period**?

☐ No pain → **Skip to question E10**
☐ Mild cramps (medication never or rarely needed)
☐ Moderate cramps (medication usually needed)
☐ Severe cramps (medication and bed rest needed)

E4. Did you take any pain-killers 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 [e.g. panadol], naproxen [e.g. apranax])?

E5. Did you take hormones to help alleviate menstrual pain **during your last period** and if so, did it help to alleviate your pain?

☐ Did not take hormones for pain
☐ Yes, but pain was not alleviated
☐ Yes, pain was at least somewhat alleviated

E6. 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

E7. During your last period, did you have to lie down for any part of the day or longer because of your period pain?

☐ No ☐ Yes

E8. 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

E9. 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**
(a) …did this pain get better or stop after you had a bowel movement?	☐	☐	☐	☐	☐
(b) …did this pain get worse after you had a bowel movement?	☐	☐	☐	☐	☐
(c) …did you have more frequent bowel movements when the pain started?	☐	☐	☐	☐	☐
(d) …did you have less frequent bowel movements when the pain started?	☐	☐	☐	☐	☐
(e) …were your stools looser when the pain started?	☐	☐	☐	☐	☐
(f) …were your stools harder when the pain started?	☐	☐	☐	☐	☐

E10. In the last 12 months, how often have you had period pain?

- ☐ Never
- ☐ Occasionally (less than a quarter of my periods)
- ☐ Often (a quarter to half of my periods)
- ☐ Usually (more than half of my periods)
- ☐ Always (every period)

E11. Please rate how severe your period pain was <u>at its worst</u> **in the last 12 months** 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

The following questions are about the time <u>in your life</u> when your period pain was <u>at its worst</u>.

E12. How old were you when your period pain was <u>at its worst</u>? ……. years

E13. Please rate how severe your period pain was when it was <u>at its worst</u> using a scale from 0 to 10 where 0=no pain and 10=worst imaginable pain.

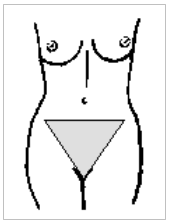
No pain										**Worst imaginable pain**
0	1	2	3	4	5	6	7	8	9	10

E14. During the time in your life when your period pain was <u>at its worst</u>, were you taking any medication to help alleviate the pain? (*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

The following questions are about pain <u>during or after vaginal intercourse or penetration</u>.

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* E27.**

If you have never had intercourse, please check here ___ and skip to question E27

E15. Have you ever had pain during intercourse or in the 24 hours following vaginal sexual intercourse/penetration**?**

☐ No → Please skip to question **E27**

☐ Yes → **If yes**: E15.1. At what age did this pain start? ____

E16. When did you last have vaginal intercourse?

☐ In the last month

☐ 1-3 months ago

☐ 4-12 months ago

☐ More than 12 months ago → **If so: E16.1.** Did you avoid intercourse because of pelvic pain?

☐ No ☐ Yes

If you had vaginal intercourse more than 12 months ago, please go to question E27

E17. When you last had vaginal intercourse/penetration, did you have pelvic pain during or in the 24 hours following sexual intercourse**?**

☐ No → if No, please continue with question E27

☐ Yes, during intercourse/penetration

☐ Yes, in the 24 hours following intercourse/penetration

☐ Yes, both during intercourse/penetration and in the 24 hours following

E18. When you last had vaginal intercourse/penetration, where did you feel the pain? *(Please 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: _____

E19. 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.

No pain										**Worst imaginable pain**
0	1	2	3	4	5	6	7	8	9	10

E20. Please rate how severe your pain was at its worst **in the 24 hours after the last time you had vaginal intercourse/penetration** 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

E21. 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)

E22. In the last 12 months, was there a time of the month in which vaginal intercourse/penetration was more painful than at other times? *(Please 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?
E22.1. During a period?	☐ No ☐ Yes	→	☐ No ☐ Yes
E22.2. A few days before a period	☐ No ☐ Yes	→	☐ No ☐ Yes
E22.3. A few days after a period	☐ No ☐ Yes	→	☐ No ☐ Yes
E22.4. At mid cycle (around ovulation)	☐ No ☐ Yes	→	☐ No ☐ Yes

E23. In the last 12 months, did you ever **interrupt** vaginal intercourse/penetration because of pelvic pain?

☐ No

☐ Yes

E24. In the last 12 months, did you ever **avoid** vaginal intercourse/penetration because of pelvic pain?

☐ No

☐ Yes

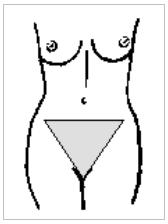
The following questions are about the time in your life when your pain with vaginal intercourse/penetration was <u>at its worst</u>.

E25. How old were you when your pain with vaginal intercourse/penetration was at its worst? ……. years

E26. Please rate how severe your pain with vaginal intercourse/penetration was when it was <u>at its worst</u> 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

The questions in this section ask about <u>pelvic/lower abdominal pain in general</u>.



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:

*Please **<u>do not count</u>**: pain related to periods or intercourse, pregnancy or childbirth, any surgery, sports-related or other injury, food poisoning or stomach flu.*

E27. Have you ever experienced pelvic pain in general? ***<u>Do not count</u>**: pain caused by menstrual cramps, intercourse, surgery, pregnancy, childbirth, sports-related or other injury, food poisoning, or stomach flu.*

☐ No → **Skip to E46**

☐ Yes → **E27.1** At what age did you start having this pelvic pain? ___ years

E27.2 When did you last have this pain?

☐ In the last month

☐ 1-3 months ago

☐ 4-6 months ago

☐ 7-12 months ago → Please go to question **E41**

☐ longer than 12 months ago

E28. To what extent has your pain interfered with your normal social activities with each of the following activities **in the last 3 months**:

	Not At All	Slightly	Moderately	Quite A Bit	Extremely	Not Applicable
Work or school:	☐	☐	☐	☐	☐	☐
Daily activities at home:	☐	☐	☐	☐	☐	☐
Sleep:	☐	☐	☐	☐	☐	☐
Sexual intercourse:	☐	☐	☐	☐	☐	☐
Exercise/sports:	☐	☐	☐	☐	☐	☐
Social activities	☐	☐	☐	☐	☐	☐

E29. Approximately how long in total did you have this pain for **in the last 3 months**?

☐ Less than one day ☐ One day a week
☐ One day ☐ More than one day a week
☐ Two to three days ☐ Every day

E30. 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……

E31. 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

E32. Please rate how severe your pelvic pain was **<u>at its worst</u> in the last 3 months** 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

E33. Please rate how severe your pelvic pain was **<u>on average</u> in the last 3 months** 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

E34. Please rate how severe your pelvic pain was **<u>at its worst</u>, during your last internal gynaecological examination,** going from no pain (0) to worst possible pain (10)**:**

No pain										**Worst imaginable pain**
0	1	2	3	4	5	6	7	8	9	10

E35. 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
Gnawing	☐ 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
Splitting	☐ 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

E36. What makes your pelvic pain worse? (*Please tick ✓all that apply*)

☐ Sitting	☐ Stress	☐ Standing or walking
☐ Full bladder or urinating	☐ Time of day	☐ Exercise
☐ Bowel movement	☐ Full meal	☐Coughing/sneezing
☐ Nothing makes my pain worse	☐ Weather	☐ Constipation
☐ Intercourse or orgasm	☐ Exercise	☐ Other, please specify_____

E37. What helps your pelvic pain? (*Please tick ✓all that apply*)

☐ Pain medication	☐ Hot bath
☐ Relaxation	☐ Meditation
☐ Lying down	☐ Laxatives / enema
☐ Music	☐ TENS Unit
☐ Massage	☐ Emptying bladder
☐ Ice	☐ Hot water bottle
☐ Heating pad	☐ Nothing helps
☐ Bowel movement	☐ Other: .....

E38. The following questions are about your bowel movements/stool when you had pelvic pain **in the last 3 months:**

When you had pelvic pain in the last 3 months, how often…	**Never/ Rarely**	**Some-times**	**Often**	**Most of the time**	**Always**
(a) …did this pain get better or stop after you had a bowel movement?	☐	☐	☐	☐	☐
(b) …did this pain get worse after you had a bowel movement?	☐	☐	☐	☐	☐
(c) …did you have more frequent bowel movements when the pain started?	☐	☐	☐	☐	☐
(d) …did you have less frequent bowel movements when the pain started?	☐	☐	☐	☐	☐
(e) …were your stools looser when the pain started?	☐	☐	☐	☐	☐
(f) ...were your stools harder when the pain started?	☐	☐	☐	☐	☐

The following questions are about the time <u>in your life</u> when your pelvic/lower abdominal pain was <u>at its worst</u>. *Please **<u>do not count</u>**: pain related to periods or intercourse, pregnancy or childbirth, any surgery, sports-related or other injury, food poisoning or stomach flu.*

E39. How old were you when your pelvic/lower abdominal pain was **<u>at its worst</u>**? ……. years old

E40. Please rate how severe your pelvic/lower abdominal pain was when it was <u>at its worst</u> 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

E41. During the time in your life when your pelvic/lower abdominal pain was <u>at its worst</u> were you taking any medication to help alleviate the pain? (*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

E42. Have you ever received a diagnosis for the pain from a doctor?

- ☐ No
- ☐ Yes (*Please 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*) …….

E43. The following questions are about **bladder pain <u>in the last 7 days</u>.**

In the past 7 days.....	**Never**	**Rarely**	**Often**	**Most of the time**	**Always**
(a) .... when you urinated, how often was it because of pain in your bladder?	☐	☐	☐	☐	☐
(b) ..... how often did you still feel the need to urinate just after you urinated?	☐	☐	☐	☐	☐
(c) ..... how often did you urinate to avoid pain in your bladder from getting worse?	☐	☐	☐	☐	☐
(d) ..... how often did you have a feeling of pressure in your bladder?	☐	☐	☐	☐	☐
(e) ..... how often did you have pain in your bladder?	☐	☐	☐	☐	☐
(f) ..... how bothered were you by frequent urination during the daytime?	☐	☐	☐	☐	☐
(g) ..... how bothered were you by having to get up during the night to urinate?	☐	☐	☐	☐	☐

E44. Please rate on the following scale **your worst bladder pain in the last 7 days**.

No bladder pain										Worst possible bladder pain
0	1	2	3	4	5	6	7	8	9	10

E45. 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

E46. Have you ever been significantly bothered by recurrent headaches?

☐ No → Please skip to question **E59**

☐ Yes → Please continue with question **E47**

E47. Do you still have recurrent headaches?

☐ No ☐ Yes

E48. Have you had at least five separate attacks of headache severe enough to require that you stop or decrease your activities or take a medication for pain?

☐ No → Please skip to question **E59**

☐ Yes → Please continue with question **E49**

E49. Do you have (head) pain-free intervals of days to weeks between severe headache attacks?

☐ No ☐ Yes

E50. If left untreated, would your headache attacks usually last more than four hours and less than three days?

☐ No → Please skip to question **E59**

☐ Yes → Please continue with question **E51**

E51. Are your most troublesome headaches…

(a) Often pulsating *(*"throbbing*"*)?

☐ No ☐ Yes

(b) Often unilateral (left or right side of head) for at least a portion of the headache attack?

☐ No ☐ Yes

(c) Severe enough to cause you stop or decrease your activities?

☐ No ☐ Yes

(d) Made worse by physical activity?

☐ No ☐ Yes

E52. Are your headache attacks usually accompanied by ...

(e) Nausea or vomiting?

☐ No ☐ Yes

(f) Sensitivity to light?

☐ No ☐ Yes

(g) Sensitivity to noise?

☐ No ☐ Yes

E53. With at least two of your headache attacks have you had temporary visual disturbances (e.g. shimmering lights, zigzags, blind spots, circles, crescent shapes) just before or during the headache?

☐ No → Please skip to question **E57**
☐ Yes → Please continue with question **E54**

E54. Which of the following **best** describes your visual disturbances? Please choose **only one**.

☐ Light objects appearing excessively bright	☐ White lights	☐ Flashing gold lights
☐ All objects appearing grey or yellow	☐ Heat waves	☐ Moving black veils
☐ Distortion of all linear objects	☐ Sparklers	☐ Herringbone
☐ Dancing and moving cobwebs	☐ Silver streaks	☐ Double vision
☐ Scintillating picket fences	☐ Blind spot	☐ Silver stars
☐ Zigzag streaks of light	☐ None of these (*Please describe):* _____	

E55. Does the visual disturbance change (e.g. worsen, change character) within four minutes?

☐ No ☐ Yes

E56. Does the visual disturbance go away completely within 60 minutes?

☐ No ☐ Yes

E57. With at least two of your headache attacks have you had temporary numbness, tingling, or both, involving the lips, tongue, fingers or legs occurring just before or during the headache?

☐ No ☐ Yes

E58. Have you had headaches accompanied by both visual disturbance and temporary numbness/tingling?

☐ No ☐ Yes

E59. Have you ever had any other type of chronic pain lasting at least six months?

☐ No ☐ Yes → **If yes: E59.1.** 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	Mild	Moderate	Severe
Back Pain						
Neck Pain						
Post-Surgical Pain(including scar pain)						
Other (*Please specify*): ……						

Medical history

F1. Please tick whether you have had any of the following medical conditions and at what age you were first diagnosed by a doctor. (*Please tick ✓all that apply*)

Yes	Medical Condition	Age diagnosed	Yes	Medical Condition	Age diagnosed
☐	Anxiety requiring medication or therapy	.....	☐	SLE (Lupus)	.....
☐	Asthma	.....	☐	Migraine	.....
☐	Cardiovascular disease	.....	☐	Pelvic Inflammatory Disease (PID)	.....
☐	Mitral valve prolapse (Murmur syndrome)	.....	☐	Painful bladder/interstitial cystitis (NOT bacterial bladder infection)	.....
☐	Angina	.....	☐	Fibromyalgia	.....
☐	Stroke (Heart attack)	.....	☐	Fibroid uterus	.....
☐	Arrythmias	.....	☐	Glandular fever	.....
☐	Congenital heart disease	.....	☐	Cushing's Disease	.....
☐	Chronic Fatigue Syndrome (CFS) / Myalgic encephalomyelitis (ME)	.....	☐	Crohn's Disease	.....
☐	Deafness/difficulty hearing	.....	☐	Scoliosis (curvature of the spine)	.....
☐	Depression requiring medication or therapy	.....	☐	Spine problems (excluding scoliosis)	.....
☐	Type 1 Diabetes	.....	☐	Sjogren's syndrome	.....
☐	Type 2 Diabetes: ☐ Diabetes requiring diet control ☐ Diabetes requiring insulin or tablets ☐ Diabetes requiring diet, insulin and tablets	.....	☐	Adrenal insufficiency	.....
☐	Insulin resistance	.....	☐	Inflammatory bowel disease (IBD)	.....
☐	Hypoglycemia	.....	☐	Addison's Disease	.....
☐	High cholesterol	.....	☐	Ulcerative Colitis	.....
☐	Thyroid diseases: ☐ Hyperthyroid ☐ Graves' disease ☐ Hypothyroid ☐ Hashimoto's Disease ☐ Guatr	.....	☐	Fibrosis: ☐ Hepatit Fibrosis (Liver) ☐ Pulmonary Fibrosis (Lungs)	.....
☐	Vitamin D deficiency	.....	☐	Dupuytren's disease	.....
☐	High blood pressure	.....	☐	Parkinson's disease	.....
☐	Low blood pressure	.....	☐	Multiple Sclerosis (MS)	.....
☐	Uterine Fibroids	.....	☐	Uveitis	.....
☐	Ovarian Cysts	.....	☐	Psoriasis	.....
☐	Eating disorders ☐ Bulimia ☐ Anorexia ☐ Undefined	.....	☐	Thalassamia ☐ Carrier ☐ Diseased Beta Thalassamia ☐ Carrier ☐ Diseased Alpha-thalassamia ☐ Carrier ☐ Diseased	.....
☐	Clinical obesity	.....	☐	Hemochromatosis	.....
☐	Clinical Iron-deficiency	.....	☐	Behcet's disease	.....
☐	Endometriosis (Chocolate cyst)	.....	☐	Eczema	.....
☐	Polycystic Ovary Syndrome (PCOS)	.....	☐	Sickle-cell anemia ☐ Carrier ☐ Diseased	.....
☐	Bone disorders ☐ Osteoporosis ☐ Rheumatoid Arthritis ☐ Reiter's Syndrome (Reactive arthritis)	.....	☐	Early onset dementia: ☐ Alzheimer's ☐ Vascular ☐ Frontotemporal ☐ Other _____	.....
☐	Irritable Bowel Syndrome (IBS)	.....	☐	Hirsuitism (Male-pattern body hair)	.....
☐	Other: _____	.....	☐	Other: _____	.....
☐	Other:_____	.....	☐	Other: _____	.....

F2. Have you been told that you were born with a structural problem / birth defect of your uterus, cervix, or vagina?

☐ No

☐ Yes → **If yes: F2.1.** Did you have surgery for this issue?

☐ No

☐ Yes → **If Yes: F2.1.1** Was the problem improved or corrected after surgery?

☐ No

☐ Yes

F3. Have you ever been diagnosed by a doctor with cancer or a malignancy of any kind?

☐ No ☐ Yes

If Yes: F3.1. 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)

F4. Have you had any of the following 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 Procedures	No	Yes	If Yes: How many times?	If Yes: Please list age(s)	If Yes: What was the reason for the surgery?	If Yes: How was this funded?
Tubal ligation (sterilisation/tubes tied)	☐	☐				☐ State Insurance ☐ Private Insurance ☐ Out of Pocket
Appendix removed	☐	☐				☐ State Insurance ☐ Private Insurance ☐ Out of Pocket
Hysterectomy	☐	☐			…… ……	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket
Oophorectomy **If yes**, how many of your ovaries have been removed? ☐ 1 ☐ both ☐ unsure	☐	☐			…… ……	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket
Dilatation and Curettage (D&C)	☐	☐			…… ……	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket
Cervical surgery (LEEP or conization)	☐	☐			…… ……	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket
Hysteroscopy	☐	☐			…… ……	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket
Gall bladder surgery	☐	☐			…… ……	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket
Hernia operation	☐	☐			…… ……	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket

Surgical Procedures	No	Yes	If Yes: How many times?	If Yes: Please list age(s)	If Yes: What was the reason for the surgery?	How was this funded?
Sigmoidoscopy/colonoscopy (insertion of a tube to look inside your bowel)	☐	☐			…… ……	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket
Laparoscopy (surgery involving insertion of a telescope into you abdomen)	☐	☐			…… ……	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket
Thyroidectomy (Thyroid removal; total or partial)	☐	☐			…… ……	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket
Bariatric surgery	☐	☐			…… ……	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket
Angioplasty	☐	☐			…… ……	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket
Bypass surgery	☐	☐			…… ……	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket
Other surgery: ……	☐	☐			…… ……	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket

F5. 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: F5.1. Where have you experienced such hair growth? On your:

Upper lip	☐ Yes	☐ No	**Thighs**	☐ Yes	☐ No
Chin	☐ Yes	☐ No	**Chest**	☐ Yes	☐ No
Upper back	☐ Yes	☐ No	**Upper abdomen**	☐ Yes	☐ No
Lower back	☐ Yes	☐ No	**Lower abdomen**	☐ Yes	☐ No
Upper arms	☐ Yes	☐ No			

F6. Have you had acne after the age of 18 (adult acne)?

☐ No ☐ Yes

F6.1. Have you had acne after the age of 25 (adult acne)?

☐ No ☐ Yes

F6.1.1. Where have you had acne? *(Please respond for each item)*

Face or throat	☐ Yes	☐ No
Chest or back	☐ Yes	☐ No
Upper arms	☐ Yes	☐ No

F7. Have you experienced thinning or loss of your hair (not including hair-thinning side-effects of medications or treatments)?

☐ No ☐ Yes

F8. Do you have darkening of the skin around your neck, under your arms, on your hands or in your groin?

☐ No ☐ Yes

F9. The following questions are about your bowel movements/stool in general **in the last 3 months:**

In the last 3 months, how often...	**Never/ Rarely**	**Some-times**	**Often**	**Most of the time**	**Always**
…did you have loose, mushy, or watery stools?	☐	☐	☐	☐	☐
… did you have blood in stools?	☐	☐	☐	☐	☐
…did you have hard or lumpy stools?	☐	☐	☐	☐	☐

F10. Have you had any of the following in the **last month**? (*Please tick ✓all that apply*)

☐ Rectal bleeding or blood in your stool
☐ Less than 3 bowel movements per week
☐ More than 3 bowel movements per day
☐ Passing mucus at the time of bowel movements
☐ Nausea and/or vomiting
☐ Straining during a bowel movement
☐ Urgent need to have a bowel movement
☐ Feeling of incomplete emptying with bowel movements
☐ Abdominal fullness, bloating, or swelling
☐ Intestinal cramping

F11. In the **last 3 months**, have you experienced any of the following? (*Please tick ✓all that apply*)

☐ Loss of urine when coughing, sneezing or laughing
☐ Difficulty passing urine
☐ Frequent bladder infections
☐ Blood in the urine
☐ Still feeling full after urination
☐ Having to urinate again within minutes of urinating

F12. Has a doctor or other health care provider ever diagnosed you with endometriosis?

☐ No → Skip to **F13.**
☐ Yes → **If Yes:**

F12.1. How was the diagnosis made? (*Please tick ✓all that apply*)

☐ laparoscopy or other surgical procedure
☐ ultrasound/MRI scan
☐ based on symptoms
☐ other, please describe: _____

F12.2. 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

F12.3. How old were you when you first had symptoms? _____ years old

F12.4. What symptoms, if any, prompted you to see a health care provider before your diagnosis with endometriosis? (*Please tick ✓all that apply*)

☐ Pain
☐ Infertility
☐ No symptoms
☐ Other (please specify): _____

F12.5. How old were you when you were diagnosed with endometriosis? _____ years old

F13. Have you ever had surgery to look for endometriosis and none was found?

☐ No

☐ **Yes → If yes: F13.1.** What symptoms prompted the surgery? (*Please tick ✓all that apply*)

☐ Pain

☐ Infertility

☐ Other *(Please specify):* _____

F14. 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	☐	☐	☐	☐	☐	☐	☐	☐

F15. At what age did your biological mother reach the menopause (stop having periods) naturally?

..... years or: ☐ She has not reached the menopause yet, aged ..... years

☐ Don't know / her periods did not stop naturally

F16. At what age did your biological sister(s) reach the menopause (stop having periods) naturally?

……..years or ☐ She has not reached the menopause yet, aged ..... years

☐ Don't know / her periods did not stop naturally

……years or ☐ She has not reached the menopause yet, aged ..... years

☐ Don't know / her periods did not stop naturally

……..years or ☐ She has not reached the menopause yet, aged ..... years

☐ Don't know / her periods did not stop naturally

Medication history

G1. 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**.

☐ Yes → Please fill out the **Prescription Drug Table below (G1.1)**

☐ No → Skip to **G2.**

G1.1 PAIN RELIEF DRUG TABLE

Type of drug	Ever used? ✓ *if yes*	Currently taking? ✓ *if yes*	If you are currently taking this drug, how is this funded?	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 Other painkillers: Please specify _____	☐	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	____	☐ 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)	☐	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	____	☐ Pelvic pain ☐ Other pain ☐ Both	☐ 1 ☐ 2-3 ☐ 4-5 ☐ 6+	☐ 1-2 ☐ 3-5 ☐ 6-14 ☐ 15+	____ months ____ years
Ibuprofen (e.g., Brufen,Nurofen)	☐	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	____	☐ 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)	☐	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	____	☐ 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)	☐	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	____	☐ 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)	☐	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	____	☐ 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)	☐	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	____	☐ 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)	☐	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	____	☐ Pelvic pain ☐ Other pain ☐ Both	☐ 1 ☐ 2-3 ☐ 4-5 ☐ 6+	☐ 1-2 ☐ 3-5 ☐ 6-14 ☐ 15+	____ months ____ years
Herbal medicines (e.g. Capsicum,Vitex agnus-cactus)	☐	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	____	☐ Pelvic pain ☐ Other pain ☐ Both	☐ 1 ☐ 2-3 ☐ 4-5 ☐ 6+	☐ 1-2 ☐ 3-5 ☐ 6-14 ☐ 15+	____ months ____ years

G2. 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 (G2.1)**

☐ No → Please skip to **H1**

G2.1. 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?**	**If you are currently taking this drug, how is this funded?**	**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:*
Diuretic (water pill)	☐	__ __	__ __	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	
Diabetic tablets (e.g. metformin)	☐	__ __	__ __	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	
Insulin	☐	__ __	__ __	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	
Thyroid drugs (e.g. Levothyrox)	☐	__ __	__ __	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	
Drugs for epilepsy	☐	__ __	__ __	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	
Sleeping tablets / tranquilisers	☐	__ __	__ __	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	
Anti-depressants	☐	__ __	__ __	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	
Other drugs to treat mental illness	☐	__ __	__ __	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	
Drugs for osteoporosis ("brittle bones")	☐	__ __	__ __	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	
Drugs for rheumatoid arthritis	☐	__ __	__ __	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	
Antibiotics for a month or more	☐	__ __	__ __	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	
Antacids	☐	__ __	__ __	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	
Drugs for stomach ulcer / gastritis	☐	__ __	__ __	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	

Type of drug	**Have you <u>ever</u> taken this drug <u>every day</u> for <u>over a month</u>?**	**At what age did you <u>first</u> 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 <u>currently</u> taking this drug every day?**	**<u>If you are currently taking this drug</u>, how is this funded?**	**Please write down the specific <u>name</u> of the drug you have used <u>most recently</u> if known:**
	✓ *if yes*	*Age 1st*	*Years taken:*	✓ *if yes*		*Name of drug:*
Drugs for high cholesterol (e.g. Statins)	☐	__ __	__ __	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	
Drugs for allergies (antihistamines)	☐	__ __	__ __	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	
Steroids (oral, inhaled, or nasal)	☐	__ __	__ __	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	
Chemotherapy for cancer	☐	__ __	__ __	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	
Tamoxifen for cancer	☐	__ __	__ __	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	
Drugs for Blood pressure (e.g. beta-blockers)	☐	__ __	__ __	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	
Drugs for angina (chest pain) (e.g. beta-blockers)	☐	__ __	__ __	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	
Other drugs for a heart condition (e.g. beta-blockers)	☐	__ __	__ __	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	
Inhaler for asthma	☐	__ __	__ __	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	
Warfarin / heparin to thin blood	☐	__ __	__ __	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	
Migraine tablets/injections	☐	__ __	__ __	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	
Vitamin D supplements	☐	__ __	__ __	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	
Other 1: ……..	☐	__ __	__ __	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	
Other 2: ……..	☐	__ __	__ __	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	
Other 3: ……..	☐	__ __	__ __	☐	☐ State Insurance ☐ Private Insurance ☐ Out of Pocket	

Personal Information and lifestyle

H1. What is your date of birth? __ __ / __ __ / __ __ __ __
DD MM YYYY

H2. How would you describe your ethnic origin?

☐ Cypriot → ☐ Turkish Cypriot ☐ Greek Cypriot ☐ Maronite ☐ Armenian ☐ Latin

☐ Turkish
☐ Greek
☐ Mixed: _____ *(Please specify)*
☐ Other: _____ *(Please specify)*

H3. What is your place of birth? (City/Country) _____

H4. Was your mother or father born in Cyprus?

☐ No
☐ Yes
☐ Do not know

If no → H4.1. Your father's place of birth (City/Country): _____ ☐Do not know

H4.2. Your mother's place of birth (City/Country):_____ ☐Do not know

H5. Was one of your grandparents born outside Cyprus?

☐ No
☐ Yes → **If yes, please specify: _____**
☐ Do not know

H6. What is your marital status?

☐ Single (never married) ☐ Married ☐ Divorced/ separated ☐ Widowed

H7. Are you currently living with a partner?

☐ No, I am not in a relationship ☐ No, but I am in a relationship ☐ Yes

H8. Are you currently in school?

☐ No ☐ Yes

H9. 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

H10. What is your occupation/job? _____

H11. What is your current height? _____ cm or if you prefer, _____ feet _____ inches

H12. What is your current weight? _____ kg or if you prefer, _____ pounds or _____ stones

H13. Since 18 years of age, what is **the most** that you have weighed (*Not including pregnancy and the 12 months following pregnancy*)?_____ kg or if you prefer, _____ pounds or _____ stones

H13.1. How old were you when you weighed that amount? _____

H14. Since 18 years of age, what is **the least** that you have weighed? _____ kg or if you prefer, _____ pounds or _____ stones

H14.1. How old were you when you weighed that amount? _____

H15. Do you know what your weight/height at birth was?

☐ No ☐ Yes

If Yes: H15.1.: Birth weight: ……pounds ……ounces or ……kilograms

H15.2.: Birth height: …… cm or …… inches

H16. At age 18, what was your natural hair colour? *(Please tick one)*

☐ Red ☐ Dark brown ☐ Blonde ☐ Light brown ☐ Black

H17. What is your eye colour? *(Please tick one)*

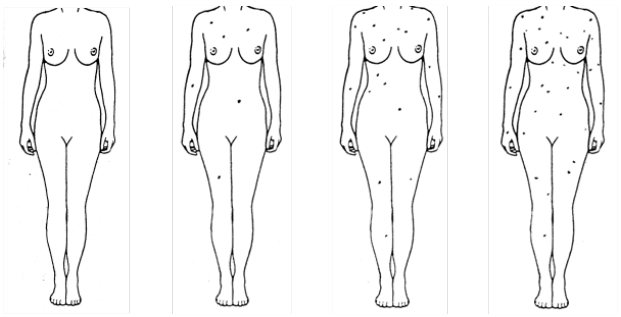
☐ Blue ☐ Hazel ☐ Gray ☐ Brown ☐ Green

H18. How would you describe your natural skin tone before tanning or on areas not exposed to the sun (*e.g. on your upper inner arm*)?

☐ Very light or white (often sunburns) ☐ Light intermediate (rarely sunburns) ☐ Dark (sunburns very rarely)
☐ Light (usually sunburns) ☐ Dark intermediate (rarely sunburns) ☐ Very dark (sunburns extremely rarely)

H19. Moles are brown or black spots on the skin, which usually start in childhood. They may be flat (cannot be felt) or raised (can be felt). Moles are usually darker and larger than freckles. Moles usually appear on their own, whereas freckles appear in groups. A spot that looks like a freckle but is on its own and cannot be felt is most likely a mole.

Using the diagrams below, which picture best describes how many moles you have on your body *(Please select one picture)*?



☐ No moles ☐ 1-10 moles ☐ 11-50 moles ☐ 50 and more moles

H20. On average, how much time in a week do you spend under sunlight (job, leisure, gardening, sports etc.) during the day (between 10a.m. and 4p.m.)?

	Less than an hour per week	**2-4 hours a week**	**5+ hours a week**
During Summer (April-October)			
Age <25	☐	☐	☐
Between ages 26–35	☐	☐	☐
Between ages 36–45	☐	☐	☐
Between ages 46–55	☐	☐	☐
In last 2 years	☐	☐	☐
During Winter (November-March)			
Ages <25	☐	☐	☐
Between ages 26–35	☐	☐	☐
Between ages 36–45	☐	☐	☐
Between ages 46–55	☐	☐	☐
In last 2 years	☐	☐	☐

H21. Do you regularly use sunscreen with more than 15 spf?

During summer: ☐Yes ☐No

During Winter: ☐Yes ☐No

H22. How many times **in a year** do you use solarium? (Please specify for the given time periods)

	None	1-2 times	3-5 times	6-11 times	12-23 times	24+ times
Summer months: Age <25	☐	☐	☐	☐	☐	☐
In summer between ages 26-34	☐	☐	☐	☐	☐	☐
In summer between ages 36-45	☐	☐	☐	☐	☐	☐
In summer between ages 46-55	☐	☐	☐	☐	☐	☐
In last 2 years	☐	☐	☐	☐	☐	☐

H23. 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)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Running (10 minutes/mile or faster)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Bicycling (include stationary machine)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Calisthenics/aerobics/aerobic dance/rowing machine	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Tennis, squash, racquetball	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Lap swimming	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Other aerobic recreation (e.g., lawn mowing)	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

H24. Have you smoked more than 100 cigarettes during your lifetime?

☐ No ☐ Yes

If yes: **H24.1.** How old were you when you first started smoking? _____ years old

H24.2. Do you smoke currently?

☐ No, I stopped smoking at age _____

☐ Yes, and I smoke about _____ cigarettes per week

H25. Do you drink any alcohol?

☐ No ☐ Yes

If yes: During an average week, how much do you drink of each of the following?
(*Please note exact numbers, not ranges such as 1-3*)

Type of alcohol (serving size)	Average number of each drink per week
Beer/lager/cider (330ml)	……
Whisky (50 ml)	……
Wine (125 ml)	……
Spirits, e.g. vodka (100 ml)	……
Raki (85ml)	……
Shots, e.g. zivania (15ml)	……
Other (*Please specify*)	……

H26. 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
- ☐ Unable to work because of the symptoms for which I am undergoing surgery
- ☐ In full time education
- ☐ Unable to work for other reasons
- ☐ Doing voluntary work
- ☐ Other (*Please describe*)……..

H27. **During the past four weeks**, how many days or hours did you miss from work because of problems associated with your symptoms? Include hours you missed on sick days, times you went in late, left early, etc., because of problems associated with your symptoms.

…….. days or ……..hours

H28. During the past four weeks, how many days or hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

…….. days or …….. hours

H29. During the past four weeks, how many days or hours did you actually work?

…….. days or …….. hours

H30. During the past four weeks, how much did your symptoms affect your productivity **while you were working**? *Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If your symptoms affected your work only a little, choose a low number. Choose a high number if your symptoms affected your work a great deal.*

You are asked about overall productivity on days you actually went to work. If productivity differed greatly from day to day, for example one day was 0 and one day was 10, please respond for all days, on average.

Consider only how much your symptoms affected productivity while you were working

Symptoms had no effect on my work — **Symptoms completely prevented me from working**

0 1 2 3 4 5 6 7 8 9 10

H31. 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**? *By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If your symptoms affected your activities only a little, choose a low number. Choose a high number if you symptoms affected your activities a great deal.*

You are asked about overall effect on your activities. If the effect differed greatly from day to day, for example one day was 0 and one day was 10, please respond for all days, on average.

Consider only how much your symptoms affected your ability to do your regular activities, other than work at a job.

Symptoms had no effect on my daily activities — **Symptoms completely prevented me from doing my daily activities**

0 1 2 3 4 5 6 7 8 9 10

H32. 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

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 II

Supplementary Table 1 – Frequencies of co-morbidities in endometriosis cases, symptomatic and asymptomatic pain controls

		Endometriosis (n = 410)	Symptomatic Control (n = 2,922)	Asymptomatic control (n = 4,314)
Reproductive	**Ovarian cysts**			
	No	318 (77.6%)	2,729 (93.4%)	4,102 (95.1%)
	Yes	92 (22.4%)	193 (6.6%)	212 (4.9%)
	Polycystic ovary syndrome			
	No	354 (86.3%)	2,721 (93.1%)	4,154 (96.3%)
	Yes	56 (12.7%)	201 (6.9%)	160 (3.7%)
	Uterine fibroids			
	No	336 (82.0%)	2,705 (92.6%)	3,946 (91.5%)
	Yes	74 (18.1%)	217 (7.4%)	368 (8.5%)
Autoimmune	**Asthma**			
	No	389 (94.9%)	2,757 (94.4%)	4,160 (96.4%)
	Yes	21 (5.1%)	165 (5.7%)	154 (3.6%)
	SLE			
	No	410 (100.0%)	2,919 (99.9%)	4,303 (99.8%)
	Yes	0 (0.0%)	3 (0.1%)	11 (0.3%)
	Sjogren's			
	No	401 (97.8%)	2,868 (98.2%)	4,248 (98.5%)
	Yes	9 (2.2%)	54 (1.9%)	66 (1.5%)
	Rheumatoid arthritis			
	No	407 (99.3%)	2,908 (99.5%)	4,248 (98.5%)
	Yes	3 (0.7%)	14 (0.5%)	66 (1.5%)
	MS			
	No	408 (99.5%)	2,915 (99.8%)	4,305 (99.8%)
	Yes	2 (0.5%)	7 (0.2%)	9 (0.2%)
	IBD			
	No	403 (98.3%)	2,893 (99.0%)	4,290 (99.4%)
	Yes	7 (1.7%)	29 (1.0%)	24 (0.6%)
	Graves' disease			
	No	408 (99.5%)	2,916 (99.8%)	4,298 (99.6%)
	Yes	2 (0.5%)	6 (0.2%)	16 (0.4%)

	Guatr			
	No	407 (99.3%)	2,884 (98.7%)	4,298 (99.6%)
	Yes	3 (0.7%)	38 (1.3%)	16 (0.4%)
	Hashimoto			
	No	388 (94.6%)	2,818 (96.4%)	4,128 (95.7%)
	Yes	22 (5.4%)	104 (3.6%)	186 (4.3%)
	Hyperthyroid			
	No	399 (97.3%)	2,872 (98.3%)	4,220 (97.8%)
	Yes	11 (2.7%)	50 (1.7%)	94 (2.2%)
	Hypothyroid			
	No	401 (97.8%)	2,823 (96.6%)	4,220 (97.8%)
	Yes	9 (2.2%)	99 (3.4%)	94 (2.2%)
	Unspecified thyroid disease			
	No	403 (98.3%)	2,878 (98.5%)	4,237 (98.2%)
	Yes	7 (1.7%)	44 (1.5%)	77 (1.8%)
	Type 1 diabetes			
	No	406 (99.0%)	2,904 (99.4%)	4,280 (99.2%)
	Yes	4 (1.0%)	18 (0.6%)	34 (0.8%)
Allergic	**Psoriasis**			
	No	409 (99.8%)	2,915 (99.8%)	4,299 (99.7%)
	Yes	1 (0.2%)	7 (0.2%)	15 (0.4%)
	Eczema			
	No	2,773 (94.9%)	369 (90.0%)	4,150 (96.2%)
	Yes	41 (10.0%)	149 (5.1%)	164 (3.8%)
Obesity/metabolic related	**Type 2 diabetes**			
	No	393 (95.9%)	2,830 (96.9%)	4,280 (99.2%)
	Yes	17 (4.2%)	92 (3.2%)	34 (0.8%)
	Insulin resistance			
	No	383 (93.4%)	2,768 (94.7%)	4,152 (96.2%)
	Yes	27 (6.6%)	154 (5.3%)	162 (3.8%)
	Hypoglycaemia			
	No	394 (96.1%)	2,836 (97.1%)	4,226 (98.0%)
	Yes	16 (3.9%)	86 (2.9%)	88 (2.0%)
	High cholesterol			
	No	374 (91.2%)	2,792 (95.6%)	4,101 (95.1%)

	Yes	36 (8.8%)	130 (4.5%)	213 (4.9%)
	Clinical obesity			
	No	405 (98.8%)	2,894 (99.0%)	4,270 (99.0%)
	Yes	5 (1.2%)	28 (1.0%)	44 (1.0%)
Cardiovascular	**CVD**			
	No	396 (96.6%)	2,840 (97.2%)	4,221 (97.8%)
	Yes	14 (3.4%)	82 (2.8%)	93 (2.2%)
	Mitral valve prolapse			
	No	2,876 (98.4%)	394 (96.1%)	4,264 (98.8%)
	Yes	46 (1.6%)	16 (3.9%)	50 (1.2%)
	Angina			
	No	410 (100.0%)	2,914 (99.7%)	4,302 (99.7%)
	Yes	0 (0.0%)	8 (0.3%)	12 (0.3%)
	Arrythmias			
	No	392 (95.6%)	2,859 (97.8%)	4,242 (98.3%)
	Yes	18 (4.4%)	63 (2.2%)	72 (1.7%)
	Congenital heart disease			
	No	404 (98.5%)	2,899 (99.2%)	4,288 (99.4%)
	Yes	6 (1.5%)	23 (0.8%)	26 (0.6%)
	High blood pressure			
	No	403 (98.3%)	2,783 (95.6%)	4,237 (98.2%)
	Yes	7 (1.7%)	129 (4.4%)	77 (1.8%)
	Low blood pressure			
	No	385 (93.9%)	2,781 (95.2%)	4,158 (96.4%)
	Yes	25 (6.1%)	141 (4.8%)	156 (3.6%)
Thalassaemia	**Alpha thalassaemia carrier**			
	No	406 (99.0%)	2,901 (99.3%)	4,283 (99.3%)
	Yes	4 (1.0%)	21 (0.7%)	21 (0.7%)
	Beta thalassaemia carrier			
	No	408 (99.5%)	2,907 (99.5%)	4,281 (99.2%)
	Yes	2 (0.5%)	15 (0.5%)	33 (0.8%)
	Unknown thalassemia carrier			
	No	382 (93.2%)	2,765 (94.6%)	4,103 (95.1%)
	Yes	28 (6.8%)	157 (5.4%)	211 (4.9%)

SLE, systemic lupus erythematosus; MS, multiple sclerosis; IBD, irritable bowel disease, CVD; cardiovascular disease

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METHODS
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Protocol for the Cultural Translation and Adaptation of the World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonization Project Endometriosis Participant Questionnaire (EPHect)

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Endometriosis affects 10% of women worldwide and is one of the most common causes of chronic pelvic pain and infertility. However, causal mechanisms of this disease remain unknown due to its heterogeneous presentation. In order to successfully study its phenotypic variation, large sample sizes are needed. Pooling of data across sites is not always feasible given the large variation in the complexity and quality of the data collected. The World Endometriosis Research Foundation (WERF) Endometriosis Phenome and Biobanking Harmonization Project (EPHect) have developed an endometriosis participant questionnaire (EPQ) to harmonize non-surgical clinical participant characteristic data relevant to endometriosis research, allowing for large-scale collaborations in English-speaking populations. Although the WERF EPHect EPQs have been translated into different languages, no study has examined the cross-cultural translation and adaptation for content and face validity. In order to investigate this, we followed the standard guidelines for cross-cultural adaptation and translation of the minimum version of the EPQ (EPQ-M) using 40 patients who underwent laparoscopic surgery in Turkey and 40

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women in Northern Cyprus, aged between 18 and 55. We assessed the consistency by using cognitive testing and found the EPHect EPQ-M to be comprehensive, informative, and feasible in these two Turkish-speaking populations. The translated and adapted questionnaire was found to be epidemiologically robust, taking around 30–60 min to complete; furthermore, participants reported a similar understanding of the questions, showing that common perspectives were explored. Results from the cognitive testing process led to minor additions to some items such as further descriptive and/or visuals in order to clarify medical terminology. This paper illustrates the first successful cross-cultural translation and adaptation of the EPHect EPQ-M and should act as a tool to allow for further studies that wish to use this questionnaire in different languages. Standardized tools like this should be adopted by researchers worldwide to facilitate collaboration and aid in the design and conduction of global studies to ultimately help those affected by endometriosis and its associated symptoms.

Keywords: endometriosis, standardization, harmonization, Turkish, questionnaire, EPHect, cross-cultural adaptation

INTRODUCTION

Endometriosis is a chronic inflammatory condition whereby tissue that resembles the endometrium is found at sites outside of the uterus, including the pelvis, bladder, bowel, and ovaries (1). It affects around 10% of reproductive age women worldwide (∼176 million women) and is one of the most common causes of pelvic pain and infertility (2). Endometriosis is heterogenous in presentation, with a wide variety of clinical presentations and behaviors, which means its causal mechanisms have been, so far, difficult to elucidate (1). The heterogeneity of the disease means that both its diagnosis and treatment are challenging as reliable diagnosis requires laparoscopic surgery. However, endometriomas and deep endometriosis can be visualized using ultrasonography or magnetic resonance imaging (MRI) (3, 4). Treatment options include removal or destruction of the disease tissue via laparoscopy or hormonal treatment and analgesics, which have unwanted side effects, high recurrence rates, and limited long-term support (1).

In order to successfully study the phenotypic variation seen in endometriosis, large sample sizes are needed. Given the large variation in the complexity and quality of data collection, pooling of data across study sites is not always feasible. The World Endometriosis Research Foundation (WERF) Endometriosis Phenome and Biobanking Harmonization Project (EPHect) has developed tools in order to facilitate the design and interpretation of collaborative studies, enabling large-scale, and epidemiologically robust research into endometriosis causes, diagnostic methods, and treatment improvements (5).

The WERF EPHect Working Group developed an endometriosis participant questionnaire (EPQ) (standard [EPect EPQ-S] and minimum [EPHect EPQ-M] versions) to evaluate non-surgical clinical participant characteristic data relevant to endometriosis. Although the WERF EPHect EPQs have been translated into different languages (endometriosisfoundation.org/ephect/2), no study has examined the cross-cultural translation and adaptation of the EPQ-M. Cross-cultural translation and adaptation is essential for content and face validity of the questionnaire in different languages. Using two Turkish-speaking populations to illustrate, we aim to provide a protocol to enable others to successfully implement and utilize the WERF EPQ-M, thus building upon the collaborative global effort in endometriosis research.

MATERIALS AND METHODS

Study Sample

A total of 80 women were recruited into the study between December 2017 and September 2019 with the following inclusion criteria: aged between 18 and 50, no known cognitive impairment, and the ability to give consent. All recruitment and data collection were undertaken by experienced recruitment teams. The study population was recruited from three different sites including two hospital settings, namely, the Cerrahpasa University Medical Faculty in Istanbul and Ataturk University Medical Faculty Hospital in Erzurum, Turkey. The clinical sample included 40 women who were undergoing laparoscopic surgery in Turkey, and the general population sample consisted of 40 randomly selected women from households in Northern Cyprus.

Study Design

The cross-cultural translation and adaptation of the WERF EPHect EPQ-M was carried out using the recommended guidelines (6) and to COSMIN standards (7). The process was completed as follows: (1) conceptual equivalence, (2) forward translation, (3) backward translation, (4) expert panel revision, (5) cognitive testing, and (6) proofreading (**Figure 1**).

1. **Conceptual Equivalence**

   This stage involved completing a literature review relating to endometriosis and health and well-being related concepts in the target language database. Gynecologists were consulted to ensure that all concepts and questions in the EPHect EPQ-M were well-defined and relevant as well as to allow for any modifications of potentially culturally insensitive/unsuitable

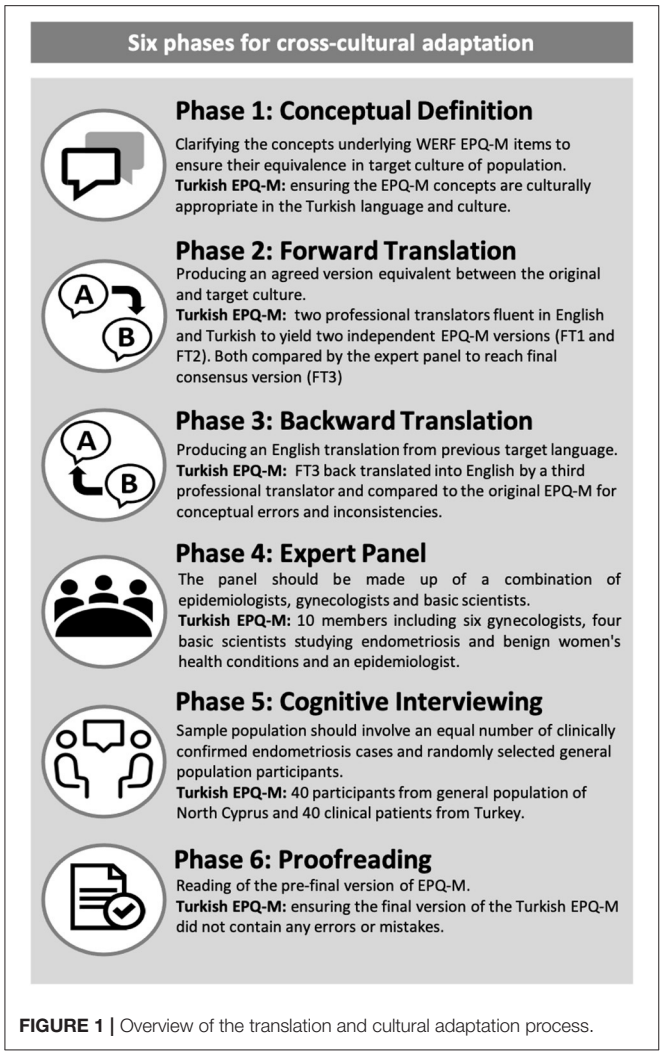

FIGURE 1 | Overview of the translation and cultural adaptation process.

differences. In our study, we used two gynecologists to complete this process. Semantic equivalences were sought prior to this and specifically focused on key concepts and their definitions in Turkish.

2. **Forward Translation**

   The forward translation was carried out by two independent professional translators who were native speakers of both the target language and English. This process produced two independent versions of the EPHect EPQ-M in the target language (FT1 and FT2), and these versions were compared by an expert panel for differences to reach a final consensus and a final forward translation version (FT3). The expert panel comprised of epidemiologists, basic research scientists, and gynecologists (some with endometriosis expertise). For the Turkish version of the EPHect EPQ-M, our translators were located in Famagusta (Cyprus) and Istanbul (Turkey). The expert panel consisted of one epidemiologist/basic research scientist (also a member of the WERF EPHect working group), six gynecologists (five with endometriosis expertise and one general gynecologist), and three basic research scientists.

3. **Backward Translation**

   The FT3 was then translated into English by a third independent professional translator. The expert panel compared the back-translated English version with the original English version of the WERF EPHect EPQ-M for conceptual errors and inconsistencies. This step is important in ensuring that the FT3 is suitably consistent with the original version. The third independent professional translator in our study was based in Famagusta (Cyprus).

4. **Expert Panel Revision**

   Here, the expert panel reviewed all forward and back translations in order to reach consensus and arrive at a pre-testing version of the EPHect EPQ-M.

5. **Cognitive Testing**

   Cognitive testing is an evidence-based methodology designed to evaluate how questions are understood and interpreted by the target population (8). The research assistants sat opposite to the participants, and the participants were asked to read the instructions, questions, and answer options of the pre-testing EPHect EPQ-M. The participants were given the opportunity to indicate if there was anything on the questionnaire that was unclear to them, and these were then reviewed by the expert panel to arrive at the final version. The outcome of this process was the final Turkish WERF EPHect EPQ-M.

6. **Proofreading**

   The final EPQ-M was proofread to ensure that it did not contain any errors or mistakes.

Ethical Approval

The COHERE Initiative was approved by the Oxford Tropical Research Ethics Committee (OxTREC) of the University of Oxford (OxTREC reference: 37-17) and the Ethics Committee of Eastern Mediterranean University (ETK00-2017-0240). The Turkish Endometriosis Genomic Study received ethics approval from the Cerrahpasa University Faculty of Medicine Ethics Group (52825153-604.01-01-20831). Informed consent was obtained from all participants.

RESULTS

Conceptual Evidence

Both a review of published articles in the Turkish database and the expert review suggested that all concepts within the Turkish EPHect EPQ-M sufficiently addressed endometriosis-related symptomatology, history, and related reproductive health and lifestyle factors in the Turkish-speaking population. The question "How would you describe your ethnic origin?" was considered too intrusive by the participants in Turkey, and although it was deemed acceptable in the Turkish Cypriot community, it was excluded in this instance and left as an optional question for future studies given the potential sensitivities around the topic.

Translations and Revisions

All of the main concepts (such as "menstrual period," "pregnancy," "fertility," and "pelvic pain") were found to have the same meaning in Turkish as they did on the original

English EPHect EPQ-M and were therefore said to have sematic equivalence. Sematic equivalence was also evidenced in the back-translation process when the Turkish EPQ-M was translated back into English.

The main challenges in the forward translation process were surrounding the linguistic typology differences between Turkish and English. The Turkish language follows a subject–object–verb (SOV) sentence structure, whereas English follows a subject–verb–object (SVO) sentence structure. The backwards translation phase produced very similar translations; the only differences were caused by variations in the sentence structure and where the back translation produced a more indirect translation, e.g., "emergency pregnancy control" instead of "emergency contraception."

Once the expert review panel had arrived at the pre-testing version of the EPHect EPQ-M, the questions were shortened to make the wording more succinct using the best colloquial terminology in Turkish reproductive health. Once consensus had been reached, the pre-testing version was taken forward into the cognitive testing phase.

Cognitive Testing

A total of 80 women between the ages of 18 and 55 took part in the cognitive testing process (**Table 1**) with duration of questionnaire completion ranging from 30 to 60 min. Ninety-five percent of the participants self-reported to have a high-school degree or above in Northern Cyprus, Istanbul, and Turkey, whereas 60% of the participants based in the Eastern Anatolian regions had only primary school degrees.

Although the majority of the participants found the questionnaire to be clear, all commented that the questionnaire was too long. Forty percent of the participants commented on the length after completing Section D, with the rest commenting after completing the whole questionnaire. Despite skip patterns being included in the questionnaire, they were missed by 10% of the participants. As a result of this, we made the skip patterns more visually distinct on the questionnaire and recommend that participants be notified about the skip patterns before the questionnaire is started. Twenty percent of all participants with primary or secondary education commented that the following questions were repetitive: pelvic pain questions (Section C2), during or after vaginal intercourse (Section C15), and pelvic pain in general (Section C27). The research assistants explained the differences between the sections, and we saw that participants had not properly read and understood the instructions at the beginning of these subsections. As a result of this, we made the instructions more visually distinct and recommend instructing the participants to read the instructions in these subsections of the questionnaire before starting. One participant from Northern Cyprus with primary school level education had difficulties in understanding some of the medical terms ("pelvic" and "anxiety"), so these were clarified by introducing a text that described the terms in parentheses next to these terminologies (e.g., pelvic—the lower part of the abdomen and/or groin, and anxiety—a worry).

The format of the items on the pregnancy/fertility history questionnaire table (Section B1) was found to be complicated

TABLE 1 | Summary of participant characteristics.

Participant profile and recruitment setting	N* of participants	Mean age (Range)	Mean BMI (Range)	Parity	Residence	Highest educational qualification obtained	Employment status	Marital status
Clinical patients: symptomatic patients undergoing laparoscopic surgery from hospital gynecology clinics	*N* = 40	34.9 (20–54)	23.0 (17.6–28.6)	*N* = 12 Nulliparous *N* = 28 Parous	*N* = 21 Istanbul *N* = 19 Eastern Anatolian region (*N* =1 Bingol, *N* = 1 Erzincan, *N* = 12 Erzurum, *N* = 3 Igdir, *N* = 1 Karliova, *N* = 1 Mus)	*N* = 11 Primary-school N = 1 Secondary-school *N* = 9 High-school *N* = 17 Undergraduate *N* = 1 Postgraduate *N* = 1 N/A	*N* = 4 Student *N* = 20 Home-maker *N* = 16 employed	*N* = 30 Married *N* = 10 Single
General population: Turkish-speaking women from random households	*N* = 40	35.5 (18–55)	23.2 (16.5–39.2)	*N* = 16 Nulliparous *N* = 24 Parous	*N* = 14 Nicosia *N* = 17 Famagusta *N* = 3 Kyrenia *N* = 2 Iskele	*N* = 2 Primary-school *N* = 10 High-school *N* = 14 Undergraduate *N* = 14 Postgraduate	*N* = 6 Student *N* = 34 Employed	*N* = 21 Married *N* = 14 Single *N* = 5 Divorced

*N, number.

and difficult to understand by 5% of the participants at first. We revised the table to fit onto a single page and made the subquestions bold to counteract this. Two and a half percent of the participants stated that they found the format of questions E1 and E2 complicated, and so similar formatting changes were made to help with the understanding and interpretation of these questions. We recommend that participants be given the opportunity to contact the research assistants on the study to ask any questions they may have before they submit their completed questionnaire. Although the presence of a research assistant when the participants were completing their questionnaire was shown to be motivational, it is important that the research assistants are fully trained so that responses to participant questions are consistent in wording, detail, and tone, not to bias the answers to be given by the participants.

At the end of Section F, we originally asked participants to provide their contact details (name, phone number, email, and address) if they wanted to be informed of future studies. However, as this then made questionnaire identifiable, we removed this section and participants were able to provide their contact information voluntarily on the consent form, which we then stored in a separate database on high-compliance servers.

DISCUSSION

The aim of this study was to provide a protocol for the cross-cultural translation and adaptation of the WERF EPHect EPQ-M. Using the Turkish language as an example, we used cognitive testing on 80 participants who found the questionnaire to be informative and feasible. Despite the participants commenting on the length of the questionnaire, all were able to fully complete it in 30–60 min and could not point out which section/questions they felt could be eliminated. Although the level of detail that the questionnaire asks is high, we believe that capturing this information is essential for the successful characterization of endometriosis as well as important exposures such as pain symptomatology, menstrual and reproductive history, medical history, hormone use, infertility, and demographic and lifestyle information. To help with the successful completion of the questionnaire, we made the skip patterns more visible using formatting techniques and recommend that participants be informed about skip patterns to avoid completion of unnecessary questions. In addition to this, using an electronic online platform to administer the questionnaire could mean that questions that need to be skipped could be done so automatically, depending on the prior responses of participants to certain questions.

A limitation of this study is that we only cross-culturally adapted and translated the minimal version of the WERF EPHect questionnaire (EPQ-M), which excludes questions on symptoms or characteristics pertaining across the life course. Hence, these additional questions in the standard (EPHect EPQ-S) questionnaire would also need to be cross-culturally adapted and translated into Turkish in subsequent studies.

Recommendations

Although the regions that we have collected data from (Turkey and Northern Cyprus) use the same wording of the Turkish language, Turkish-speaking Cypriots have a different dialect. Regardless, all participants were able to understand and complete the Turkish EPHect EPQ-M. The education level of the participants was an important factor in the participant's understanding of the medical terminology included in the questionnaire, and we clarified this by using more common terms. In addition to this, we found that participants with lower education levels appeared to pay less attention to the instructions at the start of the questionnaire, so we recommend that research assistants be available to participants so that they can ask any questions before completing the questionnaire. In order to avoid data breaches, contact information from participants should be collected on a separate form to the questionnaire.

As the physical and mental state of participants has been shown to affect the responses of participants in symptom-based questionnaires like the EPHect EPQ-M (9), we recommend that the Short Form Health Status Survey (SF-36v2) (10) or the Endometriosis Health Profile Questionnaire (EHP-30) (11) or both be administered prior to the administration of the EPHect EPQ-M in order to capture the health-related quality of life of participants. We did not include them in our study here because it requires each study to be individually registered to use them. In addition to this, depression and anxiety scales, such as the Beck Depression Inventory (BDI) (12, 13), the State Trait Anxiety Inventory (STAI) (14, 15) and/or the Hospital Anxiety and Depression Scale (HADS) (Aydemir, 1997; Zigmond and Snaith, 1983) can also be useful for stratification of participants.

This is the first paper that has successfully cross-culturally adapted and translated the WERF EPHect EPQ-M for content and face validity and should act as a tool to allow for further studies that wish to use this questionnaire in other languages. Standardized tools like these are essential in order to facilitate collaboration and aid in the design and conduction of global studies to ultimately expand our knowledge into understanding the mechanisms of endometriosis and help those affected.

Afterword

The Turkish cross-culturally translated and adapted questionnaire is freely available in the **Supplementary Material** of this paper. However, we request that researchers who wish to use it cite both the original EPHect questionnaire paper as well as this paper along with any modifications they make in order to adapt it to their population.

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.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by (1) Oxford Tropical Research Ethics Committee (OxTREC) of the University of Oxford (OxTREC reference:

37-17). (2) Ethics Committee of Eastern Mediterranean University (ETK00-2017-0240). (3) Cerrahpasa University Faculty of Medicine Ethics Group (52825153-604.01-01-20831). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CM, GK, GS, BY, PY, and NR: recruitment and cognitive testing. CM, GK, BS, MH, and NR: manuscript preparation. MH and NR: substantial contributions to conception and design of the study. BS, BY, PY, GS, BT, LH, SM, CB, KZ, UI, EO, MH, and NR: critically revised the manuscript. All authors read, contributed to, and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgwh.2021.644609/full#supplementary-material

Supplementary Material | Turkish EPHect EPQ-M.

REFERENCES

1. Zondervan KT, Becker CM, Koga K, Missmer SA, Taylor RN, Viganò P. Endometriosis. *Nat Rev Dis Primers*. (2018) 4:9. doi: 10.1038/s41572-018-0008-5
2. Shafrir AL, Farland LV, Shah DK, Harris HR, Kvaskoff M, Zondervan K, et al. Risk for and consequences of endometriosis: a critical epidemiologic review. *Best Pract Res Clin Obstetr Gynaecol*. (2018) 51:1–15. doi: 10.1016/j.bpobgyn.2018.06.001
3. Agarwal SK, Chapron C, Giudice LC, Laufer MR, Leyland N, Missmer SA, et al. Clinical diagnosis of endometriosis: a call to action. *Am J Obstetr Gynecol*. (2019) 220:354.e351. doi: 10.1016/j.ajog.2018.12.039
4. Hsu AL, Khachikyan I, Stratton P. Invasive and noninvasive methods for the diagnosis of endometriosis. *Clin Obstet Gynecol*. (2010) 53:413–9. doi: 10.1097/GRF.0b013e3181db7ce8
5. Casper RF. Introduction: new tools for enhancing collaborative endometriosis research. *Fertil Steril*. (2014) 102:1211–2. doi: 10.1016/j.fertnstert.2014.07.1211
6. Beaton DE, Bombardier C, Guillemin F, Ferraz MB. Guidelines for the process of cross-cultural adaptation of self-report measures. *Spine*. (2000) 25:3186–91. doi: 10.1097/00007632-200012150-00014
7. Mokkink LB, Terwee CB, Patrick DL, Alonso J, Stratford PW, Knol DL, et al. COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. *Qual Life Res*. (2010) 19:539–49. doi: 10.1007/s11136-010-9606-8
8. DeMuro CJ, Lewis SA, DiBenedetti DB, Price MA, Fehnel SE. Successful implementation of cognitive interviews in special populations. *Expert Rev Pharmacoeconomics Outcomes Res*. (2012) 12:181–187.
9. Vitonis AF, Vincent K, Rahmioglu N, Fassbender A, Buck Louis GM, Hummelshoj L, et al. World endometriosis research foundation endometriosis phenome and biobanking harmonization project: II Clinical and covariate phenotype data collection in endometriosis research. *Fertil Steril*. (2014) 102:1223–32. doi: 10.1016/j.fertnstert.2014.07.1244
10. Ware JE, Snow KK, Kosinski M, Gandek B. *SF-36 Health Survey Manual and Interpretation Guide*. Boston, MA: The Health Institute, New England Medical Centre (1993).
11. Jones G, Jenkinson C, Kennedy S. Evaluating the responsiveness of the endometriosis health profile questionnaire: the EHP-30. *J Quality of Life Res*. (2004) 13:705–13. doi: 10.1023/B:QURE.0000021316.79349.af
12. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of beck depression inventories-IA and -II in psychiatric outpatients. *J Personal Assessment*. (1996) 67:588–97. doi: 10.1207/s15327752jpa6703_13
13. Hisli N. Beck depresyon envanterinin üniversite ogrencileri icin gecerligi, güvenirligi. *Psikoloji Dergisi*. (1989) 1989:3–13.
14. Jacobs GA, Latham LE, Brown MS. Test-retest reliability of the state-trait personality inventory and the anger expression scale. *Anxiety Res*. (1988) 1:263–5. doi: 10.1080/08917778808248724
15. Oner N, Le Compte A. Durumluk Surekli Kaygi Envanteri El Kitabi. *Bogazici Universitesi Yayinlari*. (1983) 1–26.

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The Cyprus Women's Health Research (COHERE) initiative: normative data from the SF-36v2 questionnaire for reproductive aged women from the Eastern Mediterranean

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Abstract

Purpose Describe the health-related quality of life for a representative cohort of women aged 18–55 in Northern Cyprus.

Methods We utilised the SF-36-Health-Survey-version-2 (SF-36v2) questionnaire as part of the COHERE Initiative study to calculate the eight physical and mental subscale scores, as well as the two overall summary measures for physical and mental health, where we present results using Cyprus-specific scoring as well as scores based on the test developers' algorithms. We examined associations between sociodemographic characteristics for both scores.

Results A total of 7089 women fully completed the SF-36v2 questionnaire (mean age = 36.9), which was reliable and valid in this population. We observed better physical health in ages 18–25 compared to 46–55 (53.32 vs. 46.72 ($p < 0.001$)) and better mental health in women aged 46–55 compared to 18–25 (52.07 vs. 47.95 ($p < 0.001$)). Women in employment had better physical and mental health compared to those who were unemployed (physical: 50.25 vs 49.95, $p < 0.001$ and mental: 50.25 vs 49.24, $p = 0.083$) and scores increased as educational attainment increased (physical: 47.55 for primary to 51.58 for postgraduate, mental: 48.88 to 50.59, $p < 0.001$). Turkish Cypriot women had higher scores than Turkish women (physical: 50.42 vs 49.30, mental: 50.43 vs 49.10, $p < 0.001$).

Conclusion These are the first population normative values published from a large representative sample of women between 18 and 55 years from the Eastern Mediterranean region. We found better physical health in younger women and better mental health in older women. Turkish Cypriot women and non-migrant women had better mental health, and HRQOL was highest in those in paid employment and those with a higher educational achievement.

Keywords SF-36 · Health-related quality of life · Northern Cyprus, Population norms · Women's health · Patient-reported outcome (PRO)

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Introduction

Health-related quality of life (HRQOL) is important when exploring the general wellbeing of the population, as well to evaluate specific health states. The Short Form-36 Health Survey (SF-36) is a self-reported multi-dimensional measure widely used across countries, with its use ranging from monitoring the burden of disease, to examining the cost-effectiveness of a treatment [1]. In order to aid interpretation of the data, the developers recommend that a normative-based scoring method using US weights is used to provide a standard with which scores from other populations can be compared. However, there is much discussion surrounding whether it is appropriate to use weights that may not be culturally specific, especially when there are differences in health states.

Cyprus is the third largest Mediterranean island with around 300,000 Turkish Cypriot and 700,000 Greek Cypriot residents. There is a lack of population-level health data from Northern Cyprus due to unresolved political circumstances [2, 3] and as a result, this part of the island is absent from any published health statistics from the region. To date, there are no published studies that have provided population normative values in Cyprus for the SF-36, and it is inappropriate to use published values from other countries given the differences in healthcare. A cross-sectional study in Limassol, Republic of Cyprus examined HRQOL in the region [4], but it did not provide normative values for the island and instead used normative values derived from the U.S.A. Another cross-sectional study in Izmir, Turkey, used the SF-36 to provide population norms for the urban population [5]. However, the study took part just after a major economic crisis which is likely to have had an impact on the mental health component of the quality of life scores.

This paper seeks to address the lack of normative data applicable to Northern Cyprus and also serves to add further reference values for the Eastern Mediterranean region. We use data from the Cyprus Women's Health Research (COHERE) Initiative, to provide population norms for the eight SF-36-Health-Survey version 2 (SF-36v2) health domains as well as the two higher-order summary scores; Physical Component Summary (PCS) and Mental Component Summary (MCS). We examine the reliability and the validity of this dataset and its ability to provide this information, as well as testing the construct validity by investigating statistical relationships between each domain and a range of demographic variables that are known to be related to health outcomes including age, ethnicity, migration status, educational attainment, region of residence, civil status and employment status.

Methods

Study sample: the COHERE Initiative

Normative values for the SF-36v2 and the physical and mental health scoring coefficients were estimated using data collected as part of the COHERE Initiative. The COHERE Initiative is a population based cross-sectional study that has recruited 7646 consenting women between the ages of 18–55 in Northern Cyprus. The aim of COHERE is to determine the relative burden of women's health conditions and related co-morbidities in women living in Northern Cyprus and as such, establish a women's health cohort for future follow-up. In short, each participant completed the baseline questionnaire—an expanded version of the Endometriosis-Phenome-and-Biobanking-Harmonization-Project (EPHect) questionnaire [6] which included the SF-36v2 generic health measurement. Data were collected through a combination of household (16%, ($n = 1208$)) and workplace (84% (6438)) face-to-face visits (93% (7128)) as well as through online (7% (518)) recruitment methods [7], between January 2018 and February 2020. Women aged between 18 and 55 at recruitment, who were either citizens of Northern Cyprus or had been residing there for the past 5 years and were able to give informed consent were eligible to participate in the study. Women were recruited into the study from the 6 main districts in Northern Cyprus (Nicosia, Kyrenia, Famagusta, Morphou, Trikomo and Lefke) with recruitment targets being set using geographic population densities.

We compared the age, educational attainment, civil status, employment status, and city of residence structure of our sample with the projected 2019 population figures for Northern Cyprus obtained from the Northern Cyprus Statistics Institution (available on request from: http://www.stat.gov.ct.tr/). Our sample was broadly representative of these projected values with the main differences being seen in age and education. We calculated weights for age and education and present all SF-36v2 scores obtained from the sample both unweighted and weighted.

Ethics

The study was approved by the Oxford Tropical Research Ethics Committee (OxTREC) of the University of Oxford (OxTREC reference: 37–17). The study also received local ethics approval from the Eastern Mediterranean University Ethics Committee (ETK00-2017-0240).

SF-36v2 health domain subscales

The SF-36 has been validated previously in the Turkish language [8, 9]. Within the SF-36, there are 36 items that measure 8 domains as follows: limitations in physical activity due to health problems (physical functioning, 10 items), limitations in social activities due to physical or emotional problems (social functioning, 2 items), limitations in usual role activities due to physical health problems (role physical, 4 items), limitations in usual role activities due to emotional problems (role emotional, 3 items), wellbeing and psychological distress (mental health, 5 items), energy and fatigue (vitality, 4 items), bodily pain (bodily pain, 2 items) and perceptions of general health (general health, 5 items). Within the 36 items, there is a singular additional question asking about changes in health over the past year. Using the methods set out by Ware et al. [10, 11], the items within each of the above dimensions were coded, summed, and transformed (calculated by subtracting the lowest possible raw score from the actual raw score, dividing by the possible raw score range, and multiplying this by 10. This gave a

scale from 0 (worst possible health state as measured by the questionnaire) to 100 (best possible health state).

We also calculated the 8 health domains using norm-based scoring using a T-score transformation where the mean was set to 50 and the standard deviation to 10 in the current sample.

SF-36v2 component summary scores

Following the methods set out in the SF-36v2 manual, the data were factor analysed to produce scoring coefficients for PCS and MCS [11]. In short, we used principal components analysis to produce factor loadings, applied an orthogonal varimax rotation to rotate these loadings and then obtained scores. Calculating PCS involved multiplying each SF-36 scale z-score (calculated by subtracting the mean of SF-36 scale and dividing the difference by the corresponding scale standard deviation) by its respective factor score coefficient and in the case of the MCS, this involved multiplying each SF-36 scale z-score by its respective factor score coefficient. Finally, a T-score transformation was used to standardise the scores whereby the mean was set to 50 and the standard deviation to 10. PCS and MCS are two clusters that are produced from each of the eight scales and allow for further interpretation of the results.

Although no previous studies have investigated the SF-36v2 measures in Northern Cyprus, a cross-cultural adaptation of the survey was shown to be successful in Turkey and demonstrated an acceptable level of reliability and validity in its use in Turkish speaking individuals [5, 8]. To investigate whether the SF-36v2 questionnaire was valid in Northern Cyprus, reliability and validity was assessed. We also calculated summary measures using US-specific health domain subscale scores from 1998 and US-specific factor score coefficients from 1990 [12].

Reliability

Cronbach's alpha was used to examine internal consistency reliability; a value of > 0.7 was considered satisfactory. To assess whether the summary measures, PCS and MCS were reliable, the reliability of each of the eight subscales, the covariances among them and the factor score coefficients were calculated.

Validity

Principal components analysis, item-subscale correlations (item-rest correlations for the subscales and their respective items) and inter-scale correlations (Spearman correlations) were used to assess construct validity. A value of > 0.4 for item-rest correlations was considered satisfactory. If the correlation between an item and the sum of the other items its respective subscale (item-rest correlation) was shown to be significantly higher than its correlation with other subscales (item-subscale correlations) then the item's inclusion in its subscale was supported. If the correlation between two subscales was less than their reliability coefficients (Cronbach's alpha), then it can be said that there is evidence of reliable variance measured by the respective subscales.

Sociodemographic characteristics

We used self-reported data from the COHERE questionnaire in order to obtain potential covariates. Age was calculated by subtracting birthyear from survey completion date and categorised into the following four groups: 18–25, 26–35, 36–45 and 46–55. Ethnicity was split into 3 groups: Turkish Cypriot, Turkish, Mixed/Other (women reporting to have 2 ethnicities and women reporting to be a single ethnicity other than Turkish Cypriot or Turkish). Migration status (born in Northern Cyprus or parents born in Northern Cyprus, not born in Northern Cyprus and therefore recent migrant to the island). Highest educational achievement (primary or middle school, high school or post-secondary, undergraduate and postgraduate), employment status (employed or unemployed), civil status (single, married, divorced/widowed), city of residence (Nicosia, Famagusta, Trikomo, Lefke, Morphou, Kyrenia) were also assessed using the questionnaire data.

Missing data

As we used a large sample size ($n = 7646$) and the intention of this primary analysis was to obtain the factor loadings to construct the summary scores, data substitution algorithms were not used. In addition to this, there has been speculation that substitution of mean values may have either a conservative or attenuated bias [13]. Given these are the first normative scores to be calculated for women in Northern Cyprus between the ages of 18–55, it is also important to report 'actual' scores, so that normative scores here can be used for future analyses and are not differentially attenuated according to the amount of missing data that has been recorded [14]. This approach is consistent with previously published studies [15, 16].

Statistical analyses

Descriptive statistics for each of the eight subscales for the included sample and different subsamples according to age, ethnicity, migration status, educational achievement, civil status, city of residence and employment status were calculated. Differences in means of the eight health subscales for each of the subscales were tested using linear regression. Regressions were computed both crudely and

after adjustment for age, as age is usually correlated with the covariates examined here. Regressions for ethnicity and migration status were additionally adjusted for educational achievement and employment classification, as these two demographics are often correlated with non-native people. Statistical analyses were carried out using Stata SE version 16.0.810 (StataCorp LP, College Station, Texas, USA) and R Studio.

Results

Sample population and data completion

Our sample population consists of 7646 women with a mean age of 36.9 years. Women in our cohort were more likely to be Turkish Cypriot (73.8%), native to the island (74.6%) have a university degree (52.7%), be married (66.5%), be in paid employment (81.2%) and reside in the capital city, Nicosia (43.2%) (Table 1). Percentages for whom scale scores could not be calculated due to incomplete items for a particular scale was low and ranged from 0.5 to 2.9% (data not shown).

Validation of the SF-36v2 questionnaire for women in Northern Cyprus

Regarding reliability, Cronbach's alpha coefficients were found to be satisfactory (> 0.70) for all health domains (Table 2), apart from general health (0.69). Reliability of the summary measures was 0.89 for both PCS and MCS.

When looking at validity, item-rest correlations were all satisfactory apart from PF10 of the physical functioning perception subscale (0.38). The principal components analysis produced two factors with eigenvalue > 1 which indicates a two-factor structure. All items were satisfactory when looking at differences between item-rest correlations and inter-scale correlations i.e. correlations were higher between individual items and their respective subscales, than between individual items and the other 7 subscales. It was also found that the correlations between subscales were lower than their respective Cronbach's alpha values which suggest that there is unique reliable variance (Table 2). Ceiling effects were highest in physical functioning and role physical subscales (39–42%) with the bodily pain subscale having the highest floor effect (1.20%).

Table 1 Comparison between various demographics of participants within the Cyprus Women's Health Research (COHERE) Initiative and the census for Northern Cyprus

	Characteristics	*N* (%)	
		COHERE	Census
Age at study (years)	18–25	1108 (14.5)	22,355 (22.7)
	26–35	2383 (31.2)	31,228 (31.6)
	36–45	2447 (32.0)	25,318 (25.7)
	46–55	1708 (22.3)	18,784 (20.0)
Education	Primary or middle school	845 (11.8)	28,426 (33.4)
	High school or post-secondary	2557 (35.6)	31,748 (37.3)
	Undergraduate	2583 (35.9)	19,713 (23.2)
	Postgraduate	1204 (16.8)	5206 (6.1)
Civil status	Single	1753 (24.1)	24,015 (23.8)
	Married	4839 (66.5)	68,257 (67.5)
	Divorced/separated or widowed	684 (9.4)	8809 (8.7)
Employment[a]	In paid employment	5929 (81.2)	46,089 (91.1)
	Not in paid work	1374 (18.8)	871 (1.9)
City of residence	Famagusta	1611 (21.1)	25,300 (25.6)
	Kyrenia	1263 (16.5)	23,848 (24.2)
	Lefke	2691 (3.7)	261 (3.4)
	Morphou	585 (7.7)	6095 (6.2)
	Nicosia	3301 (43.2)	32,503 (32.9)
	Trikomo	625 (8.2)	7249 (7.3)

Only includes women between the ages 18–55. Ethnicity and migration status were not available

[a]In paid employment includes both employees and self-employed. Not in paid work includes students, homemakers, retirees, and those without employment

Table 2 SF-36v2 health domain subscales: mean 0–100 scores with 95% confidence intervals, standard deviation, percentage floor, percentage ceiling, factor score coefficients, and Cronbach's alpha

Scale	*N*	Mean 0–100 score	95% CI	SD	Percentage floor (%)	Percentage ceiling (%)	Factor score coefficients		Cronbach's alpha
							PCS	MCS	
Physical functioning (PF)	7607	88.28	(87.92, 88.63)	15.84	0.17	39.49	0.49	− 0.21	0.87
Role Physical (RP)	7558	80.67	(80.15, 81.18)	22.81	0.48	41.81	0.41	− 0.11	0.92
Bodily pain (BP)	7596	68.22	(67.67, 68.77)	24.38	1.20	22.63	0.35	− 0.08	0.87
General health (GH)	7548	63.79	(63.35, 64.24)	19.82	0.21	1.50	0.17	0.08	0.69
Vitality (VT)	7426	57.50	(57.03, 57.97)	20.71	0.83	1.25	− 0.15	0.37	0.74
Social functioning (SF)	7577	77.40	(76.87, 77.92)	23.27	0.73	35.87	0.03	0.22	0.74
Mental health (MH)	7455	64.05	(63.60, 64.50)	19.81	0.31	1.99	− 0.20	0.41	0.83

CI confidence interval, *SD* standard deviation, *PCS* physical component summary, *MCS* mental component summary

Health domain subscales

Women who were younger had better physical health (PF, RP, BP) compared to older women but as age increased, mean scores for the mental health subscales also increased (VT, RE, MH) (Table 3). Though GH increased with age, this was not statistically significant. When considering ethnicity, women who self-reported to be Turkish had the lowest scores across all domains except MH, RE, SF, and all but PF remained statistically significant after adjustment for age (Table 4). Women who were not migrants had higher subscale scores for all the domains compared to women with a migration background (PF, BP, GH, VT, SF, RE, MH (Supplementary Table 2). After adjustment for age, married women generally had the best mental health (MH, RE, SF) but the worst physical health (PF, RP, BP) (Supplementary Table 3). Residency of the women in COHERE did not appear to significantly affect physical or mental health domains (Supplementary Table 4). As educational attainment increased, mean physical health also increased after adjustment for age, (PF, RP, BP, GH) as did mental health domains (VT, RE and MH) (Table 5). Generally, women who were employed had significantly better physical subscale scores (PF, RP, BP, GH) with only the VT mental health score remaining significant after adjustment for age (Table 6).

The 8 domains presented as norm-based scores can be seen in the Appendix (Supplementary Tables S4-S10).

SF-36v2 summary measures PCS and MCS

Principal components analysis and orthogonal rotation was used to factor analyse the data and led to a two-factor solution; factor labelled PCS gained an eigenvalue of 4.00, with MCS having an eigenvalue of 1.14. We found better physical health (PCS) in younger women and generally better mental health in older women (Table 7). Higher scores were seen in women with a higher educational achievement and those in paid employment. Single women appeared to have the best physical health and the worst mental health (mean age in single women = 27.03 (SD 7.20) vs married women = 39.74 (SD 8.16)). Women residing in Morphou had the lowest PCS scores and those in Famagusta the worst MCS scores, with women in Kyrenia having the highest PCS scores and those in Lefke the highest MCS scores. These associations were not significant once adjusting for age (mean age and SD in each district as follows: Famagusta (mean = 35.5 (SD 9.8)), Kyrenia (mean = 37.2 (SD 9.4)), Lefke (mean = 38.1 (SD 9.5)), Morphou (mean = 37.6 (SD 10.2)), Nicosia (mean = 37.4 (SD 9.3)) and Trikomo (mean = 36.1 (SD 10.3)) (Table 7). Turkish Cypriot women had both the best physical (with other/mixed ethnicities) and mental health scores after adjustment for age as did those women with a non-migration background. After further adjustment for education and occupation classification, associations were especially attenuated for migration status and health scores and although the effect was also lessened between ethnicity and the two health scores, associations remained significant for MCS (not shown).

After weighting our data by age and education we did not see great differences in the results (Supplementary Tables S11-S19).

PCS estimates calculated using US coefficients were broadly similar to those generated using our sample; however, we found that the MCS estimates were substantially lower (Supplementary Tables S20-S21).

Discussion

We have shown that the SF-36v2 questionnaire is both reliable and valid in women between the ages of 18–55 residing in Northern Cyprus in evaluating HRQOL. We found better physical health in younger women and better

Table 3 SF-36v2 health domain subscales: mean 0–100 scores with 95% confidence intervals, standard deviation, *p* values from linear regression (global test) according to age (18–25, 26–35, 36–45, 46–55)

Scale	18–25 years				26–35 years				36–45 years			
	N	Mean 0–100 score	95% CI	SD	*N*	Mean 0–100 score	95% CI	SD	*N*	Mean 0–100 score	95% CI	SD
Physical functioning (PF)	1107	93.23	(92.50, 93.97)	12.46	2374	90.97	(90.42, 91.53)	13.77	2431	87.90	(87.28, 88.52)	15.61
Role Physical (RP)	1103	85.17	(83.94, 86.41)	20.93	2361	82.09	(81.19, 82.99)	22.30	2407	79.50	(78.58, 80.41)	22.84
Bodily pain (BP)	1100	72.07	(70.64, 73.49)	24.08	2370	69.93	(68.98, 70.89)	23.71	2426	67.28	(66.31, 68.25)	24.39
General health (GH)	1098	63.41	(62.22, 64.60)	20.07	2361	64.35	(63.57, 65.13)	19.32	2413	62.87	(62.07, 63.68)	20.18
Vitality (VT)	1086	56.19	(54.95, 57.43)	20.84	2315	57.35	(56.54, 58.17)	20.08	2372	57.18	(56.34, 58.02)	20.86
Social functioning (SF)	1100	77.32	(75.95, 78.68)	23.07	2363	76.78	(75.82, 77.73)	23.74	2420	77.71	(76.80, 78.61)	22.75
Role emotional(RE)	1093	73.73	(72.22, 75.23)	25.33	2333	76.79	(75.82, 77.75)	23.85	2379	77.78	(76.83, 78.72)	23.50
Mental health (MH)	1085	62.09	(60.87, 63.32)	20.57	2339	63.91	(63.13, 64.69)	19.30	2370	63.73	(62.94, 64.53)	19.71

Scale	46–55 years				*p* value
	N	Mean 0–100 score	95% CI	SD	
Physical functioning (PF)	1695	81.81	(80.92, 82.69)	18.50	**< 0.001**
Role physical (RP)	1687	77.39	(76.25, 78.54)	23.98	**< 0.001**
Bodily pain (BP)	1700	64.68	(63.50, 65.87)	24.92	**< 0.001**
General health (GH)	1676	64.58	(63.63, 65.53)	19.76	0.665
Vitality (VT)	1653	59.03	(58.01, 60.05)	21.21	**0.001**
Social functioning (SF)	1694	77.88	(76.76, 79.00)	23.47	0.146
Role emotional (RE)	1652	78.80	(77.68, 79.93)	23.25	**< 0.001**
Mental health (MH)	1661	65.99	(65.03, 66.95)	19.98	**< 0.001**

N total number *CI* confidence interval, *SD* standard deviation

p values from linear regression (crude)

p values < 0.05 are bold

Table 4 SF-36v2 health domain subscales: mean 0–100 scores with 95% confidence intervals, standard deviation, *p* values from linear regression (global test) without and with adjustment for age according to ethnicity (Turkish Cypriot, Turkish, Other/Mixed)

Scale	Turkish Cypriot				Turkish			
	N	Mean 0–100 score	95% CI	SD	*N*	Mean 0–100 score	95% CI	SD
Physical functioning (PF)	5359	88.71	(88.30, 89.13)	15.52	1516	87.30	(86.45, 88.15)	16.91
Role physical(RP)	5323	81.26	(80.67, 81.86)	22.23	1507	79.69	(78.46, 80.93)	24.40
Bodily pain (BP)	5346	69.40	(68.76, 70.04)	23.79	1516	64.72	(63.40, 66.03)	26.09
General health (GH)	5317	64.61	(64.08, 65.13)	19.60	1501	61.54	(60.49, 62.59)	20.75
Vitality (VT)	5238	58.53	(57.99, 59.08)	20.21	1472	54.38	(53.26, 55.51)	22.04
Social functioning (SF)	5335	78.13	(77.53, 78.74)	22.58	1512	76.58	(75.33, 77.83)	24.77
Role emotional (RE)	5260	77.94	(77.32, 78.57)	23.22	1480	75.72	(74.42, 77.02)	25.45
Mental health (MH)	5261	64.86	(64.34, 65.38)	19.22	1481	62.29	(61.22, 63.37)	21.14

Scale	Other/mixed				*p* value	
	N	Mean 0–100 score	95% CI	SD	Crude	Adjusted for age
Physical functioning (PF)	383	89.92	(88.66, 91.19)	12.63	0.362	0.116
Role physical (RP)	384	80.32	(78.03, 82.62)	22.96	**0.042**	**0.020**
Bodily pain (BP)	384	67.21	(64.72, 69.69)	24.85	**< 0.001**	**< 0.001**
General health (GH)	386	63.85	(61.95, 65.75)	19.04	**< 0.001**	**< 0.001**
Vitality (VT)	381	55.61	(53.40, 57.82)	22.01	**< 0.001**	**< 0.001**
Social functioning (SF)	386	73.45	(70.87, 76.02)	25.83	**< 0.001**	**< 0.001**
Role emotional (RE)	379	74.85	(72.38,77.31)	24.51	**< 0.001**	**< 0.001**
Mental health (MH)	379	61.46	(59.24, 63.69)	22.13	**< 0.001**	**< 0.001**

N total number *CI* confidence interval, *SD* standard deviation

p values from linear regression (crude) and with adjustment for age (adjusted for age)

p values < 0.05 are bold

mental health in older women. Turkish Cypriot women and non-migrant women had both better mental and physical health, and HRQOL was highest in those in paid employment as well as in those with a higher educational achievement. Here we have provided the first normative values for women in Northern Cyprus aged between 18 and 55 and our analysis suggests that choosing culturally specific weighting coefficients is important when investigating HRQOL.

Reliability and validity

Internal consistency reliability of the scales was high (above 0.8) for 5 of the eight scales with the general health scale being the only one to fall somewhat short of the accepted Cronbach's alpha level of 0.7 (0.69). However, we believe this to be sufficiently close to argue that this scale too had adequate internal consistency reliability. The highest ceiling value in our sample was 41.8%, for the role physical scale, suggesting that the SF-36v2 was well interpreted and suited to our population of Northern Cyprus.

Physical and mental health domains

This study has shown that the highest score of the eight health domains for participants in COHERE was physical functioning and the lowest was vitality. This pattern is consistent with various other studies conducted in a number of high-income countries such as the United Kingdom [16], Switzerland [17] and the United States [11], as well as countries within the Mediterranean region such as Turkey [5] and Greece [18]. Although the scores we present here vary from those presented by other countries, this does not necessarily mean that there are international health differences; there are a number of reasons normative scores may differ between countries, such as differences in culture, expectation of health and mode of administration of the questionnaire.

We observed that as age increased, mean physical health decreased and mean mental health increased, as seen in various other studies [11, 16, 17]. Education and employment

Table 5 SF-36v2 health domain subscales: mean 0–100 scores with 95% confidence intervals, standard deviation, *p* values from linear regression (global test) without and with adjustment for age according to educational attainment (Primary or middle school, high school or post-secondary, undergraduate degree, postgraduate degree)

Scale	Primary or middle school				High school or post-secondary			
	N	Mean 0–100 score	95% CI	SD	*N*	Mean 0–100 score	95% CI	SD
Physical functioning (PF)	838	84.18	(82.87, 85.48)	19.29	2538	87.23	(86.59, 87.87)	16.53
Role physical (RP)	834	77.63	(75.80, 79.46)	26.97	2516	80.00	(79.09, 80.91)	23.34
Bodily pain (BP)	843	61.37	(59.47, 63.28)	28.24	2537	67.43	(66.46, 68.40)	24.87
General health (GH)	831	58.42	(56.96, 59.88)	21.44	2516	63.45	(62.65, 64.26)	20.67
Vitality (VT)	820	51.27	(49.69, 52.84)	23.01	2467	57.14	(56.27, 58.01)	22.03
Social functioning (SF)	842	76.68	(74.92, 78.44)	26.03	2526	77.39	(76.47, 78.31)	23.55
Role emotional (RE)	816	77.15	(75.37, 78.94)	26.00	2478	76.70	(75.75, 77.65)	24.14
Mental health (MH)	821	61.19	(59.64, 62.73)	22.58	2486	63.44	(62.62, 64.25)	20.70

Scale	Undergraduate degree				Postgraduate degree				*p*value	
	N	Mean 0–100 score	95% CI	SD	*N*	Mean 0–100 score	95% CI	SD	Crude	Adjusted for age
Physical functioning (PF)	2579	90.27	(89.75, 90.79)	13.56	1203	90.54	(89.74, 91.34)	14.12	**< 0.001**	**< 0.001**
Role physical (RP)	2570	81.96	(81.15, 82.77)	20.99	1197	82.84	(81.63, 84.05)	21.36	**< 0.001**	**< 0.001**
Bodily pain (BP)	2570	69.94	(69.06, 70.83)	22.95	1196	71.55	(70.27, 72.82)	22.44	**< 0.001**	**< 0.001**
General health (GH)	2566	64.86	(64.14, 65.58)	18.63	1193	66.79	(65.72, 67.85)	18.76	**< 0.001**	**< 0.001**
Vitality (VT)	2525	58.85	(58.09, 59.60)	19.32	1183	59.95	(58.89, 61.00)	18.49	**< 0.001**	**< 0.001**
Social functioning (SF)	2566	77.84	(76.97, 78.71)	22.38	1198	78.01	(76.74, 79.27)	22.37	0.162	0.094
Role emotional (RE)	2540	77.54	(76.65, 78.44)	23.07	1189	78.30	(77.02, 79.58)	22.58	0.095	**0.012**
Mental health (MH)	2535	65.02	(64.30, 65.74)	18.46	1182	65.79	(64.75, 66.83)	18.22	**< 0.001**	**< 0.001**

N total number *CI* confidence interval, *SD* standard deviation

p values from linear regression (crude) and with adjustment for age (adjusted for age)

p values < 0.05 are bold

Table 6 SF-36v2 health domain subscales: mean 0–100 scores with 95% confidence intervals, standard deviation, *p* values from linear regression (global test) without and with adjustment for age according to employment status (In paid employment, not in paid employment)

Scale	In paid employment				Not in paid employment				*p* value	
	N	Mean 0–100 score	95% CI	SD	*N*	Mean 0–100 score	95% CI	SD	Crude	Adjusted for age
Physical functioning (PF)	5901	88.49	(88.10, 88.88)	15.26	1370	88.28	(87.36, 89.21)	17.50	0.659	**< 0.001**
Role physical (RP)	5865	80.97	(80.40, 81.53)	21.98	1362	80.51	(79.15, 81.87)	25.67	0.506	**0.029**
Bodily pain (BP)	5890	68.56	(67.96, 69.17)	23.62	1368	67.33	(65.87, 68.80)	27.58	0.093	**0.003**
General health (GH)	5860	64.58	(64.09, 65.08)	19.34	1357	61.12	(59.97, 62.28)	21.63	**< 0.001**	**< 0.001**
Vitality (VT)	5762	58.19	(57.67, 58.72)	20.21	1343	54.79	(53.57, 56.01)	22.81	**< 0.001**	**< 0.001**
Social functioning (SF)	5878	77.33	(76.74, 77.92)	23.05	1367	78.45	(77.17, 79.72)	24.09	0.110	0.066
Role emotional (RE)	5780	77.64	(77.04, 78.24)	23.25	1351	75.98	(74.60, 77.36)	25.84	0.021	0.127
Mental health (MH)	5781	64.32	(63.82, 64.82)	19.40	1352	63.44	(62.29, 64.59)	21.54	0.143	0.430

In paid employment includes both employees and self-employed. Not in paid work includes students, homemakers, retirees, and those without employment

N total number *CI* confidence interval, *SD* standard deviation

p values from linear regression (crude) and with adjustment for age (adjusted for age)

p values < 0.05 are bold

Table 7 PCS, MCS: mean (T-scores) with 95% CI, SD and *p* values from linear regression (global test) without and with adjustment for age for the overall sample ($n=7089$) and subsamples according to age, ethnicity, educational achievement, civil status, city of residence, employment status*

Characteristics	PCS			*p* value		MCS			*p* value	
	Mean T-score	95% CI	SD	Crude	Adjusted for age	Mean T score	95% CI	SD	Crude	Adjusted for age
Overall sample	50.10	(49.87, 50.34)	9.97	–	–	50.01	(49.78, 50.25)	10.01	–	–
Age				<0.001					<0.001	
18–25	53.32	(52.82, 53.83)	8.34		–	47.95	(47.31, 48.59)	10.50		–
26–35	51.50	(51.12, 51.87)	9.10			49.43	(49.02, 49.84)	9.97		
36–45	49.58	(48.17, 50.00)	10.01			50.13	(49.72, 50.53)	9.86		
46–55	46.72	(46.18, 47.26)	10.96			52.07	(51.59, 52.54)	9.56		
Ethnicity				0.072	0.014				<0.001	<0.001
Turkish Cypriot	50.42	(50.15, 50.69)	9.76			50.43	(50.16, 50.70)	9.76		
Turkish	49.30	(48.74,49.86)	10.71			49.10	(48.55, 49.66)	10.59		
Other/mixed	50.82	(49.88, 51.76)	9.05			48.40	(47.26, 49.55)	11.06		
Educational achievement				**< 0.001**	**< 0.001**				**< 0.001**	**< 0.001**
Primary or middle school	47.55	(46.70, 48.40)	12.17			48.88	(48.14, 49.63)	10.64		
High school or post-secondary	49.60	(49.18, 50.01)	10.26			49.95	(49.53, 50.37)	10.42		
University	51.04	(50.69, 51.39)	8.84			50.24	(49.86, 50.63)	9.57		
Postgraduate	51.58	(51.05, 52.11)	9.13			50.59	(50.03, 51.14)	9.59		
Civil status				**< 0.001**	**< 0.001**				**< 0.001**	**0.047**
Single	52.70	(52.28, 53.12)	8.77			48.61	(48.10, 49.11)	10.53		
Married	49.21	(48.91, 49.51)	10.10			50.64	(50.35, 50.92)	9.69		
Divorced/separated or widowed	50.68	(49.87, 51.48)	10.41			49.80	(48.97, 50.62)	10.65		
Migration status				**< 0.001**	**0.002**				**< 0.001**	**< 0.001**
Non migration status	50.48	(50.22, 50.75)	9.70			50.33	(50.06, 50.61)	9.87		
Migration status	49.39	(48.89, 49.90)	10.56			49.18	(48.68,49.68)	10.47		
City of residence				**0.019**	0.182				0.243	0.578
Famagusta	50.43	(49.93, 50.94)	9.90			49.60	(49.08, 50.11)	10.11		
Kyrenia	50.62	(50.07, 51.16)	9.59			50.04	(49.46, 50.62)	10.12		
Lefke	49.86	(48.63, 51.08)	9.68			51.37	(50.20, 52.53)	9.19		
Morphou	49.14	(48.24, 50.04)	10.83			50.20	(49.33, 51.07)	10.48		
Nicosia	50.08	(49.74, 50.42)	9.68			50.03	(49.68, 50.38)	9.87		
Trikomo	49.38	(48.45, 50.31)	11.45			50.20	(49.38, 51.02)	10.05		
Employment status[a]				0.317	**< 0.001**				**0.001**	0.083
In paid employment	50.25	(50.00, 50.50)	9.50			50.25	(49.99, 50.51)	9.87		
Not in paid work	49.95	(49.32, 50.58)	11.59			49.24	(48.66, 49.82)	10.65		

PCS Physical Component Summary *MCS* Mental Component Summary, *CI* confidence interval *SD* standard deviation

P values from linear regression (crude) and with adjustment for age (adjusted for age)

P values < 0.05 are bold

[a]In paid employment includes both employees and self-employed. Not in paid work includes students, homemakers, retirees, and those without employment

are two demographics that can be used as proxies for the sociodemographic position of people within society. As our results showed higher mean scores in those who had obtained higher educational qualifications as well as in those who were in paid employment, we can be confident that the SF-36v2 was capable of detecting these known differences amongst different socioeconomic positions.

Compared to migrant women, non-migrants had the highest mean scores after adjustment for age only, consistent with previously published studies [17, 19]. Once education and occupation type had been adjusted for, the associations were no longer statistically significant, suggesting the observed associations may be partly explained by social disadvantages that arose from lower socioeconomic status immigrants in this sample. When examining ethnicity, after adjustment for age, education, and occupation class, the statistically significant association between ethnicity and mental health remained, with Turkish Cypriot women having the highest mean scores. Most studies examining HRQOL in non-natives show that they suffer from higher stressors when compared to their native counterparts, not only due to differences in socioeconomics, but due to other migration-specific difficulties [20, 21].

The area most similar to Northern Cyprus both geographically and culturally to have produced normative values for the SF-36v2 is Turkey [5]. Mean health domain scores in COHERE were lower for all scales, apart from physical functioning (88.3 vs 80.6). The study in Turkey was focussed on an urban region with a small sample size (670 women) which is not representative of the population of Turkey. In addition to this, five of the eight scales had a median ceiling score of 100 (perfect) which is unusually high. We believe this is why normative HRQOL scores should be both country and culturally specific.

Strengths and limitations

The cross-sectional design of our study means that we cannot infer causality of measured variables. Gandek and Ware [22] recommend that the minimum sample size used to produce country specific normative values for HRQOL using the SF-36v2 should be between 2500 and 3000 respondents. Here our large sample size ($n = 7646$) means we can be confident in the accuracy of our values and in addition to this, the demographic and social background characteristics of participants in our sample are broadly representative of women between the ages of 18–55 in Northern Cyprus. However, there is some over-representation of women with university degrees and in employment compared to the general population and this should be considered when carrying out any further analyses.

Although the SF-36v2 is a self-administered questionnaire and therefore may suffer from reporting bias, it is reliable and valid as well as being a widely used tool to assess HRQOL. Our study is unique in that it provides normative values for a female population. It is well established that HRQOL is significantly lower in women compared to men and therefore using female-specific normative values from a population of premenopausal women is especially advisable when investigating the impact of women's reproductive diseases, such as endometriosis, on HRQoL. The main aim of the COHERE Initiative is to investigate reproductive health conditions and so our study is restricted to women between the ages of 18–55. Therefore, it is not generalisable to women above and below these ages or to men and so further research in these groups would be needed to discover if similar patterns exist and to provide normative values for all age groups.

Conclusion

Here we present the normative values for women aged 18–55 in Northern Cyprus using the SF-36v2 questionnaire. In accordance with the literature, we saw higher mean physical health scores in younger women and higher mean mental health scores in older women. Non-Turkish Cypriot women and migrants had lower mean scores for both domains, as did those who had lower educational attainments and those who were not in paid employment. This research will allow future studies to measure HRQOL as assessed by the SF-36v2 questionnaire using female-specific data in Northern Cyprus, which we argue is essential in order to investigate the impact women's health diseases have on HRQOL.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11136-022-03100-7.

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Author contributions NR, CB, and KZ contributed to the study conception and design. BS analysed and wrote the first draft of the manuscript. NR, HN, BT, CB, and KZ critically revised the results and manuscript. NR and BT supervised data collection. All authors read and approved the final manuscript.

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Data availability The datasets generated and/or analysed during the current study will be published in open access journals and anonymous data will be available from the corresponding author on reasonable request.

Code availability Not applicable.

Declarations

Conflict of interest CMB declares that he is part of a scientific collaboration between Oxford University and Bayer Healthcare Ltd. for the purpose of drug target identification in endometriosis. He holds/has held research grants from Bayer Healthcare, Volition Rx, MDNA Life Sciences and Roche Diagnostics and has in recent years been a consultant for Abbvie Inc. and Roche Diagnostics. KTZ declares that she has scientific collaborations outside the submitted work with Bayer Healthcare, MDNA Life Sciences, Roche Diagnostics Inc., and Volition Rx and is a Board member (Secretary) of the World Endometriosis Society, Research Advisory Board member of Wellbeing of Women, UK (research charity) and Chair of the Research Directions Working Group, World Endometriosis Society. NR declares that she is the founding president of Cyprus Women's Health Research Society in Northern Cyprus.

Ethical approval Two ethics approvals were obtained for the study: (1) International ethics approval from the Oxford Tropical Research Ethics Committee (OxTREC) of the University of Oxford (OxTREC reference: 37–17) and (2) Local ethics approval from the Eastern Mediterranean University Ethics Committee (ETK00-2017-0240).

Consent to participate After the participant had been informed about the study and made the decision to take part, a written consent was obtained.

Consent for publication Not applicable.

References

1. Ware, J. E., Jr., & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care, 30*, 473–483.
2. Bryant, R. (2014). History's remainders: On time and objects after conflict in Cyprus. *Journal of the American Ethnological Society, 41*, 681–697. https://doi.org/10.1111/amet.12105
3. Rahmioglu, N., Naci, H., & Cylus, J. (2012). Improving health care services in Northern Cyprus: a call for research and action. *The European Journal of Public Health*, *22*(6), 754–755. https://doi.org/10.1093/eurpub/cks145.
4. Ellina, P., Middleton, N., Lambrinou, E., & Kouta, C. (2021). Social gradient in health-related quality of life among urban middle-age residents in Limassol, Cyprus. *BMC Public Health, 21*, 608. https://doi.org/10.1186/s12889-020-10027-6
5. Demiral, Y., Ergor, G., Unal, B., Semin, S., Akvardar, Y., Kıvırcık, B., & Alptekin, K. (2006). Normative data and discriminative properties of short form 36 (SF-36) in Turkish urban population. *BMC Public Health, 6*, 247. https://doi.org/10.1186/1471-2458-6-247
6. Vitonis, A. F., Vincent, K., Rahmioglu, N., Zondervan, K. T., & Missmer, S. A. (2014). World endometriosis research foundation endometriosis phenome and biobanking harmonization project II. Clinical and covariate phenotype data collection in endometriosis research. *Fertility and Sterility, 102*, 1223–1232. https://doi.org/10.1016/j.fertnstert.2014.07.1244
7. Hocaoglu, M. B., Karaderi, T., Taneri, B., Erguler, K., Barin, B., Bilgin, E. M., Eralp, G., Allison, M., Findikli, N., Boynukalin, K., Bahceci, M., Naci, H., Vincent, K., Missmet, S. A., Becker, C. M., Zondervan, K. T., & Rahmioglu, N. (2019). Cyprus Women's Health Research (COHERE) initiative: Determining the relative burden of women's health conditions and related co-morbidities in an Eastern Mediterranean population. *BMC Women's Health*. https://doi.org/10.1186/s12905-019-0750-1
8. Celik, D., & Coban, O. (2016). Short form health survey version-2.0 Turkish (SF-36v2) is an efficient outcome parameter in musculoskeletal research. *Acta Orthopaedica et Traumatologica Turcica, 50*(5), 558–561. https://doi.org/10.1016/j.aott.2016.08.013
9. Kocyigit, H., Aydemir, O., Fisek, G., Olmez, N., & Memis, A. (1999). Validity and reliability of Turkish version of Short form 36: A study of patients with romatoid disorder. *Journal of Drug and Therapy, 12*, 102–106.
10. Ware, J. E., Jr., Snow, K. K., Kosinski, M., & Gandek, B. (1993). *SF-36 health survey manual & interpretation guide*. Boston, MA: The Health Institute, New England Medical Centre.
11. Ware, J. E., Jr. (1994). *SF-36 physical and mental health summary scales: A user's manual*. Boston, MA: The Health Assessment Lab, New England Medical Centre.
12. Ware, J. E., Jr., Kosinski, M., & Dewey, J. E. (2000). *How to score version 2 of the SF-36 health survey*. Lincoln, RI: QualityMetric Incorporated.
13. Acock, A. C. (2005). Working with missing values. *Journal of Marriage and Family, 67*, 1012–1028. https://doi.org/10.1111/j.1741-3737.2005.00191.x
14. Acock, A. C., Namboodiri, K., & Corwin, R. (1989). Measurement error in secondary data analysis. *Research in Sociology of Education and Socialization, 8*, 201–230.
15. Hawthorne, G., Osbourne, R. H., Taylor, A., & Sansoni, J. (2007). The SF-36 version 2: Critical analyses of population weights, scoring algorithms and population norms. *Quality of Life Research, 16*, 661–673. https://doi.org/10.1007/s11136-006-9154-4

16. Jenkinson, C., Stewart-Brown, S., Peterson, S., & Paice, C. (1999). Assessment of the SF-36 version 2 in the United Kingdom. *Journal of Epidemiology and Community Health, 53*, 46–59.
17. Roser, K., Mader, L., Baenziger, J., Sommer, G., Kuehni, C. E., & Michel, G. (2019). Health-related quality of life in Switzerland: Normative data for the SF-36v2 questionnaire. *Quality of Life Research, 28*, 1963–1977. https://doi.org/10.1007/s11136-019-02161-5
18. Pappa, E., Kontodimopoulos, N., & Niakas, D. (2005). Validating and norming of the Greek SF-36 health survey. *Quality of Life Research, 14*(5), 1433–1438. https://doi.org/10.1007/s11136-004-6014-y
19. Morawa, E., & Erim, Y. (2015). Health-related quality of life and sense of coherence among Polish immigrants in Germany and indigenous Poles. *Transcultural Psychiatry, 52*, 3. https://doi.org/10.1177/1363461514565851
20. Lindström, M., Sundquist, J., & Östergren, P.-O. (2001). Ethnic differences in self reported health in Malmö in southern Sweden. *Journal of Epidemiology and Community Health, 55*, 97–103. https://doi.org/10.1136/jech.55.2.97
21. Wiking, E., Johansson, S. E., & Sundquist, J. (2004). Ethnicity, acculturation, and self reported health. A population based study among immigrants from Poland, Turkey, and Iran in Sweden. *Journal of Epidemiology and Community Health, 58*, 574–582. https://doi.org/10.1136/jech.2003.011387
22. Gandek, B., & Ware, J. E., Jr. (1998). Methods for validating and norming translations of health status questionnaires: The IQOLA Project Approach. *Journal of Clinical Epidemiology., 51*, 953–959.