

**A multi-centre study of the impact of
endometriosis
on
Health-Related Quality of Life
and
Work Productivity**

**by
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**A thesis submitted for the degree of
Doctor of Philosophy**



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Abstract

Background: Endometriosis is a common condition in women of reproductive age, causing pelvic pain and subfertility, but little is known about its impact on health-related quality of life (HRQoL) and work productivity worldwide.

Methods: In 10 countries across five continents, this study recruited 1,418 women, aged 18-45, without a previous surgical diagnosis of endometriosis, scheduled to undergo a laparoscopy to investigate symptoms suggestive of endometriosis or to be sterilised. Pre-operatively, women completed a standardised questionnaire assessing symptoms, diagnostic delay, HRQoL and work productivity using validated instruments. Surgeons completed a standardised questionnaire incorporating findings at laparoscopy including endometriosis stage according to revised American Fertility Society criteria.

Results: There was a mean delay of 9.2 years (SD 8.8), principally in primary care, between the onset of symptoms and diagnostic laparoscopy. This diagnostic delay was longer in centres where healthcare was predominantly state-funded (12.8 vs. 7.6 years; $p<0.001$). In multivariate analyses, the delay was positively associated with the number of pelvic symptoms (chronic pelvic pain, dysmenorrhoea, dyspareunia and heavy periods; $p<0.001$) and a higher body mass index ($p<0.001$). Physical HRQoL was significantly reduced in affected women compared to those with similar symptoms and no endometriosis ($p=0.012$). Not being in paid employment, severe pelvic pain and moderate-severe disease were associated with reduced physical HRQoL (all $p<0.001$). Each affected woman lost on average 10.0 hours (SD 10.6) of work weekly, due mainly to reduced effectiveness while working. The annual indirect cost of endometriosis associated with work productivity loss ranged from US\$399 per woman in Ibadan (Nigeria) to US\$18,586 per woman in Boston (USA).

Conclusions: Endometriosis significantly impairs HRQoL and work productivity across countries and ethnicities, yet women continue to experience diagnostic delays in primary care. A higher index of suspicion is needed to expedite specialist assessment of symptomatic women. Future research should seek to clarify pain mechanisms in relation to endometriosis severity.

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Chapter 2 contains material that was published in the Journal of Endometriosis and chapters 4, 7 and 8 contain material that is part of a manuscript now approaching the final phases of peer review for publication in the Fertility & Sterility Journal.

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Preface

This thesis describes the results of the Global Study of Women's Health (GSWH), a collaborative study involving the Department of Public Health at the University of Oxford, the Nuffield Department of Obstetrics & Gynaecology at the University of Oxford and the GSWH World Endometriosis Research Foundation (WERF) consortium. The study was supported by a steering group comprising the following persons:

Dr. Krina Zondervan	Senior Scientist, Wellcome Trust Centre for Human Genetics and Nuffield Department of Obstetrics & Gynaecology
Mr. Stephen Kennedy Department	Clinical Reader and Head of Department, Nuffield of Obstetrics & Gynaecology
Dr. Premila Webster Director	Head of School of Public Health / Training Programme
Prof. Crispin Jenkinson	Professor of Health Services Research
Dr. Lone Hummelshoj	Chief Executive, World Endometriosis Research Foundation
Dr. Kelechi Nnoaham	DPhil candidate

To date, the study has resulted in the following publication:

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Table of Contents

CHAPTER 1.....	1
BACKGROUND AND LITERATURE REVIEW	1
1 Introduction.....	2
1.1 Definition of endometriosis.....	6
1.2 Frequency of occurrence of endometriosis.....	7
1.2.1 Prevalence	7
1.2.2 Incidence.....	9
1.3 Pathophysiology of endometriosis	10
1.4 Diagnosis of endometriosis	14
1.5 Risk factors for endometriosis.....	17
1.6 Health-related quality of life (HRQoL) and work productivity in endometriosis	42
2 Overview and aims of thesis.....	44
3 Ethical approval	45
CHAPTER 2.....	46
STUDY METHODS.....	46
4 Study design.....	47
4.1 Rationale of study design	48
5 Study population	51
5.1 Description of study population	52
5.2 Eligibility criteria	52
5.3 Rationale for choice of study population	52
6 Recruitment.....	53
6.1 Sample size estimation	55
7 Data collection methods.....	56
7.1 Design of patient questionnaire	56
7.2 Design of surgical questionnaire	59
7.3 Validation of questionnaires.....	59
7.4 Online programming of questionnaires and database design	60
7.5 Administration of exposure questionnaire.....	61
7.6 Collation of responses	62
8 Surgical procedures	62
CHAPTER 3.....	64
GSWH PILOT STUDY	64
9 Background and aims	65
10 Methods.....	65
10.1 Data Analysis.....	66

11	Results	67
11.1	Response rates.....	67
11.2	Characteristics of study sample.....	69
11.3	Characteristics associated with endometriosis	70
11.4	Health-related Quality of Life impact of endometriosis.....	70
12	Discussion	71
MAIN STUDY RESULTS		72
CHAPTER 4.....		73
CHARACTERISTICS OF THE STUDY POPULATION AT RECRUITMENT		73
13	Introduction	74
14	Methods.....	75
14.1	Diagnostic incidence and stages of endometriosis	75
14.2	Comparison groups.....	75
14.3	Variable description.....	76
14.3.1	Sociodemographic characteristics and past medical history	76
14.3.2	Reproductive characteristics	77
14.3.3	Gynaecological characteristics	77
14.3.4	Personal habits	77
14.3.5	Body characteristics.....	78
14.3.6	Other key variables.....	78
14.4	Statistical Methods	79
14.4.1	Descriptive statistics	79
14.4.2	Diagnostic incidence of endometriosis.....	80
14.4.3	Distribution of variables in the study population.....	80
14.4.4	Centre-wise comparisons	80
14.4.5	Comparisons across disease outcome groups.....	81
14.4.6	Principal component analysis	81
14.4.7	Unconditional logistic regression modelling	81
14.4.8	Missing values.....	82
15	Results	82
15.1	Study population	82
15.2	Diagnosis of endometriosis	83
15.2.1	Diagnostic incidence of endometriosis in study population and centres	83
15.2.2	Centre-wise comparisons of diagnostic incidence	85
15.2.3	Severity of endometriosis disease.....	85
15.3	Characteristics of the study population	87
15.3.1	Sociodemographic characteristics and past medical history	87
15.3.2	Gynaecological characteristics	101

15.3.3	Reproductive characteristics	109
15.3.4	Body characteristics.....	112
15.3.5	Personal habits	116
15.4	Principal component analysis	120
15.5	Unconditional multivariate logistic regression.....	123
16	Discussion	124
CHAPTER 5.....		136
SYMPTOMS ASSOCIATED WITH ENDOMETRIOSIS		136
17	Introduction.....	137
18	Methods.....	138
18.1	Comparison groups.....	138
18.2	Variable description.....	138
18.2.1	General	138
18.2.2	Pelvic pain with/without subfertility	139
18.2.3	Pelvic pain severity	139
18.2.4	Number of symptoms	139
18.3	Statistical Methods	140
18.3.1	Frequency of symptoms	140
18.3.2	Centre-wise comparisons	140
18.3.3	Comparisons across disease outcome groups.....	140
18.3.4	Principal component analysis	140
19	Results	141
19.1	Pelvic pain and subfertility	141
19.1.1	Severity of pelvic pain (dysmenorrhoea, dyspareunia and CPP).....	143
19.2	Description of individual symptoms presented by women.....	145
19.2.1	Centre-wise comparisons on key individual symptoms presented by women ..	148
19.2.2	Age of women at onset of symptoms.....	150
19.2.3	Mean number of individual symptoms presented by women	152
19.3	Symptoms and disease location	154
19.4	Ethnic differences in symptoms leading to diagnosis	155
19.5	Endometriosis and Irritable Bowel Syndrome.....	156
20	Discussion	157
CHAPTER 6.....		163
ENDOMETRIOSIS: ONSET, CARE-SEEKING AND DIAGNOSIS		163
21	Introduction.....	164
22	Methods.....	165
22.1	Comparison groups.....	165
22.2	Outcome description	166

22.2.1	Onset of symptoms.....	166
22.2.2	Care-seeking and referral to specialists.....	166
22.2.3	Diagnostic delay.....	166
22.3	Statistical methods	167
23	Results	167
23.1	Onset of symptoms and physician contact.....	167
23.1.1	Age at symptom onset & physician contact in study population and centres ...	167
23.1.2	Age at symptom onset and physician contact in disease outcome groups	170
23.1.3	Further characterisation of symptom onset.....	171
23.2	Care-seeking and referral to specialists.....	172
23.2.1	Care-seeking and referral to specialists in study population and centres	172
23.2.2	Care-seeking and referral to specialists in disease outcome groups	173
23.2.3	Further characterisation of care-seeking and referral to specialists.....	173
23.3	Diagnostic delay.....	174
24	Discussion	177
CHAPTER 7.....		184
ENDOMETRIOSIS AND HEALTH-RELATED QUALITY OF LIFE.....		184
25	Introduction.....	185
25.1	Health-related Quality of Life (HRQoL).....	185
25.2	Aim of study.....	186
26	Methods and statistical analysis.....	186
27	Results	187
27.1	SF36v2 mean dimension scores.....	188
27.1.1	Study population dimension scores	188
27.1.2	Centre-wise comparisons on dimension scores	188
27.1.3	Disease outcome group comparisons on dimension scores	194
27.2	SF36v2 component summary scores.....	195
27.2.1	Study population and centre-wise component summary scores.....	195
27.2.2	Disease outcome group comparisons on component summary scores.....	197
27.3	HRQoL and self-reported symptoms as reasons for surgery.....	198
27.4	Pelvic pain severity and HRQoL	199
27.5	Endometriosis severity and HRQoL	200
28	Discussion	201
CHAPTER 8.....		211
ENDOMETRIOSIS AND WORK PRODUCTIVITY IMPAIRMENT		211
29	Introduction.....	212
30	Methods.....	213
30.1	Description of comparison groups	213

30.2	Assessment of work productivity impairment	214
30.3	Adjusting for potential confounding variables	214
30.4	Missing values.....	215
30.5	Statistical Methods	215
30.5.1	Work and work productivity impairment parameters	215
30.5.2	Centre-wise comparisons	216
30.5.3	Comparisons across disease outcome groups.....	216
30.5.4	Work productivity loss in monetary terms.....	216
30.5.5	Missing values.....	217
31	Results	217
31.1	Missing values.....	217
31.2	Employment status.....	218
31.3	Description of work productivity impairment in study population and centres.....	218
31.3.1	Time paid to work and time actually worked.....	218
31.3.2	Absenteeism	219
31.3.3	Presenteeism	220
31.3.4	Overall work productivity loss	221
31.3.5	Centre-wise comparisons	221
31.4	Description of work productivity impairment in disease outcome groups.....	222
31.4.1	Endometriosis and work productivity loss	223
31.5	Endometriosis severity and work productivity loss.....	224
31.6	Endometriosis and activity impairment	224
31.7	Monetary value of work productivity losses	225
32	Discussion	226
CHAPTER 9.....		233
SUMMARY AND CONCLUSIONS.....		233
1	Summary of the key findings of study	234
1.1	Characteristics of population and diagnostic incidence of endometriosis	234
1.2	Presenting symptoms	236
1.3	Disease onset and care-seeking in endometriosis	237
1.4	Endometriosis and HRQoL.....	238
1.5	Endometriosis and work productivity	241
2	Strengths and limitations of the study	243
References		247
Appendix 1 - Characteristics of women at recruitment in GSWH		266
Appendix 2 - Unconditional multiple logistic regression models for endometriosis vs. symptomatic controls and endometriosis vs. sterilisation controls.....		267

Index of Tables

Table 1 - Collaborating centres.....	55
Table 2 - Sample size calculation for GSWH based on risk estimates and prevalence in controls ..	55
Table 3 - Demographic characteristics of the pilot study population	69
Table 4 - Median scores and 25% and 75% values for SF36v2 dimensions.....	70
Table 5 - Comparison of SF36v2 HRQoL dimensions by endometriosis status	70
Table 6 - Diagnostic incidence of endometriosis.....	84
Table 7 - Diagnostic incidence of endometriosis in all symptomatic women	84
Table 8 - Centre-wise comparisons of the diagnostic incidence of endometriosis.....	85
Table 9 - Prevalence of stages of endometriosis in study population.....	86
Table 10 - Centre-wise comparisons of prevalence of moderate-severe endometriosis	87
Table 11 - Mean interval in days between questionnaire completion and surgery.....	89
Table 12 – Centre-wise comparison of proportions of White women in study population	92
Table 13 - Highest attained educational level in women by centre	95
Table 14 - Marital status of women in GSHW by Centre.....	97
Table 15 - Percentage of women reporting a history of medical conditions, by Centre	100
Table 16 - Hormonal contraceptive use in past 3 months by Centre	102
Table 17 - Reasons for use of hormonal contraception in past 3 months by Centre.....	103
Table 18 – Percentages of women who reported menstrual cycles of specific lengths by Centre	105
Table 19 - Reported menstrual duration by Centre	108
Table 20 - Gravidity of women in study population who reported a previous pregnancy	109
Table 21 - Subfertility in the GSWH study population by Centre	110
Table 22 - Parity of women by Centre	111
Table 23 - Mean Body Mass Index (BMI) of women by Centre.....	113
Table 24 - Frequency of natural hair colours in women by Centre	115
Table 25 - Hair colour by ethnicity and Centre.....	115
Table 26 – Proportions of women reporting skin moles by Centre	116
Table 27 - Smoking status of women in the study population by Centre	117
Table 28 - Centre-wise comparisons for smoking history	118
Table 29 – History of any vigorous exercise by Centre	119
Table 30 - Centre-wise comparisons for proportions of women who reported regular exercise ..	119
Table 31 - Rotated factor pattern for reasons for undergoing surgery in GSWH	120
Table 32 - Selected factors and loading variables	121
Table 33 - Centre-wise comparisons of number of symptoms in symptom groups	122
Table 34 - Univariate association of key variables with key study outcomes	124
Table 35 - Pelvic pain and subfertility as reasons for laparoscopy.....	141
Table 36 - Centre-wise comparisons for nature of symptoms presented by women.....	142
Table 37 - Reasons for undergoing laparoscopy	147
Table 38 - Centre-wise comparisons of proportions of women who presented with symptoms at centre vs. remainder of study population	148
Table 39 - Proportions of women in disease outcome groups who reported other symptoms.....	149
Table 40 – Mean (SD) age of onset of specific symptoms.....	151
Table 41 - Selected factors and loading variables	152
Table 42 - Centre-wise comparisons of number of individual symptoms in symptom groups presented by women.....	154
Table 43 – Percentage of women who underwent laparoscopy for symptoms by ethnicity	155
Table 44 - Endometriosis and Irritable Bowel Syndrome (IBS).....	156
Table 45 – Mean age at symptom onset, physician contact and interval, by centre.....	169
Table 46 - Average ages at onset of symptoms for symptomatic women in the study population	170

Table 47 - Care-seeking for symptoms	171
Table 48 - Number of primary care physician visits before specialist referral, by Centre	172
Table 49 - Referral to other specialists.....	174
Table 50 - Diagnostic interval for symptomatic women by Centre	175
Table 51 – Energy/vitality – Centre-wise comparisons	193
Table 52 – Mental health – Centre-wise comparisons.....	193
Table 53 - Health perception – Centre-wise comparisons	193
Table 54 – Bodily pain – Centre-wise comparisons.....	193
Table 55 – Social functioning – centre-wise comparisons	193
Table 56 – Role-limitation (mental) – Centre-wise comparisons	193
Table 57 – Role-limitation (physical) – Centre-wise comparisons	193
Table 58 – Physical functioning – centre-wise comparisons.....	193
Table 59 – p values for association of variables with endometriosis and SF36v2 dimensions	194
Table 60 - Comparison of SF36v2 dimension scores across disease outcome groups, with adjusted p values (following adjustment for relevant confounding variables as detailed in Table 59)	194
Table 61 - Physical and Mental Component Summary scores compared for each centre vs. the normative population (mean 50, SD 10)	196
Table 62 - Physical and Mental Component Summary scores compared for each disease outcome group vs. the normative population (mean 50, SD 10)	197
Table 63 - Comparison of sf36v2 dimension scores across groups of self-reported symptoms for which women underwent surgery, with p values	199
Table 64 - Adjusted p values ^a for association of HRQoL and pelvic pain severity	200
Table 65 – SF36v2 dimension and component summary scores by endometriosis disease stage (with multivariate regression coefficient and p values)	201
Table 66 – Comparison of women with missing and those without missing observations for specific variables in relation to work and work productivity parameters, stratified by disease outcome (endometriosis and symptomatic controls)	218
Table 67 - Centre wise comparisons of work productivity impairment indices.....	222
Table 68 - Work productivity in symptomatic women with and without endometriosis	223
Table 69 – Annual indirect cost of endometriosis associated with work productivity loss and expressed as a percentage of Gross Domestic Product for countries.....	225

Index of Figures

Figure 1 - Recruitment flowchart for the Global Study of Women's Health (GSWH)	54
Figure 2 - Screenshot of GSWH welcome page	61
Figure 3 - Screenshot of research assistant administration page	63
Figure 4 - Flow chart showing response to invitation in pilot study	68
Figure 5 - Characteristics on which population is described	76
Figure 6 - Participating centres and numbers of women recruited in the GSWH.....	83
Figure 7 - Diagnostic incidence of endometriosis and disease stage by Centre of recruitment	86
Figure 8 - Numbers of women recruited & recruitment rates by Centre	87
Figure 9 - Mean interval (SD) and 95% CIs between questionnaire completion and surgery (in days) by centre	88
Figure 10 - Age distribution of women in GSWH, by Centre	90
Figure 11 - Mean ages of women with standard deviations, by Centre	90
Figure 12 - Ethnic origins of women in the GSWH study population	91
Figure 13 - Ethnic origins of women in GSWH by Centre	91
Figure 14 - Employment status of women by Centre.....	93
Figure 15 - Percentages of women reporting specific reasons for not being in employment.....	94
Figure 16 - Comparison of proportions of employed women in each centre vs. remainder of study population	94
Figure 17 - Percentages of unemployed women not working due to symptoms indicating surgery by centre.....	95
Figure 18 - Post-secondary educational attainment in Centres vs. remainder of study population	96
Figure 19 - Marital or co-habiting status of women in Centres, compared to remainder of study population	98
Figure 20 - Frequency of reporting of conditions in the past medical history	99
Figure 21 - Mean age (SD) at menarche by Centre with p values for comparison with the remainder of study population.....	101
Figure 22 - Proportions of women reporting hormonal contraceptive use in last 3 months in Centres, compared to remainder of study population	103
Figure 23 - Proportions of women in GSWH study population reporting different cycle lengths	105
Figure 24 - Percentages of women who had menstrual cycle length of ≤ 24 days	106
Figure 25 - Percentages of women reporting heavy menstrual flow by Centre	107
Figure 26 - Percentage of women who reported heavy menstrual bleeding by Centre.....	107
Figure 27 - Proportions of women in study population in BMI categories, with 95% confidence intervals	112
Figure 28 - Proportions of women in study population in BMI categories by Centre.....	113
Figure 29 - Mean (SD) number of symptoms in symptom groups reported by women in the study population	121
Figure 30 - Mean number of symptoms presented by women by endometriosis status	123
Figure 31 - Hosmer-Lemeshow test of goodness of fit	123
Figure 32 - Comparison of pelvic pain and subfertility as reasons for laparoscopy by endometriosis status, with Pearson's χ^2 test p values for test of equality of the proportions ...	142
Figure 33 - Mean severity (SD) of different types of pelvic pain reported by women in the study population	144
Figure 34 - Mean severity (SD) of pelvic pain (CPP, dysmenorrhoea and dyspareunia) by centre	144
Figure 35 - Centre-wise comparisons for mean severity of pelvic pain, with p values for t-test of difference mean in centre vs. remainder of study population	145
Figure 36 - Frequency of symptoms for which women underwent laparoscopy.....	145

Figure 37 - Comparisons of proportions of women in disease outcome groups who reported key symptoms (p values are for χ^2 test of equality of proportions for endometriosis vs. symptomatic controls and endometriosis vs. sterilisation controls)	149
Figure 38 – Comparison of proportions of women with minimal-mild vs. moderate-severe endometriosis who presented with key symptoms (p values are for χ^2 test of equality of proportions).....	150
Figure 39 - Mean age of women at symptom onset by Centre.....	151
Figure 40 - Mean (SD) number of symptoms in symptom groups reported by women in the study population	152
Figure 41 - Mean number of symptoms presented by women with endometriosis vs. symptomatic controls	154
Figure 42 - Mean number (SD) of symptoms in symptom groups reported by women	156
Figure 43 - Mean age at reported symptom onset by centre, with 95% confidence intervals.....	167
Figure 44 - Mean age of women at symptom onset by Centre.....	168
Figure 45 - Centre-wise comparisons of interval between symptom onset and first physician contact for symptoms.....	169
Figure 46 - Centre-wise comparisons of number of general physician visits before referral to specialist	173
Figure 47 - Relative contributions (in years) of patient- and physician-related delay to overall diagnostic delay (% contributed by patient delays labeled)	175
Figure 48 - Diagnostic delay by Centre of recruitment in GSWH	176
Figure 49 - Mean dimension score and SD for SF36v2 dimensions.....	188
Figure 50 – Mean study population scores (SD) in the SF36v2 dimension of energy/vitality.....	188
Figure 51 - Mean study population scores (SD) in the SF36v2 dimension of mental health	189
Figure 52 - Mean study population scores (SD) in the SF36v2 dimension of health perception ...	189
Figure 53 - Mean study population scores (SD) in the SF36v2 dimension of bodily pain	189
Figure 54 - Mean study population scores (SD) in the SF36v2 dimension of social functioning ...	189
Figure 55 - Mean study population scores (SD) in the SF36v2 dimension of role limitation (mental)	190
Figure 56 - Mean study population scores (SD) in the SF36v2 dimension of role limitation (physical).....	190
Figure 57 - Mean study population scores (SD) in the SF36v2 dimension of physical functioning.....	190
Figure 58 - Mean (SD) SF36v2 component summary scores for the study population, with 95% confidence intervals	195
Figure 59 - Mean (SD) sf36v2 component summary scores for centres, with 95% confidence intervals	196
Figure 60 – Mean sf36v2 component summary scores by outcome groups, with adjusted p values for comparisons.....	197
Figure 61 - Mean weekly hours (SD) employed women were contracted to work by centre	219
Figure 62 - Mean weekly hours (SD) employed women were contracted to work by centre	219
Figure 63 – Mean absenteeism (SD) by Centre	220
Figure 64 - Mean presenteeism (SD) by Centre	220
Figure 65 - Mean overall work productivity impairment (SD) by Centre	221
Figure 66 – Work productivity impairment outcomes by endometriosis severity (rASRM) ^a	224
Figure 67 – Weekly monetary loss from endometriosis-associated work absenteeism and presenteeism	225

CHAPTER 1

BACKGROUND AND LITERATURE REVIEW

1 Introduction

Endometriosis is an oestrogen-dependent, chronic inflammatory condition characterised by benign proliferation of endometrial-like tissue in the peritoneal cavity, resulting in inflammation and scarring, with associated symptoms of pelvic pain and subfertility [1]. Owing to the need for surgery to establish a diagnosis, precise prevalence rates in the general population are unknown. Reported prevalence rates in specific groups of women also vary but estimates indicate that endometriosis affects up to 10% of pre-menopausal women, rising to 30-50% of women presenting with pelvic pain and/or subfertility [2,3].

Although there is a growing body of evidence to suggest that endometriosis is a complex disease caused by the interplay between environmental and genetic factors [4,5], the mechanisms of disease onset and progression remain largely unclear. It is generally accepted that the initial step in pathogenesis involves retrograde menstruation, the reflux of menstrual debris containing viable endometrial cells into the pelvic cavity [6]. This hypothesis is supported by the observation that endometriosis occurs spontaneously only in species that menstruate [7], and that women with increased exposure to menstruation (longer, heavier flow; shorter cycle length, earlier age at menarche) are at increased risk of endometriosis [7-9]. However, retrograde menstruation has been observed to varying degrees in up to 90% of women [10], yet only a proportion of these women go on to develop endometriosis. Thus, the underlying mechanisms responsible for the survival, proliferation and neo-vascularisation of endometriotic deposits have been an important focus of aetiological research in more recent years. Indeed, increasing understanding of the molecular basis of endometriosis is leading some researchers to consider it to be a chronic systemic disorder [11].

Other than menstrual characteristics, few other risk-factors (low body mass index and birth weight being possible exceptions) have been robustly associated with endometriosis in well-

designed epidemiological studies [12,13]. A well-designed epidemiological study should ideally enrol surgically confirmed cases to mitigate misclassification, provide clear criteria for control selection and adjust for potential confounding variables but only few studies to date have met these requirements [14,15].

Health-related quality of life (HRQoL) is a multi-dimensional concept that includes the physical, psychological, and social functioning associated with an illness or its treatment [16]. Women with endometriosis experience greater HRQoL impairment than the general population. In one review, three of the six included studies used generic instruments for descriptive assessment of health status - principally the General Health Questionnaire [17] and the Modified Social Adjustment Scale [18] - to compare HRQoL in women with Chronic Pelvic Pain (CPP) due to endometriosis versus CPP due to other causes [19]. Women with endometriosis were found to suffer greater HRQoL impairment in the domains of pain, distress, anxiety and social adjustment compared to those without a diagnosis [20-22]. Other studies using similar instruments have highlighted the impact of endometriosis on work, intercourse and social relationships [23]. However, these studies principally involved UK and US populations; this and the potential for significant bias (e.g. due to failure to account for the impact of comorbidities) impair the generalisability and reliability of these findings. Other important questions regarding the impact of endometriosis on women's lives remain unanswered: for instance, to what extent do demographic, life-style, and health-care seeking factors influence HRQoL, and how generalisable are patterns across different countries and ethnicities.

CPP is an important factor affecting HRQoL in endometriosis, particularly in the HRQoL domains of general bodily pain and physical functioning [24]. Other HRQoL domains such as psychological functioning may be influenced by the pain experience as well as, more directly, by other factors. For example, the long delays in surgical diagnosis that characterise the illness experience and

care-seeking trajectory of women with symptoms of endometriosis [25] may contribute to the feelings of anxiety and consequent reduced psychological functioning reported by sufferers. This delay typically averages 8-12 years [26,27] and in one UK study, a third of women had consulted their family physician six or more times before being diagnosed [28].

The personal and wider societal costs of endometriosis are substantial but poorly elucidated [29]. Although the direct costs of endometriosis associated with healthcare resource use are relatively well documented, the indirect costs of the condition, principally those associated with lost work productivity, are less well documented. When lost productivity has been evaluated in the literature, much attention has been paid to quantifying a narrow set of proxy dimensions such as absence from paid work. A fuller understanding of the societal costs of endometriosis is, however, key to raising awareness of this sometimes poorly understood illness and attracting the necessary support for research into its epidemiological determinants and treatment strategies.

The lack of robust information on the global impact of endometriosis and the difficulty in interpreting the relative impact of risk-factors from different studies led to the initiation of a large-scale, multicentre research effort to gather prospective, standardised, epidemiological data on endometriosis. This initiative is in line with the 'Priorities for Endometriosis Research', which outlined the need for 'collaborations to be established between research groups with sufficient participant numbers and appropriate standardisation of sample and information collection [3]. To this end, *the Global Study of Women's Health (GSWH)* was designed to enable the collaborative investigation of key research questions at an unprecedented global scale.

Following a standardised protocol, clinical centres across a number of countries in Africa, Asia, Europe, and North and South America, collected comprehensive and robust epidemiological information from prospectively recruited women aged 18-45, with and without symptoms, who

were undergoing a laparoscopy. The study aimed to provide novel insights into the impact of endometriosis and its associated symptoms on women's lives across different countries, as well as explore associations of various putative risk-factors for endometriosis in this cross-sectional sample of prospectively recruited women. It is hoped that this study will contribute to a clearer understanding of the epidemiological determinants of endometriosis, inform preventive efforts and draw attention to the public health importance of endometriosis. The resulting data registries also have the potential to serve as a framework for future studies, such as the longitudinal assessment of the effectiveness of different treatment options for endometriosis and the investigation of biological influences and diagnostic markers.

This DPhil thesis is based on the *GSWH* and will focus specifically on: 1) identifying characteristics associated with endometriosis in cross-sectional analyses of data from a prospectively recruited sample of women undergoing laparoscopy on account of symptoms or for sterilisation, and 2) using validated methods and instruments to describe and quantify the impact of endometriosis on (a) health-related quality of life and (b) work productivity in women with symptoms suggestive of the condition.

Although aspects of this thesis present a detailed literature review and analysis of the association of endometriosis with a number of specific risk factors, such risk factor analysis is not intended to establish or refute putative associations reported in the literature as a different design of study would be required to achieve that. Instead, the detailed analysis of risk factor associations in this thesis is intended to support adequate control of the influence of variables that potentially confound the association between endometriosis and key study outcomes, specifically diagnostic delay, health-related quality of life and work productivity.

1.1 Definition of endometriosis

A 1991 consensus panel of European gynaecologists defined endometriosis as “the presence of ectopic endometrium, in association with evidence of cellular activity in the lesions and of progression, such as the formation of adhesions or interference with normal physiological processes” [30]. Despite this comprehensive definition, there is as yet no worldwide consensus on what exactly constitutes endometriosis disease. Generally however, it is thought of as an oestrogen-dependent, chronic inflammatory condition characterised by benign proliferation of endometrial-like tissue in the peritoneal cavity [1]. The proliferation of this ectopic tissue results in inflammation and scarring, with associated symptoms of pelvic pain and subfertility.

Consistent with the oestrogen-dependent nature of the disease, endometriosis commonly affects women of reproductive age, although it has rarely been reported outside that age group and even in men receiving high dose oestrogen therapy [31]. The defining feature of endometriosis is the presence of endometrial-like tissue in sites outside the uterine cavity, principally the pelvic peritoneum and ovaries [11]. Indeed, endometriosis occurring on the surface of the peritoneum or ovaries (peritoneal endometriosis) must be distinguished from endometriotic nodules in the rectovaginal septum (deep endometriotic nodules) and ovarian cysts lined by endometrial-like tissue (endometriomas), two other distinct clinical forms of endometriosis that probably have their own specific aetiopathogenesis [32].

A generally well-accepted classification system distinguishes four stages of endometriosis (I: minimal, II: mild, III: moderate, IV: severe) based on clinical characteristics of the lesions such as type, size and location of the lesions, as well as the presence of adhesions [33]. This classification system is however an unreliable aid in managing the associated symptoms of endometriosis such as subfertility and pelvic pain. This has resulted in calls for a review of the classification system using empirically derived weights and breakpoints to define disease stages [34]. Furthermore, it

has been suggested that only moderate-severe, rather than minimal-mild endometriosis, represents clinically significant endometriosis disease as the latter may only be a transient phase (and therefore a non-disease) in an on-going process that often ends up in cytolysis of recently implanted endometrial cells [35]. The relatively high percentage of minimal-mild endometriosis found in populations of asymptomatic women undergoing sterilisation [36] would appear to support this position and perhaps casts doubts on the validity of widely accepted definition of the disease.

1.2 Frequency of occurrence of endometriosis

1.2.1 Prevalence

Prevalence is a function of incidence and duration of disease. The prevalence of endometriosis is increasing in both developing and industrialised countries [37,38] but due to the need for diagnosis by pelvic surgery (either on laparoscopy or laparotomy), its prevalence is difficult to define. For the same reason, reported prevalence also varies by the presenting symptoms of the women under surveillance (e.g., subfertility, pain, or surgical indications for laparoscopy or laparotomy), as well as by study definitions [39].

The characteristics of women under investigation largely determine reported endometriosis prevalence. In hospitalised or surgical populations, prevalence rates of endometriosis ranging from 0.7% to 43% have been reported in women undergoing laparoscopy for sterilisation [2]. The prevalence rate amongst women having a laparoscopy to investigate the cause of their subfertility ranges from 2.1% to 78%, and from 4.5% to 82% in those women being investigated for pelvic pain. The rather wide variations in reported prevalence rates by symptom group (subfertility, pelvic pain or sterilisation) may be linked to the underlying characteristics of those groups. For example, asymptomatic women undergoing sterilisation are less likely to report

subfertility, a feature of endometriosis. Also, women reporting pelvic pain may be more likely to have endometriosis compared to controls who do not report pelvic pain. Consequently, the reported prevalence rates in asymptomatic women undergoing sterilisation may be artificially low while the reported prevalence rates among symptomatic women undergoing surgery for diagnosis may be exaggerated.

Notably too, the reported prevalence rate of endometriosis appears to vary by whether the disease is detected during diagnostic surgery (as above) or other types of surgery, such as fertility-regulating surgery or hysterectomy [40]. Although only an index of prevalence in the groups studied by Hemmings et al., the proportion of cases was 50% among subjects who underwent diagnostic laparoscopy, whereas only 18% of cases were found among subjects who underwent surgery for sterilisation, and 35% among subjects who underwent hysterectomy [40]. The difference in reported prevalence rate by type of surgery may be related to the fact that the type of surgery performed affects the ability of the surgeon to visualise the lesions and the amount of material that can be sent for histology.

The problems associated with the use of surgical patients to define the prevalence of endometriosis are well recognised [2]. Whether an individual goes on to be scheduled for surgical confirmation of suspected endometriosis depends on a number of personal, social, cultural and financial issues. The perceived seriousness of symptoms and the availability or access to self-treatment can determine whether a woman seeks care and thus her chances of being scheduled for laparoscopy or laparotomy [41]. The pain threshold at which referral for surgical assessment is made may vary by clinician or hospital. Health systems may also vary in the pathway or ease of access to secondary care services. Furthermore, the likelihood of a woman being diagnosed with endometriosis at surgery may depend on the experience of the surgeon in identifying the lesions [2].

1.2.2 Incidence

Endometriosis affects women in the prime of their lives but its incidence in the general population is not known exactly. An early US study [42] reported that the incidence rate of histologically confirmed endometriosis among white, 15-49-year-old women in a Minnesota city over a 10-year period was 160 per 100,000 woman-years (0.16%). Incidence increased with age from 17 per 100,000 woman-years among those aged 15-19 to 285 per 100,000 woman-years among those aged 40-44, falling to 184 per 100,000 woman-years among women aged 45-49 years. In another Norwegian study of 40-42 year old women, the annual incidence of endometriosis was reported to be less than 0.3% [43], a figure approximating that reported by authors of the Minnesota study. In another prospective US study [13], the overall incidence rate among women with no past history of subfertility was 237 per 100,000 person-years and did not begin to decrease significantly until women were in their late 30s to early 40s, again roughly reflecting previously reported incidence rates for endometriosis. The incidence rates reported for endometriosis are generally much smaller than reported prevalence rates but this reflects the fact that prevalence is generally higher than incidence for chronic diseases, as the former includes the incidence and duration of illness.

An important limitation of most studies that report incidence rates for endometriosis relates to the fact that they are largely based on analyses of the incidence of 'endometriosis diagnosis' rather than incidence of disease onset because it is impossible to know the exact onset of disease as opposed to the date of diagnosis. Although the age of symptom onset might be used as an indicator of disease onset, this is likely to be inaccurate as symptom characteristics do not necessarily reflect disease progress in endometriosis.

1.3 Pathophysiology of endometriosis

Despite several studies on the subject, the pathophysiology of endometriosis remains poorly understood but is, however, likely to include hormonal, anatomical, genetic, and immunological factors.

1.3.1.1 Cellular mechanisms

The histological origin of endometriosis is disputed. Three major theories have been proposed separately to explain the cellular origins of endometriosis but these are difficult to prove or disprove owing to the challenges of constructing clinically valid models of these theories.

1.3.1.1.1 *Coelomic metaplasia*

It has been suggested that peritoneal endometriosis may arise from metaplasia of the coelomic epithelium - the differentiation of mesothelial cells into endometrial-like tissue - perhaps induced by environmental factors [44]. It is also thought that some endometriotic plaques, particularly those that involve the ovaries, are generated by monoclonal tumours that arise from a somatic mutation of ovarian epithelium or pelvic peritoneal mesothelium [15]. The fact that early foci of endometriosis sometimes contain other Müllerian elements such as tubal or endocervical type cells probably supports this theory [45]. Some experimental models also appear to support the coelomic metaplasia theory. For example, in one in vitro experimental model where both ovarian surface epithelium and ovarian stromal cells were co-cultured with 17- β oestradiol in a three-dimensional collagen gel lattice, the ovarian surface epithelial cells formed a lumen structure surrounded by endometrial stromal cells with an epithelial mesenchymal structure [46]. Immunoreactivity for epithelial membrane antigen and cytokeratin in the glandular cells and cilia suggested that endometriosis manifested as a serial change from the adjacent mesothelial cells.

1.3.1.1.2 Lymphatic and venous dissemination

This hypothesis suggests that menstrual tissue from the endometrial cavity travels in a metastatic-like manner to other sites through veins or lymphatic vessels [6]. A similar theory suggests that endometriosis develops from the transfer of bone marrow cells. Indeed transfer of endometrial cells via the bloodstream or lymphatic system may be the most likely explanation for the rare cases of endometriotic deposits found in the brain and other organs that are distant from the pelvis. If this is valid, it would raise important questions about the factors that determine whether blood/lymphatic spread occurs and how well it is supported by what is currently known about the epidemiology of the condition.

1.3.1.1.3 Retrograde menstruation

The most commonly held view of the origin of endometriosis is probably Sampson's hypothesis of retrograde menstruation - the backward flow of menstrual effluent into the fallopian tubes and out into the pelvis [6]. The anatomical distribution of endometriotic implants, the higher prevalence of endometriosis in women with obstructive uterine anomalies and the association of specific menstrual characteristics (short cycle length, longer cycle duration and early menarche) with increased endometriosis risk probably support the theory of a transtubal transportation of endometrial tissue into the peritoneal cavity. Clinical work has indeed shown that viable endometrial cells can be found in menstrual and peritoneal fluid [47], and endometrium has been implanted experimentally and grown within the peritoneal cavity [10]. One of the earliest relevant studies involved the construction of a mathematical model to examine the factors controlling the directionality of menstrual flow [48]. Flow rates through the model fallopian tube ostia and cervical os were calculated using the Darcy-Weisbach equation. The authors concluded that at cervical os diameters of less than 0.5 mm, over a wide range of modelled values for cervical length and fallopian tube ostial diameter and length, more than half of menstrual flow was through the fallopian tube ostia. The direct implication of this finding was that cervical os

diameter was a more important predictor of the direction of menstrual flow than were fallopian tube diameter or cervical os and fallopian tube lengths.

As retrograde menstruation occurs in 90% of women, other factors probably modify the risk related to it. More specifically, in most women, peritoneal macrophages clear the refluxed cells. In those women who develop disease, the volume or frequency of efflux may overwhelm this clearance, resulting in the development of endometriosis. Alternatively, immunological alterations may play an important role in allowing endometriotic implants to persist and progress. More recent thinking indeed suggests that molecular defects could also explain the successful implantation of refluxed endometrium onto the peritoneal surface [49]. Eutopic endometrium in endometriosis has subtle but biologically important molecular abnormalities such as oncogene activation and biosynthetic cascades that favour excessive production of oestrogens, prostaglandins, cytokines and metalloproteinases [11]. When the eutopic endometrium attaches to mesothelium, these molecular abnormalities are greatly enhanced in magnitude, encouraging implant survival.

It is clear that while the transportation (retrograde menstruation, blood/lymphatic) and coelomic metaplastic theories may explain the start of endometriosis, they do not explain the evolution of the disease process or its diverse clinical forms. Koninckx et al. [50] therefore proposed the endometriosis disease theory to highlight the possibility that endometriosis may develop in a similar fashion to a neoplasm in the sense that an initiation/propagation phase is clearly distinguishable and determined by different mechanisms. Indeed, what is currently clinically defined as endometriosis may actually have heterogeneous origins, one that arises from retrograde menstruation and the other from metaplasia, with both potentially influenced by the hormonal milieu and immune system abnormalities [15].

1.3.1.2 Molecular mechanisms

Oestrogen production plays a fundamental role in endometriosis. In brief, Steroidogenic Acute Regulatory (STAR) protein facilitates the entry of cholesterol into mitochondria. Cholesterol is then converted through a series of enzyme-catalysed steps into biologically active oestrogens. Oestrogen in endometriosis is produced from three major sources: (1) follicle stimulating hormone (FSH) and luteinising hormone (LH) acting on the ovary to induce the production of oestrogens, with aromatase catalysing the key step of conversion of C19 steroids to oestrogens; (2) aromatase in fat or skin converting circulating androstenedione to oestrogens, and (3) endometriotic tissue-derived aromatase converting local cholesterol to oestradiol.

Prostaglandins E_2 and $F_{2\alpha}$ are produced in excess in the eutopic endometrium and endometriotic tissue of women with endometriosis [51] through a co-ordinated up-regulation of both cyclooxygenase-2 (COX-2) and microsomal prostaglandin E synthase. These prostaglandins almost certainly contribute to the symptoms of pelvic pain and dysmenorrhoea associated with endometriosis. Furthermore, prostaglandin E_2 induces local oestrogen biosynthesis in endometriotic tissue.

Progesterone also plays an important role in the molecular and cellular pathways associated with endometriosis. It is thought that some element of progesterone resistance by endometriotic tissue must be at play in the pathophysiology of the disease. Progesterone induces, via retinoic acid formation, the production of 17β -hydroxysteroid dehydrogenase, which in turn catalyses the conversion of biologically active oestradiol to the less oestrogenic oestrone [11]. The failure of endometriotic stromal cells to respond to progesterone due to very low levels of progesterone receptor in endometriotic tissue means that the anti-oestrogenic effect that progesterone would have conferred is missing in endometriotic tissue. Although this proposed mechanism explaining progesterone's effects in endometriosis appears to contradict the fact that progestagens have

been used successfully for many years to treat the condition, it should be noted that progestagens act principally via central suppression of gonadotrophins resulting in lower circulating oestradiol levels.

1.3.1.3 The role of genes

Genetic predisposition almost certainly plays a role in endometriosis as research has demonstrated a 3- to 9-fold increased risk of developing endometriosis in the first-degree relatives of affected women. Although the risk may be attributed in a few families to one or more high-penetrance susceptibility loci with near-Mendelian inheritance [52], the evidence increasingly points to endometriosis being inherited as a complex genetic trait in which multiple genes that confer susceptibility to the disease interact with each other and the environment to produce the disease phenotype [53]. Although previous association studies have implicated glutathione S-transferase M1, *N*-acetyltransferase 2 and oestrogen receptor genes as possible disease susceptibility genes, the exact genes that play a role in the susceptibility of development and progression of endometriosis are as yet largely unknown [5]. There is evidence of linkage to chromosomes 7 and 10, but no specific genes or variants in these regions have as yet been identified [11].

1.4 Diagnosis of endometriosis

Clinicians cannot rely on symptoms alone to make a diagnosis of endometriosis as many women with suggestive symptoms do not have the disease and it is possible to find endometriosis in asymptomatic women. Diagnosis thus depends largely on use of surgical techniques, involving visualisation of the lesions with or without further histological confirmation [1].

1.4.1.1 Surgical diagnosis

It has already been highlighted that there are three distinct clinical forms of endometriosis – peritoneal endometriosis, ovarian endometriomas and deep endometriotic nodules – all of which may be outcomes of the same pathological process or results of different aetiopathogenetic events. The different locations of these endometriotic forms in the pelvis partly determine the type of diagnostic tool best suited to detecting each form of endometriosis.

Generally, for all forms of endometriosis, visual inspection of the pelvis at laparoscopy to identify the location, extent and severity of disease is the gold standard investigation, unless disease is visible in the vagina or elsewhere [1]. Although not definitely needed with peritoneal disease alone, it is often necessary to obtain samples for histology in the case of endometriomas and deep endometriotic nodules to identify endometriosis and exclude malignancies. Importantly though, positive histology confirms the diagnosis of endometriosis but negative histology does not exclude it [1].

A diagnosis of an endometrioma may be made or excluded by ultrasound scanning [54]: the presence of a cyst or mass with characteristics of endometriosis, i.e., thick walls, regular margins, and homogeneous low echogenicity of fluid.

1.4.1.2 Other investigations

Cancer Antigen 125 (CA-125) is a non-specific marker of endometriosis but its value as a diagnostic tool in endometriosis is limited [55]. Although it is often elevated in advanced disease, its low sensitivity significantly limits its usefulness in diagnosing minimal-mild endometriosis. Other difficulties with this test include the timing of blood collection as variations in levels exist across the menstrual cycle. Some reports suggest that testing in the late luteal phase or during menstruation may be more reliable than testing in the follicular phase. Later reports, however,

suggest that mid-follicular CA-125 is more reliable than the menstrual or the luteal CA-125 in detecting deep endometriosis and endometriomas [56, 57]. Also, women with superficial disease have marked variations in CA-125 levels, whereas women with deep endometriosis and endometriomas have consistently elevated CA-125 throughout the menstrual cycle [57].

Magnetic Resonance Imaging (MRI) and Computerised Tomography (CT) scanning may be advisable with deep infiltrating disease to map the extent of disease. The sensitivity of MRI clearly depends on the size, location and morphology of endometriotic implants; retroversion, endometriomata and bowel structures may however mask small nodules [58]. However, a recent randomized double-blind study using MRI for the detection of biopsy-confirmed endometriosis reported a sensitivity of only 69% and a specificity of 75% [59].

1.4.1.3 Staging of endometriosis

Endometriosis is often staged according to the revised classification of the American Society for Reproductive Medicine (rASRM) [33]. The system classifies endometriosis using cut-off points on a global severity score scale derived from a weighted point system. During visual examination, endometriotic implants on the peritoneum or ovaries are scored by their diameter and depth, and adhesions by their density and degree of enclosure. Total rASRM scores of <5, 6-15, 16-40, and >40 correspond to minimal (stage I), mild (stage II), moderate (stage III), and severe (stage IV) endometriosis, respectively.

Although the staging system was designed to categorize women by likelihood of pregnancy, there is much evidence to suggest that rASRM-defined stage does not correlate well with subfertility or with the severity of symptoms [60].

1.4.1.4 Challenges of surgical diagnosis

The fact that endometriosis is diagnosed only at the time of a surgical procedure presents both clinical and epidemiological challenges. Clinically, the likelihood of making a diagnosis by visual examination during surgery depends on a number of factors including the type of surgery, the skill or attentiveness of the surgeon, as well as the size and location of lesions. One finding that underscores this fact is the low kappa coefficients for visual diagnosis of endometriosis of 0.45 for intra-observer agreement and of 0.28 for inter-observer agreement [61]. It follows therefore that lesions may be missed leading to a false negative diagnosis. For example, at least 6% of women who have no visible endometriosis on visual inspection actually have microscopic endometriotic lesions [62]. On the other hand, without a follow-up biopsy of excised lesions, some non-endometriotic lesions may be incorrectly ascribed a diagnosis of endometriosis. The consequences of a misdiagnosis could be significant especially if the actual diagnosis was a malignancy or other life-threatening condition. Similarly, there are important economic costs and psychological consequences of treating 'endometriosis' in such situations.

Epidemiologically, the need for surgery to diagnose endometriosis means that in most studies of the condition, cases are often clinic- or hospital-based and therefore probably a non-representative sample of all women with endometriosis in the source population. Non-surgical, symptom- or medical history-based approaches to classifying women by endometriosis status have been explored with mixed and perhaps discouraging results [63, 64]. Furthermore, the global utility of symptomatic prediction of endometriosis is hampered by inconsistencies in the definition of endometriosis and associated symptoms across studies and populations [65].

1.5 Risk factors for endometriosis

I have highlighted the potential role of retrograde menstruation as an underlying initiation mechanism for most endometriotic lesions and noted that other forms of the disease (particularly

endometriomas) may be linked to other aetiological mechanisms such as coelomic metaplasia. A relatively consistent finding in the literature that is probably consistent with the retrograde menstruation theory is the association between the risk of endometriosis and increased exposure to menstruation. In addition to menstrual characteristics, several factors in the domains of reproductive, sociodemographic, lifestyle and physical characteristics are putatively associated with the risk of endometriosis but a number of practical difficulties often threaten the validity of the methodological approaches used in the definition and quantification of this risk.

Firstly, as endometriosis is only diagnosed through visual examination of the pelvis at surgery, most studies generating estimates of the risk of endometriosis associated with certain characteristics are based on hospital or clinic populations – women who seek health care for specific symptoms or other endometriosis-related complaint such as subfertility. Therefore, assessment in such a population may actually yield risk factors associated with ‘disease detection’ rather than with disease itself. This is because the factors that determine disease onset may be completely different to those that determine care-seeking and eventual disease detection. Furthermore, hospital patients may not be representative of the general population, casting doubts on the validity of risk estimates derived from such studies.

Secondly, controls should be representative of the population from which cases are drawn but often, hospital-based controls are employed in studies of endometriosis risk [66]. This can artificially reduce risk estimates since such controls may share similar lifestyle and other characteristics as patients. Also, when hospital-based controls with other gynaecological problems are employed, risk may be underestimated if those gynaecological problems share common risk factors as endometriosis. These challenges mean that any study that generates risk estimates must pay careful attention to the definition of its study population and to control selection.

A related issue in identifying and quantifying endometriosis risk is the need to deal with potential confounders of the relationship between endometriosis and putative risk factors. A confounder is related independently both to the outcome (endometriosis) and risk factor and must not lie on the causal pathway. In the literature, most studies use either established confounders or the change-in-estimate approach to determine confounders to control for. In the latter approach, confounders are added to a model if their addition or deletion from the original model changes the estimate of risk by 10% or more [67].

1.5.1.1 Sociodemographic factors

1.5.1.1.1 Age

The risk of endometriosis may increase with age in women of reproductive age. In one study of subfertile Caucasian women, after adjusting for age at menarche, education and obstetric history, women less than 25 years old were less likely to have minimal-mild endometriosis than those older than 25 and the risk of endometriosis was greatest in women aged 30-34 years [68]. In the same study, age ≥ 30 was associated with deep endometriotic lesions. This finding of an association of increasing age with greater endometriosis risk in subfertile women is consistent with similar findings in fertile women. For example, in one study of multiparous women, those aged ≥ 36 had twice the odds of being diagnosed with endometriosis than those < 25 [69]. In another longitudinal cohort study of women attending 17 family planning centres across England and Scotland, the risk of endometriosis was observed to increase sharply from age group 25-29 to 40-44 and to fall thereafter [70].

An interesting observation is that amongst subfertile women, the rise in risk with increasing age appears to peak earlier (30-34 years) than in fertile women (40-44 years). It is possible that

subfertility manifests as a concern in the first few years of marriage when couples are likely to be trying to conceive, leading to a generally earlier age at diagnosis of endometriosis.

The association of endometriosis with increasing age may be consistent with the conceptual link between greater endometriosis risk and increased cumulative exposure to menstruation. If this is true, one might expect that the risk of endometriosis with age would be modified by characteristics of the menstrual cycle such as cycle length, cycle duration and menstrual volume.

1.5.1.1.2 Race and ethnicity

A 1984 review [71] set out evidence from primary studies suggesting that the risk of endometriosis is greater in Caucasians compared to Blacks and Orientals. It also tracked the historical changes in the perceived infrequency of endometriosis in Blacks and noted how more recent primary studies contributing to the review had highlighted the possible role of diagnostic bias in which symptoms were attributed to pelvic inflammatory disease. The review also considered the reasons for the findings around differences in endometriosis risk by race. Key reason included an almost consistent lack of adjustment for socioeconomic status, age and reasons for undergoing laparoscopy. Clearly, socioeconomic status differences between races (particularly Caucasians and Blacks) can confound the relationship of race and endometriosis risk and it may be that many of the included primary studies would have found no association if differences in socioeconomic status was duly accounted for.

Indeed, more recent primary studies indicate that there are no differences in endometriosis risk by race or ethnic background [40,72] but these did not clearly adjust for the effect of socioeconomic status either. One study of a North American population which did adjust for the effect of socioeconomic status using income as a proxy found that compared to white women, Black and Hispanic women were at lesser risk for endometriosis but this was not significant. Asian

women had significantly greater risk of endometriosis but there were only 4 Asian women in the study population [69].

1.5.1.1.3 Socioeconomic status

In the literature assessing the risk factors for endometriosis, a number of proxy variables have been used as indices of socioeconomic status. These include education, occupation, social class, religion, nationality and class of hospital admission. Amongst these however, the most commonly used index is education.

Most studies report a clear effect of education on the risk of endometriosis. In the study by Hemmings et al. [40], amongst women undergoing laparoscopy and hysterectomy (but not sterilisation), endometriosis risk was greater if women were college or university educated. After adjusting for age at first pregnancy, subfertility and time lag between first pregnancy and menarche, the risk remained significant (OR = 1.6, 95% CI 1.2-2.2 for hysterectomy and OR = 1.5, 95% CI 1.2-2.2 for laparoscopy). In one case control study of 114 women with endometriosis and 1,127 controls with acute non-gynaecological conditions, compared to women with less than six years of education, those who had 7-11 years of education had a 30% greater risk of endometriosis and those with ≥ 12 years of education had 90% greater risk of endometriosis. The trend of increasing risk with a longer period in formal education was significant [39,73,74]. Other studies have however not found similar association between endometriosis and length of time in formal education [43, 75].

In one study where the occupation of the head of household was used as an index of socioeconomic status, an increased risk of endometriosis in women of higher socioeconomic status was found [74]. A study of Lebanese women however did not find a similar relationship but the authors noted that women with first class hospital admission had greater odds (OR = 2.77,

95% CI 1.73 – 4.42) of being diagnosed with endometriosis compared to women with 2nd and 3rd class admission [76]. The risk of endometriosis did not vary by socioeconomic status when the index used was nationality or religion. Similarly, when religion was used as an index of socioeconomic status, no relationship was found with endometriosis risk in the study by Buck-Louis [77].

In summary, there may be some evidence to suggest that endometriosis risk increases with socioeconomic status measured by most indices. One possible explanation for this association might be selection bias - endometriosis is surgically diagnosed and women with higher education or social class are likely to have more access to diagnostic facilities, in this case investigative laparoscopy [71]. However, even within varying levels of healthcare utilisation (measured by a recent gynaecological examination), socioeconomic status has been found to predict risk of endometriosis [13].

1.5.1.2 Menstrual and reproductive factors

1.5.1.2.1 Cycle length and endometriosis risk

There is relative consistency in the literature regarding the relationship between short cycle length (defined as cycle length ≤ 27 days) and the risk of endometriosis. One case control study compared 305 women with endometriosis recruited from a gynaecology clinic with 305 controls from the same clinic but who were free of endometriosis at laparoscopy [78]. Women with cycle lengths < 28 days had 3.36 times greater unadjusted odds of endometriosis compared to those whose cycle length was > 28 days. After adjustment for nulliparity, age at first childbirth and social class, the odds ratio was 1.83 (95% CI 1.60 – 2.55).

In contrast, another study, which focused on subfertile women with mild and minimal endometriosis and who had regular menstrual cycles, found that compared to women with cycle lengths ≥ 30 days, those who had cycle lengths ≤ 27 days in the previous six months had 1.63 times greater odds of endometriosis (95% CI 1.02 – 2.60) [68]. It was however unclear whether potential confounders were accounted for. Another case control study [79] of subfertile women and fertile controls found similar doubling of the odds of endometriosis in women with cycle lengths ≤ 27 days compared with those with lengths 28-34 days (OR 2.1; 95% CI 1.5 – 2.9) .

Waller and Shaw in their study of newly diagnosed cases and controls recruited from well-women clinics, found a statistically significant trend in shorter cycles being associated with increased risk of endometriosis [75]. After adjusting for marital status, parity and length of menses, the association between endometriosis and shorter cycle lengths was not significant but the trend remained statistically significant ($\chi^2 = 4.51$, $p = 0.03$).

Of note are two other studies that found no relationship between cycle length and endometriosis risk. In their discussion, Darrow et al. [80] noted that their result differed from Cramer and co-authors' [79] finding that shorter cycle lengths were a risk factor for endometriosis. They highlighted that their study included women with pelvic symptoms and secondary as well as primary subfertility. Although they did not specify the implication of this for the measure of association they reported, the fact that the controls may have had a higher rate of the exposure than the source population (short cycle length may be associated with other gynaecological symptoms) suggests they may have underestimated the association. Heilier et al. [81] similarly found no significant differences in the odds of endometriosis and deep endometriotic nodules in women by the length of their menstrual cycles.

The finding that shorter cycle lengths are a risk factor for endometriosis is consistent with the conceptual role of increased exposure to menstruation and the role of oestrogen exposure in endometriosis.

1.5.1.2.2 Duration of menstrual bleeding and endometriosis risk

The relationship of longer duration of menstruation as a risk factor for endometriosis is less well established in the literature. In Arumugam's case-control study, the unadjusted odds ratio for endometriosis in women with menstrual duration >5 days compared to those with ≤5 days duration was 1.21 (95% CI 0.86-1.70) [78]. In another Canadian study of subfertile women with minimal-mild endometriosis, there was no significant difference when menstrual duration was compared to that in subfertile controls [68]. In that study however, menstrual bleeding of ≥5 days was associated with higher odds of endometriosis in women whose cycle length averaged 27 days or less. A similar direct, albeit not statistically significant, association was reported by Heilier et al. who found that the risk of deep endometriotic nodules increased by 4% for each additional day of menstruation, and the risk of endometriosis increased by 7% for each additional day of menstruation [81].

Other studies conclusively report that menstrual duration is a risk factor for endometriosis. In one case control study which compared subfertile women to fertile controls, women with menstrual periods lasting more than one week had 2.4 times (95% CI 1.4 – 4.0) greater odds of endometriosis compared to women with periods lasting ≤7 days[79]. A comparison of 104 laparoscopically confirmed cases of endometriosis to 100 friend and 98 hospital controls (some of whom had gynaecological problems), after controlling for pregnancy, religion and BMI, found that cases under the age of 30 years were significantly more likely to have a menstrual flow lasting ≥6 days per month (OR 2.5, 95% CI 1.1 – 5.9) compared to age-matched friend controls[80].

1.5.1.2.3 Parity and endometriosis risk

Parity refers to the number of times a woman has given birth to a foetus after 24 weeks of gestation irrespective of whether the foetus was live or stillborn. Gravidity refers to the number of times a woman has been pregnant.

The evidence for a link between parity/gravidity and endometriosis risk is relatively consistent. In the case-control study by Berube et al. [68], women who were gravida >0 and para >0 had 39% (CI 4% – 61%) lesser risk of minimal-mild endometriosis than those women who were gravida 0. Being gravida >0 but para = 0 did not significantly lessen a woman's risk of endometriosis, suggesting that parity may be a greater determinant of endometriosis risk than gravidity. In the study by Buck-Louis et al., gravidity ≥ 2 was associated with a 90% reduction in endometriosis risk compared to zero gravidity [82]. Similarly, parity ≥ 1 was associated with an 80% reduction in endometriosis risk compared to zero parity. Parity is protective for endometriosis independently of factors such as age and height (OR 0.21, 95% CI 0.07 – 0.69) [39] and this is consistent with the findings in a separate study which suggested that the proportion of women who had never been pregnant was higher amongst endometriosis cases than amongst controls (47% versus 27%; $X^2 = 6.16$, $P = 0.01$); the proportion of women who had never given birth was also higher in cases than controls (58% versus 36%; $X^2 = 7.77$, $P = 0.005$) [83]. Mean parity and gravity are in addition observed to be significantly higher in ever-married controls than in ever-married endometriosis cases. Similar findings of increased endometriosis risk with lesser gravidity and parity have been reported in other studies [69, 84].

One common shortcoming of most studies that have reported a positive relationship between parity and endometriosis risk appears to be a failure to control for the potential effect of subfertility. Since subfertile women generally have lower parity than the general population [85], underlying subfertility, being related inversely to parity and directly to endometriosis, may in fact

positively confound the association between endometriosis and parity, resulting in over-estimated measures of association in those studies. However, the fact that increasing parity reduces endometriosis risk even amongst parous women [12] would suggest that low parity is more likely than not to represent a genuine risk factor for endometriosis.

The conceptual link between parity/gravidity and the risk of endometriosis may relate both to the retrograde menstruation theory and the role of oestrogens. With respect to the retrograde menstruation theory, cervical os diameter has been proposed as a greater determinant of the directionality of menstrual flow than cervical length and fallopian tube length and ostial diameter [48]. Although parity may have no effect on internal cervical os [86], external cervical os diameter is increased by childbearing. The increase in external cervical os diameter associated with higher parity may thus reduce the possibility of retrograde menstruation. Pregnancy, on the other hand, reduces a woman's lifetime exposure to menstruation, thereby reducing her exposure to oestrogens and consequently her risk of endometriosis.

As earlier established, parity probably reduces endometriosis risk by increasing cervical ostial diameter during parturition but in women who undergo elective caesarean section before the onset of true term labour, an increased risk of scar endometriosis is reported. Operative scar endometriosis occurs in 0.03-0.047% of cases [87] and may appear any time from 2 to 19 years after surgery [88]. The most common site for extra-genital endometriosis to occur is the pfannenstiel scar of caesarean section [89], although it could also occur following episiotomy and hysterectomy. The underlying event initiating the process that results in scar endometriosis is thought to be contact of decidual cells with the surgical incision. Scar endometriosis is however more common after caesarean section occurring before onset of true term labour than with episiotomy wounds following vaginal labours, even though decidual cells keep in touch with surgical incisions in both procedures. As far back as the 1950s, a possible link had been

established with the endometrial changes associated with the development of pregnancy [90]. In more recent years, it has been proposed that the immune tolerance maintained at the maternal-foetal interface throughout gestation plays a key role in allowing decidual cells to implant [91]. Term delivery is known to coincide with the termination of this specific immune tolerance but elective caesarean section is often performed before true labour. It is believed that elective caesarean surgery before spontaneous onset of labour is performed during the active immune tolerance and this enables easier implantation of the decidual cells within the surgical wound.

1.5.1.2.4 Tampon use and risk of endometriosis

The evidence for tampon use as a risk factor for endometriosis is inconsistent. One of the earliest studies on the subject was a cross sectional, postal questionnaire survey of 470 white women who were members of the Endometriosis Association [92]. The authors compared the rates of reported tampon use in those women to use in the general population and found that reported use in the survey population (75-83%) was not different to that in the general population. Notably, younger women in the study population were more likely to have started using tampons earlier in life than the older women. In another case-control study comparing women with laparoscopically confirmed disease to friend and hospital controls, the odds ratio for endometriosis was 3.6 in those women aged <30 years who reported over 14 years' tampon use (95% CI 1.04 – 13.5)[80]. Compared to friend controls, more cases reported starting to use tampons before the age of 16, using tampons for more than 14 years and sleeping with tampons *in situ*.

The logic of tampon use being a risk factor for endometriosis is principally based on the retrograde menstruation theory. Cervical obstruction increases the likelihood of endometriosis by increasing the menstrual debris available to the pelvic cavity [93]. Use of tampons therefore represents a form of uterine outlet obstruction, which increases the likelihood of retrograde flow

of menstrual effluent. Furthermore, it has been suggested that the link between endometriosis and tampon use also involves dioxins, which were a constituent of tampons until the 1980s. However, the relationship between dioxins and endometriosis in humans remains largely unsubstantiated [94, 95].

One retrospective case-control study which drew cases and some controls from membership of the Endometriosis Association (controls were predominantly friends of cases without endometriosis) found that compared to women who reported only tampon use, the risk of endometriosis was significantly greater in those who reported using only pads during menstrual periods (OR 2.6, 95%CI 1.9 – 3.5) [94]. The authors expressed surprise at the unexpected findings and admitted the shortcomings of their study and its design, particularly the poor response rates and the dependence on women's awareness of their diagnosis of endometriosis. They however postulated that if the relationship they found was true, it could be that tampons are better at removing menstrual fluid compared to pads. Subsequent studies have however found no relationship between tampon use and endometriosis risk [81].

A common limitation of many studies examining the role of tampons in endometriosis is a failure to control for the effect of potential confounding variables. For example, young white women are more likely than their black counterparts to use tampons [96] and endometriosis is probably more likely in white than black women. Controlling for race or ethnicity is therefore important in any analysis of tampon use and endometriosis risk to avoid obtaining spuriously exaggerated measures of association. Furthermore, menstrual volume, which is related to the risk of endometriosis, may actually influence a woman's choice of tampons or pads and controlling for it is essential in analysing the role of tampons in endometriosis.

1.5.1.3 Contraception and endometriosis

1.5.1.3.1 *Oral contraceptives and endometriosis risk*

Oestrogen production plays a key role in endometriosis disease. Biological hypotheses in favour of a positive association between oral contraceptive use and endometriosis risk relate to the fact that oral contraceptives reduce oestrogen production and may therefore reduce the risk of endometriosis. Oral contraceptive use is also associated with endometrial atrophy and may inhibit the development of endometriosis [97]. Furthermore, they produce a reduction in menstrual flow and this in turn reduces the likelihood of retrograde menstruation. In support of a negative association between oral contraceptive use and endometriosis risk is the fact that even low doses of oestradiol and progesterone increase risk by increasing the likelihood of implantation and lesion growth [2].

One of the earliest studies on oral contraception and endometriosis suggested that women using oral contraception had a reduced chance of developing endometriosis but the study lacked appropriate controls [98]. Among previously fertile women in another study, oral contraceptive pill use was associated with a lower risk of endometriosis [99]. These studies, however, did not explore variations in the effect of oral contraceptives by current or past use, but later studies attempted to examine those effects. In one study of women admitted to an obstetrics and gynaecology clinic with histologically confirmed ovarian endometriosis and controls with acute conditions, oral contraceptive use was more frequent in cases than controls (RR = 2.1, 95% CI = 1.2-3.6). The risk of endometriosis also increased with duration of oral contraceptive use and with years since last use [74]. In a later study by the same authors using similar methods, women who reported 'ever use' of oral contraceptives had a relative risk for endometriosis of 1.6 (95% CI 1.2-2.2) [100]. When the risk was partitioned by latency of oral contraceptive use, it was found that the increased risk was restricted to ex-users (RR 1.7, 95% CI 1.3-2.4), the estimated RR for current

users being 0.9 (95% CI 0.5-1.9). Sangi-Haghpeykar and Poindexter studying parous women, and Vessey et al. in a study population of women attending family planning clinics, reported similar protective effects of current oral contraceptive use on endometriosis [69,70]. However, the latter study additionally found a protective effect if stopping oral contraceptive use occurred within the past 12 months. Women who stopped oral contraceptives over 12 months before were at greater risk of endometriosis than current users and those who had never used them. Notably, a number of studies have found no effect of oral contraceptive use on endometriosis risk [75,80,81].

There are some difficulties with understanding the exact nature of the relationship between endometriosis risk and oral contraceptive use. First, oral contraceptives are often provided as a first line treatment to women complaining of menstrual cycle irregularity, heavy flow and dysmenorrhoea, i.e. symptoms associated with endometriosis. In fact, oral contraceptive treatment and subsequent laparoscopic diagnosis of endometriosis are likely to be prompted by endometriosis-specific symptoms [8]. It is therefore difficult to determine if a woman developed endometriosis before commencing oral contraceptives or if oral contraceptive use precipitated the disease. Furthermore, in analyses of 'ever use' versus 'never use', women with endometriosis-induced dysmenorrhoea would be selectively excluded from the 'never use' category, because of the tendency to use oral contraceptives as first-line treatment of endometriosis-related symptoms, yielding artificially increased risk for 'ever use' [100]. The increasingly accepted position, however, seems to be that oral contraceptive use has no effect on long term endometriosis risk but suppresses the symptoms of endometriosis, which emerge after use has been stopped. This would seem to fit with the findings of an increased likelihood of endometriosis in 'ever users' compared to current users or 'never users'. It would, however, not explain why risk appears to be greater the longer oral contraceptives were last used.

1.5.1.3.2 Intra-uterine devices and endometriosis risk

Non-hormonal intrauterine devices (IUDs) increase menstrual bleeding and it is therefore possible that they increase the probability of retrograde menstruation. A number of investigators have evaluated this relationship.

Darrow et al. [80,101] assessed women with endometriosis (manifesting with pelvic symptoms or subfertility) using friend and medical controls. The use of IUDs did not differ between cases and controls but the authors noted that IUD use was contraindicated in nulliparity and that this might have limited use in cases (56% of cases were nulliparous compared to 23% of controls). Moen's study of parous symptom-free Norwegian women who had undergone sterilisation also found no significant difference between cases (20% of sample) and controls in IUD usage rates [43]. No differences are similarly reported in IUD use between women with ovarian endometriomas and controls [74].

Obermeyer's study of Lebanese women, however, found that significantly more controls than cases used an IUD, although this study was not designed in a way that differentiated between current and past use [76]. A similar pattern to that for oral contraceptives has also been observed in other settings, for example compared to never users, Vessey et al. noted that current users had lower risk (RR 0.4, 95% CI 0.2 – 0.7) and past users (stopped 49-72 months previously) had higher risk (RR 1.4 95% CI 0.4 – 3.2) [70]. The authors speculated that in some women developing endometriosis while using IUDs, the disease goes unrecognised and they are treated by removal of the device rather than by laparoscopy. As with oral contraceptives, the disease symptoms then re-emerge sometime after removal of the device, then prompting a diagnosis.

1.5.1.4 Lifestyle and environmental factors

1.5.1.4.1 Smoking and endometriosis risk

Smoking reduces the levels of circulating oestrogens [102]. Two components of cigarette smoke - nicotine and cotinine - are known to interfere with aromatase activity, thus impairing the conversion of androgens into oestrogens [103, 104]. Therefore, the risk of endometriosis would be expected to be lower in smokers in order to concur with prevailing knowledge about the role of oestrogens in endometriosis.

One of the earliest reports on the relationship between smoking and endometriosis risk [79] found that current heavy smoking commencing before the age of 17 years was protective against endometriosis (OR 0.5, 95% CI 0.3 – 0.9). Accordingly, compared to women with greater lifetime exposure to cigarette smoking, those who have none or lower exposure to cigarette smoking have a higher risk of endometriosis [80]. However, amongst younger smokers (less than 30 years old), the risk was found to be significantly less if smoking started before the age of 16 (OR 3.0, 95% CI 1.1 – 8.4). Although authors of one study found no correlation between endometriosis risk and dose of smoking exposure, they found that amongst 'never subfertile' women, current smoking increased risk but amongst women who were concurrently subfertile, current smoking reduced the risk of endometriosis [12]. A later study [82] found similar protective effects of smoking (OR 0.3, 95% CI 0.1 – 0.8), with both intrauterine exposure to cigarette smoke and current smoking individually associated with a reduction in endometriosis risk (about 70%); combined intrauterine exposure and current smoking produced a 95% reduction in the risk of endometriosis.

The protective effect of cigarette smoking has not been found in a number of other studies, most of which report no clear relationship between endometriosis risk and cigarette smoking [40,66,68,70,74,75,81].

The conflicting nature of the findings in the literature on the relationship of endometriosis and cigarette smoking is difficult to understand. Some authors have suggested that although the contents of cigarette smoke reduce circulating oestrogens, smokers are also exposed to exogenous oestrogens in the form of dioxins, increasing endometriosis risk. The relationship of dioxins to endometriosis risk however remains highly controversial.

1.5.1.4.2 Alcohol use and endometriosis risk

Plasma oestradiol concentrations rise with the consumption of moderate amounts of alcohol [105]. Endometriosis risk, to be consistent with the theory of the role of oestrogens in endometriosis, might therefore be expected to increase with alcohol intake.

Accordingly, compared to subfertile women who do not drink any alcohol, those who have moderate alcohol intake (3-8 drinks per month) are at increased risk of minimal-mild endometriosis (OR 1.74, 95% CI 1.05 – 2.88) [68]. Alcohol intake does not, however, correlate with disease severity or the appearance of implants. Similar findings on the relationship of moderate alcohol intake (≤ 100 g per week) to risk of endometriosis have been replicated in another study of subfertile women and parous controls [106]. Similarly, a significantly elevated risk of deep endometriotic nodules has been reported in women who drink every day compared to those who do not drink at all, but information on actual quantities is not given to enable comparison with the quantification of 'moderate' intake described in earlier referenced studies [81]. In one comparison of the case notes of 535 women who, over a six-year period had endometriosis diagnosed at laparoscopy or laparotomy, with those of 200 subfertile women without endometriosis, investigators found that alcohol use was more frequent in those women with endometriosis [72].

The association between *in utero* or current exposure to alcohol and a diagnosis of endometriosis is controversial. Studies in gynaecology clinic settings and those comparing fertile women with endometriosis and subfertile women without endometriosis report no association between alcohol intake and endometriosis [66, 107]. However, one prospective cohort study reported that current greater alcohol intake was associated with a lower rate of endometriosis [12], the authors suggesting this may have been because of limited power in their study to examine the effects of more than one drink per day owing to the low consumption levels in their Nurses' Health Study II cohort.

It has been suggested that women with endometriosis may take alcohol to alleviate their pain. Some authors have investigated this by: (i) not including women with severe pelvic pain in their study sample or (ii) adjusting for pelvic pain [68]. Nevertheless, the reasons for the conflicting evidence for alcohol use as a risk factor for endometriosis remain unclear.

1.5.1.4.3 Physical activity and endometriosis risk

A plausible biological basis for a relationship between physical activity and endometriosis risk relates to the association between regular exercise and reduced cumulative exposure to menstrual flow, decreased ovarian stimulation, and oestradiol production [108]. It would be expected consequently that physical activity should reduce the risk of endometriosis.

One of the earliest studies on exercise and endometriosis risk found that exercising ≥ 4 hrs/week reduced the risk of endometriosis but this reduction in risk did not attain statistical significance [66]. In one case-control study of physical activity and endometrioma risk in 18-39 year old women, the duration, frequency and intensity of physical activity two years before a reference date and at ages 12-21 were assessed [109]. The authors found that women who reported frequent, high-intensity activity during the two years prior to the reference date had a reduced

risk of endometrioma (OR 0.24, 95% CI 0.08, 0.71) compared with women who engaged in no high-intensity activity. Physical activity during ages 12-21, as well as activities of lower intensity, frequency, and duration, was not associated with endometrioma risk. The results of this study should, however, be treated with caution as only four cases contributed data to the aspect of the analysis that resulted in the statistically significant finding. In a Belgian study, physical activity at work and during leisure time was assessed in cases and controls [81]. The authors found that compared to women who did 'high' physical activity at work, those who did 'low' physical activity at work were significantly more likely to be diagnosed with deep endometriotic nodules or peritoneal endometriosis. They did not report a similar relationship between endometriosis risk and physical activity during leisure.

In a Norwegian population survey, women were asked to self-report both a history of endometriosis diagnosis and regular exercise. The authors found no significant difference in the history of regular exercise amongst women who reported a diagnosis of endometriosis compared to those who did not (OR 0.7 95% CI 0.3-1.5) [43].

A potential explanation for an apparent inverse association between endometriosis and physical activity is that pain limits activity in cases, thereby producing the apparent protective effect of physical activity. However, in studies which have either stratified participants by severity of symptoms or excluded women with severe pain or heavy bleeding [109], the same relationship is generally reported.

1.5.1.4.4 Caffeine use and the risk of endometriosis

Caffeine (1,3,7-trimethylxanthine) is a natural alkaloid found in coffee beans, tea leaves, kola nuts, and other plants [110]. It's generally thought that caffeine may increase production and reduce metabolism of oestrogen but this effect remains contested. One study of pregnant

women found that moderate coffee intake decreased oestradiol and total oestrogen levels [111]. However, Ferrini's study suggested that at high doses, caffeine intake was positively associated with plasma oestrone concentration ($r=0.26$, $p=0.05$) [112]. Lucero et al. found that caffeine intake from all sources was linked with higher oestrogen levels after controlling for age, BMI, caloric intake, smoking, and alcohol and cholesterol intake [113].

Not surprisingly, the evidence for a role for caffeine in endometriosis is similarly inconsistent. After adjustment for centre, age, number of sex partners and current or former smoking in one study, subfertile women who consumed >7g of caffeine per month were more likely to be diagnosed with endometriosis (RR 1.6, 95% CI 1.1-2.4) than those who consumed 0-3g per month [106]. Another study found a similar positive association between caffeine intake and risk of endometriosis (OR 1.33, 95% CI 0.91-1.94) in women reporting caffeine intake of at least 300mg in the month before diagnostic laparoscopy but the risk did not reach statistical significance [68]. Although women who reported daily caffeine intake in one study had a reduced risk of endometriosis compared to those who reported no intake, this was not statistically significant [82]. Other studies have similarly found no association between caffeine intake and endometriosis risk [12,75,107]

1.5.1.4.5 Intrauterine exposures

A growing body of knowledge has its foundation in Barker's [114-118] hypothesis which posits that environmental factors, principally operating *in utero*, can affect foetal growth and development in a way that permanently programmes the developing foetus for adult onset disease. The related 'thrifty gene' hypothesis asserts that *in utero* metabolic and endocrine conditioning from such nutritional deficiency prepares a foetus to cope with continued deficiency after birth, with the same changes resulting in obesity if nutrition becomes plentiful [119]. This life-course approach has been employed in the assessment of a number of adult onset conditions

including endometriosis. In one cohort study of women undergoing laparoscopy, the consistency of a lean body over critical windows of adolescence and early adulthood was thought to suggest a potential role for *in utero* factors in the aetiology of endometriosis, perhaps as a consequence of intrauterine growth restriction and subsequent alterations of the postnatal hormonal milieu [39].

Two relatively large studies have examined the role of intrauterine factors in endometriosis. Missmer's prospective cohort data from the Nurses Health Study found that low birth weight (<5.5 pounds), compared to birth weight 7.0–8.4 pounds, increased the risk of endometriosis (RR 1.3, 95% CI 1.0-1.8) after adjusting for age, parity, calendar time, race and BMI [13]. Being part of a multiple gestation also increased the risk of endometriosis by 70% and *in utero* exposure to Diethylstilboestrol (DES) increased endometriosis risk by 80%.

Buck Louis' study of a cohort of women who underwent laparoscopy found no association of endometriosis with *in utero* alcohol and caffeine exposure [82]. However, they found that, after adjusting for age, there was a significant reduction in the odds of endometriosis with *in utero* exposure to cigarette smoke, both in the presence and absence of current cigarette smoking.

As with any self-reported variable especially in case-control study designs, key to the validity of any findings on the association of *in utero* exposures with endometriosis would be the accuracy of exposure information, as such information cannot be captured by measurements made in adulthood.

1.5.1.5 Personal characteristics and endometriosis

1.5.1.5.1 Body Mass Index (BMI)

Obesity (measured by Quetelet's BMI) is thought to increase bioavailable oestrogen levels via increased adiposity and aromatase activity [120] and, as such, might be expected to increase the risk of endometriosis. However, a number of researchers, using principally case-control designs, have found a consistent inverse relationship between BMI and endometriosis risk [73,74].

In one case-control study of subfertile women including 329 cases with minimal-mild endometriosis and 262 controls [68], compared to women with BMI <20.0, women with BMI ≥ 25.0 had a 51% lower chance of being diagnosed with minimal-mild endometriosis (OR 0.49, 95% CI 0.30-0.82). In another case-control study of Italian women, BMI was significantly lower in affected women than controls. Even amongst women with a normal BMI, the risk of endometriosis increased significantly as BMI increased [121]. Another prospective cohort study assessed BMI at age 18 and found that it was inversely associated with endometriosis risk (for BMI >30 compared to BMI 19.0-20.4, the RR was 0.8, with 95% CI of 0.6-1.1) [12]; another study in a different population found that higher current BMI was associated with a 12-14% reduction in risk of endometriosis after adjusting for age, being taller than 68 inches, and parity [39].

In a number of other studies however, there was no association found between endometriosis and BMI [40,43,75].

The apparent difficulty with assessing the relationship between endometriosis and BMI is that most studies understandably measure current or adult BMI. There is a possibility therefore that such studies may have measured an exposure that occurred after the outcome of interest. Furthermore, the endocrine imbalances associated with obesity are linked to abdominal visceral adiposity, suggesting that some other measure of adiposity that accounts for this factor might be a better correlate of endometriosis risk than obesity. Indeed, an inverse association between

endometriosis and waist-to-hip and waist-to-thigh ratios in women <30 years has been reported, suggesting that body fat distribution may be a potentially better marker for endometriosis risk than obesity by itself [122].

1.5.1.5.2 Hair colour

The putative link between red hair and endometriosis risk is weak. Red hair is coded for by a gene on chromosome 4 and brown hair by a gene on chromosome 19. Red hair is inherited as a deficit of eumelanin (coded for by the chromosome 19 gene) and not necessarily as a dominance of pheomelanin (coded for by the chromosome 4 gene) [123]. The red hair gene is also proximal to a group of genes associated with fibrinogen expression [124]. Reduced platelet function in women with red hair [125] suggests that there may be some association with red hair and increased menstrual bleeding, consequently increasing the risk of retrograde menstruation. Furthermore, red hair is associated with immune system deficits in the third component of complement coded by a gene on chromosome 19. The immune abnormalities that promote disease following menstrual effluent into the peritoneum may therefore explain the putative link of red hair and endometriosis.

In cross-sectional studies, naturally red hair has been shown to be more frequent among those with endometriosis compared with the general population [126]. In a study of hair colour at age 18 amongst women with a self-reported diagnosis of endometriosis, the incidence rate of endometriosis did not differ in women with red hair from that in women with other hair colours [123], but another study of a French cohort did find that red hair was associated with an increased odds of endometriosis compared to brown hair [127].

1.5.1.6 Endometriosis and co-morbidity

In two small cohorts in the US and Sweden, no association was found between endometriosis and melanoma [128,129]. Similarly, one US case-control study found no association between endometriosis and melanoma [130]. However, a significantly increased risk was found in a retrospective cohort of subfertile US women (RR 2.06; 95% CI 1.0-4.4) [131]. A prospective study of college alumni found a significant positive association [132]. Another prospective cohort study reported on the 12-year follow-up of over 90,000 women in France [127]: an increased risk of cutaneous melanoma was found in women who had a history of endometriosis (RR 1.62; 95% CI 1.15-2.29). The association between melanoma and endometriosis may be aetiological or purely associative. As endometriosis is positively linked to nulliparity, and the risk of melanoma is negatively linked to parity and early age at first birth, a hormonal causal mechanism is a distinct possibility but this is yet to be extensively examined. On the other hand, endometriosis is linked to allelic imbalances in certain tumour suppressor genes, loci also associated with melanoma [127].

One cross-sectional study in the USA found that women with endometriosis had a higher risk of asthma than those without endometriosis, but similar results have not been found in observational studies [121]. Whether a biological mechanism genuinely exists to explain a link between endometriosis and asthma is not clear. Approximately 40% of adults with asthma have the extrinsic/allergic type, which employs immunoglobulin E-dependent mechanisms and is associated with atopy [133]. Immunoglobulin E, however, has no role in endometriosis and, therefore, a link between endometriosis and asthma is not immediately apparent.

It has been suggested that the risk of breast cancer is increased in women with endometriosis. As premenopausal women with breast cancer are commonly treated with tamoxifen, which has also been associated directly with endometriosis [134], it is important to establish if the link between

endometriosis and breast cancer risk is mediated via tamoxifen. In a prospective cohort study of Swedish women hospitalised with endometriosis and followed up for over 11 years, the standardised incidence ratio for breast cancer was 1.3 (95% CI 1.1-1.4) [128]. However, in a similar prospective cohort study in the US, no relative increase in risk of breast cancer was found after 13 years' follow-up in women with a self-reported history of endometriosis [129]. Similarly in a Danish case-cohort study [135], no significant increase in risk of breast cancer was found with endometriosis (adjusted rate ratio 0.97; 95% CI 0.85-1.11). The authors also found that the risk of breast cancer was lower in women in whom endometriosis was diagnosed before the age of 40, but higher in women in whom it was diagnosed at ≥ 40 . A possible explanation for the association between endometriosis and breast cancer may be local or systemic enhancement of aberrant inflammatory and sex steroid hormonal mediators [136]. However, such mechanisms may not explain the increased family history of breast cancer found in women with endometriosis compared to controls unless the aberrant inflammatory mediators referred to by Ness et al. are heritable traits [72].

The possibility that endometriosis might represent an autoimmune disorder was first raised by Weed et al. in 1980 [137]. As immune surveillance is altered in endometriosis, it is thought that women with endometriosis may have an increased risk of developing autoimmune disorders. Sinaii et al. found that the risks of hypothyroidism, systemic lupus erythematosus (SLE) and Sjogren's syndrome (SS) were higher in members of the Endometriosis Association than in the general population [138] and similar findings were reported by Matarese et al. who noted an increase in autoimmune disorder risk in women with endometriosis [139]. However, the findings of the study by Sinaii et al. should be interpreted with caution as significant biases were evident, not least in the much higher proportion of white and educated women in their study population and the potential for confounding presented by fibromyalgia. A more recent study by Matorras et

al. found no increased risk of autoimmune disorders (specifically SLE and SS) in women with endometriosis [140].

The prevalence of endometriosis is higher in women with migraine than in non-headache controls, and migraine sufferers with endometriosis have more frequent and disabling headaches [141]. In one case-control study, the characteristics of headache were compared in women with histologically confirmed endometriosis and controls [142]. The presence of migraine was significantly greater and the age of onset significantly earlier in women with endometriosis compared to controls. In another case-control study, migraine sufferers were more likely to report a history of endometriosis compared to controls [143]. Although the link between endometriosis and migraine is as yet not entirely clear, the two conditions share certain biochemical mediators, principally prostaglandins. On the basis of this putative link, Ferrero et al. hypothesized that the systemic spreading of prostaglandins produced by endometriotic lesions may have contributed to the increased prevalence of migraine amongst women with endometriosis in their study population. The co-morbidity of endometriosis and migraine could also be explained by the fact that nitric oxide synthesis is up-regulated in both migraine and endometriosis [142].

1.6 Health-related quality of life (HRQoL) and work productivity in endometriosis

The impact of endometriosis transcends traditional gynaecological and fecundity complaints to involve aspects of HRQoL such as sexual and physical activity, employment and mental health [144-146]. The impact of endometriosis on HRQoL is also known to be greater than the impact of many other gynaecological and non-gynaecological conditions on HRQoL [147,148]. The impact is increased by the lack of information and uncertainties about the condition, as well as the sense of loss of control experienced by women, who sometimes turn to complementary or alternative medicines as a means of gaining control of their lives [149,150].

As indicated earlier, endometriosis principally affects pain, as well as psychosocial and social functioning, and is associated with an increase in perceived stress [19,151,152]. However, the impact on HRQoL is more complex: subjective experiences, when captured, indicate the wide-ranging nature of the effects seen in endometriosis [153].

Aside from the disease itself, its treatments also impact on HRQoL [23]. Surgery often improves HRQoL and is usually associated with adverse effects only as a result of post-operative complications. Pharmacological treatments, on the other hand, may relieve symptoms but can ultimately impair HRQoL because of side-effects [154,155]. Although it is clear that some of the impact of endometriosis on HRQoL is mediated through its symptoms, it remains to be established how much of the impact is independent of these symptoms. For example, dyspareunia, which may exist in the absence of endometriosis or be a symptom of both peritoneal disease and/or deep endometriotic nodules, has been shown to affect the self-esteem and relationships of sufferers negatively [156], while CPP, which is a common feature of endometriosis, affects HRQoL even when it exists in the absence of endometriosis [21]. Accordingly, although there is uncertainty as to whether the severity of a symptom such as pelvic pain correlates with the degree of impaired HRQoL in endometriosis [157,158], controlling symptoms in women with endometriosis clearly improves HRQoL and represents a critical element of any intervention to improve the lived experience of women who suffer from the condition [24].

The functional impairment in the mental, social, and physical aspects of HRQoL produced by endometriosis reduces the ability of women with the condition to perform normal daily activities such as a job. For example, in one survey of 2,980 respondents, patients with major depression were 4.8 times more likely than non-depressed individuals to spend all or part of a day in bed or

to abstain from usual activities because of illness; employed patients with major depression were 3.2 times more likely than asymptomatic individuals to miss work days because of their depression [159]. Similar patterns of impact on productivity might be expected in endometriosis but few studies to date have attempted to quantify the burden of endometriosis on dimensions in the socioeconomic sphere. The studies that have explored this burden have been conducted in limited populations and have only examined a narrow set of work productivity dimensions, principally absenteeism. There is therefore a great need for studies exploring absenteeism, lost on-the-job effectiveness and non-work activity-related productivity.

2 Overview and aims of thesis

The principal aim of this study is to describe and quantify the impact of endometriosis on HRQoL and work productivity in a sample of prospectively recruited women undergoing laparoscopy either for symptoms suggestive of endometriosis or for sterilisation. The foregoing review of the literature highlights the diverse putative risk factors for endometriosis as well as the inconsistencies around many of those associations. These arise from diverse factors such as limitations in study design, inadequate definitions of exposure windows, limitations in the selection of cases and controls, differences in study populations, lack of generalisability of findings and inadequate sample sizes. Although this study does not identify the risk factors that predict endometriosis risk, it explores the cross-sectional associations of key putative risk factors with endometriosis, with a view to controlling for these characteristics in multivariate analyses of the impact of endometriosis on HRQoL and work productivity. In addition, although there is evidence that endometriosis impairs HRQoL, a number of important questions regarding the impact of the disease on women's lives remain unanswered: for instance, to what extent do demographic, life-style, and health-care seeking factors influence HRQoL, and are patterns generalisable across different countries. Accordingly, the research presented in this thesis addresses two main questions:

(1) Which sociodemographic, lifestyle, and reproductive factors are associated with endometriosis diagnosis in a sample of prospectively recruited women undergoing laparoscopy for symptoms or for sterilisation?

(2) What is the nature and magnitude of the HRQoL and work productivity impact, if any, of endometriosis?

The relevance and novelty of the GSWH lies in the fact that it: (1) recruits a relatively large sample of women prospectively from diverse national and ethnic backgrounds in one methodologically robust study; (2) generates robust and novel data on the HRQoL and work productivity impact of endometriosis, and (3) informs policy-makers within the European Union and worldwide of the importance of endometriosis as a public health condition.

3 Ethical approval

Ethical approval for the study at each of the 16 centres was obtained from the relevant local ethics committee in those centres. In Oxford, ethics approval was obtained from the Mid and South Buckinghamshire Research Ethics Committee on 11th April 2008 (REC reference number 08/H0607/19). Shortly before the pilot study in Oxford, a minor amendment to the local protocol for the Oxford centre was made. Instead of the clinician or research nurse inviting women to participate in the study at clinic visits, the research nurse would identify eligible patients from the department's operative lists and case notes after the consultations during which laparoscopy was scheduled, and approach them with a letter of invitation to the study. A notice of this amendment was sent to the Ethics Committee and approval was granted in September 2008.

CHAPTER 2

STUDY METHODS

4 Study design

Over an 18 month period, a cohort of pre-menopausal women aged 18-45 years, attending gynaecology clinics for their first diagnostic laparoscopy or for laparoscopy for sterilisation were prospectively enrolled into the GSWH. Exposure information was collected via a purpose-designed questionnaire (described in a later section) prior to surgery. Women less than 18 or older than 45, and post-menopausal women were excluded. To reduce the potential bias from differential recall, women who had been diagnosed previously with endometriosis or who were currently being treated medically for endometriosis were also excluded.

Descriptive analysis of the study population addresses the cumulative diagnostic incidence of endometriosis, the prevalence of individual symptoms and symptom groups (e.g. pelvic pain with subfertility) and the distribution of specific sociodemographic and clinical variables in the study population.

In case-control analyses, cases comprised women diagnosed with endometriosis (including both symptomatic women and those attending for sterilisation) and controls were women in whom no endometriosis was found at laparoscopy, who were either symptomatic or underwent laparoscopy for sterilisation. In accordance with ESHRE guidelines [1], cases were defined by the presence of visible endometriotic lesions at the time of laparoscopy (no histological confirmation was required). All subjects who were included in the control group had no surgical evidence of endometriosis. The case-control analyses:

- examined the association of endometriosis with specific characteristics;
- compared HRQoL across disease outcome categories (i.e. cases vs. symptomatic and sterilisation controls);

- compared work productivity loss across disease outcome categories (i.e. cases vs. symptomatic controls).

More specifically, the following groups of putative risk-factors were evaluated for their association with endometriosis in the study population: (1) socio-demographic characteristics, including age, ethnic origin, and education; (2) reproductive health factors, including menstrual cycle (age at menarche, length of cycle and duration of flow) and pregnancy-related (parity) characteristics; (3) contraception; (4) lifestyle factors, including smoking and physical activity, and (5) personal characteristics, including hair colour and BMI.

4.1 Rationale of study design

The design of GSWH had two major characteristics that are critical to evaluating the impact of endometriosis: (a) all symptomatic women in the study population were at risk of endometriosis, and (b) all women underwent laparoscopy.

There are three key methodological issues that shape study design in the epidemiological investigation of endometriosis. These are: (1) the definition of endometriosis and how this definition is operationalised in study design; (2) the strategy for control selection, and (3) the characteristics of cases recruited into a study. These issues were carefully considered in designing the GSWH.

Endometriosis is defined as the presence within the pelvic cavity of functional endometrial tissue (glands and stroma) outside of the uterus. This definition infers that endometriosis is only diagnosed when endometriotic deposits are visualised during pelvic surgery. This definition and its implication for the diagnostic process present three important challenges that are worth highlighting in setting out the rationale for the design of GSWH. First, strictly according to the

definition, it is possible that asymptomatic women, undergoing laparoscopy for other reasons (e.g. sterilisation) and in whom endometriotic lesions are visualised, would be included as cases. However, from the public health standpoint, one would be interested in disease that produces symptoms and consequently affects the lives of women. Related to this, it has been suggested that the definition of endometriosis be based not just on visual identification of lesions but on the requirements of cellular activity in the lesions and affection of normal physiology as well [30]. These features may be expressed by ovarian endometriomas and deep lesions - forms of endometriosis which may represent different underlying aetiopathogenesis. Analysis of data based on the different subtypes of endometriosis is therefore advisable. A second challenge posed by the definition and its implication for the diagnostic process relates to selection bias. Depending on the health system, individual factors and access to care factors, the profile of women undergoing laparoscopy may be different from that of the general population of women with endometriosis. Furthermore, women who undergo laparoscopy may represent those with more severe disease, whose symptoms were not responsive to routine medications such as painkillers, although this possibility is not supported by studies where cases have been stratified by symptom severity. A third challenge presented by the definition is that selecting subfertile women going through surgical assessment based on the symptom of subfertility may under-sample those with pelvic pain or other symptoms who would not have come to surgical assessment if they had not attempted to become pregnant.

Bearing these important issues in mind in designing the GSWH, we enrolled both women with symptoms for which endometriosis might be a cause and those without symptoms attending for sterilisation. These groups were analysed together, and then separately, in order to preserve clarity in the nature of the public health burden presented by symptomatic disease. Furthermore, the design of GSWH allowed collection of surgical information for staging of lesions and identification of endometriomas and deep endometriotic nodules. This allowed analyses, where

needed, to be restricted to cases with severe disease, which is thought by some authors to represent genuine 'endometriotic disease'. In addition, since GSWH recruited a mixture of fertile and subfertile women, this allowed analyses to take into consideration subfertility status where needed [15].

A longitudinal cohort design is ideal for most epidemiological investigations of endometriosis, but a case-control study is an efficient way to obtain a reliable estimate of rate ratio if case and control selection is valid. Owing to the need for surgery to diagnose endometriosis, most investigators employ controls from women undergoing other pelvic surgery such as hysterectomy, sterilisation or laparoscopy for reasons unrelated to endometriosis. Such controls are a highly selected population, however, and often do not represent the exposure distributions of the populations from which the cases are drawn. Furthermore, an element of detection bias may complicate such control selection as the thoroughness of pelvic examination may differ with a symptomatic person undergoing investigative laparoscopy and an asymptomatic person undergoing laparoscopy for sterilisation [66]. For these reasons, community-based controls are advocated but these may not be ideal if there is significant undiagnosed endometriosis amongst the controls, a scenario which some authors consider unlikely at least for more severe stages of disease [14].

The design of GSWH duly took these issues into account. Controls were women (1) who underwent laparoscopic examination but were found to be free of endometriosis, and (2) who underwent laparoscopy for sterilisation and were found to be free of endometriosis. The latter group of controls could be expected to represent exposure distributions of the populations from which the cases were drawn. As the GSWH allowed more than one control group to be analysed, this would dilute the potential bias of including a specific control group that is not representative of the source population.

In GSWH, incident (i.e. newly diagnosed) rather than prevalent endometriosis cases were recruited. Well-designed case-control studies of non-genetic risk-factors for endometriosis should enrol incident cases, allowing for the collection of unbiased exposure information pre-dating disease onset and an accurate approximation of relative risk by the odds ratio [14], although the reported high (>10%) prevalence of endometriosis in symptomatic women means the odds ratios reported in this study are unlikely to approximate the relative risk [160]. If prevalent rather than incident cases were studied, any association found between the outcome (endometriosis) and the exposure would strictly not refer to the exposure itself but to its interaction with on-going disease or disease duration. However, in the case of endometriosis, the interval between risk-factor exposure and onset of disease is largely unknown. Consequently, recruiting incident cases may not necessarily guarantee exclusion of the influence of disease duration on both exposure and the reporting of exposure, especially in the context of long-standing symptoms [65].

5 Study population

This study differentiates three population types: the target population, the source population, and the sample or study population. The target population is the general population of pre-menopausal women around the world, aged 18-45, to whom the findings would be generalised or applied. The source population represents the specific population of all women attending for care at the gynaecological facilities in each of the participating centres. For example, the source population in Oxford is the population of women attending gynaecology clinics at the University of Oxford Nuffield Department of Obstetrics and Gynaecology (NDOG) either because of symptoms or for sterilisation. The source population is the population to which the inclusion and exclusion criteria were applied to determine the eligible population for invitation to participate in the study. The sample or study population comprises all eligible women who consented to take part in the study upon invitation, having read the patient information leaflet and given proper

consent. Ideally, the source population must be representative of the exposure distribution in the target population and, similarly, the study population must be representative of the exposure distribution in the source population. If selection bias was avoided, the former would be assured; if the response rate was optimal and balanced across study population groups, the latter would be assured.

5.1 Description of study population

A cohort of 1,418 consecutively enrolled women undergoing laparoscopy for the first time took part in the study at 16 hospitals in 10 countries across five continents (Africa, Asia, Europe, South America and USA) between June 2008 and January 2010.

5.2 Eligibility criteria

This prospective study with analytical cross-sectional and case-control evaluations is based on baseline (pre-surgical) data collected on women participating in GWSH. Participants were recruited between June 2008 and January 2010 among women attending gynaecology clinics and who were scheduled for a diagnostic laparoscopy or laparoscopy for sterilisation in the 16 hospitals in five continents. All women met the following eligibility criteria for inclusion in the study: aged 18-45, pre-menopausal, and no prior surgical diagnosis of endometriosis. Women who satisfied the eligibility criteria and agreed to participate gave written or online informed consent as appropriate before the laparoscopy.

5.3 Rationale for choice of study population

As the study sought, amongst other things, to examine the relationship of certain menstrual and reproductive characteristics to endometriosis, women younger than 18 or older than 45, or who were post-menopausal were excluded. Women were also excluded if they had had endometriosis diagnosed in the past or were receiving treatment for endometriosis. This way, incident rather

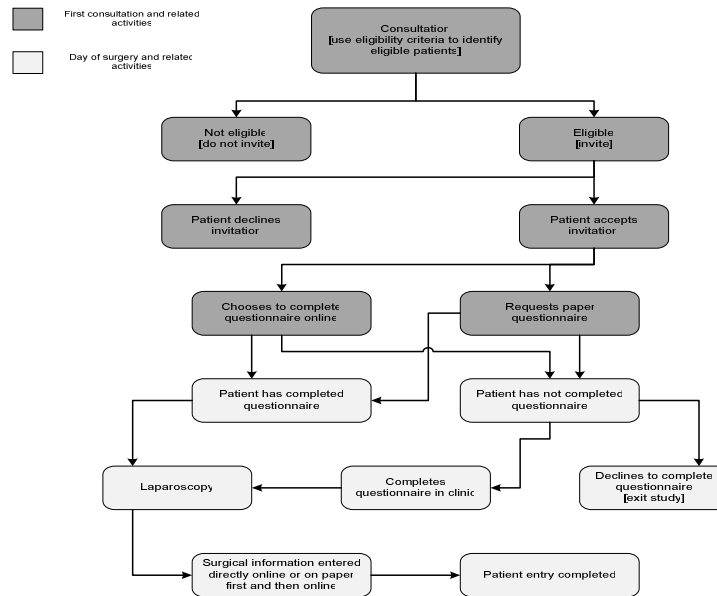
than prevalent cases of endometriosis were recruited (the caveat regarding this issue has been highlighted earlier). This would avert the influence of recall bias and eliminate the potential of studying the interaction of exposure with duration of illness (rather than exposure strictly).

Any findings on the risk factors for and the impact on HRQoL of endometriosis should be generalisable to the general population of premenopausal women world-wide. Thus, the study design needed to ensure that the source population was representative of this general population and that all premenopausal women in the general population had similar chances of being part of the source population. However, it is highly unlikely that this could have been achieved since most participating hospitals mainly serve populations within their geographical reach. Nevertheless, none of the participating centres was known to attract patients of highly different profiles from the general populations of premenopausal women in those countries.

6 Recruitment

Recruitment into the study (Figure 1) took place between June 2008 and January 2010 in 16 collaborating centres across Africa, Asia, Europe, South America and the USA (Table 1).

Figure 1 - Recruitment flowchart for the Global Study of Women's Health (GSWH)



Women who met the inclusion criteria were invited by the collaborating clinician or research nurse at each centre to participate in the study. Those women who agreed to participate were asked to complete an online questionnaire that sought retrospective information on symptoms, use of health care resources, quality of life, medical and family history, and life-style factors. Questionnaires had to be completed before surgery. Women who wished to complete a paper questionnaire were able to do so, and were asked to bring the completed questionnaire to the hospital when they attended for their surgery. The paper questionnaire was subsequently entered into the online system by the research nurse. If the patient had not completed the questionnaire by the time she attended for surgery, she was given the opportunity to do so in hospital before the scheduled surgery. Women were not asked to complete the questionnaire after they had had surgery and their diagnosis was known. Following surgery, a surgical questionnaire was completed online by the research nurse using the surgical notes.

Table 1 - Collaborating centres

Country: Centre	Recruitment start date
Argentina: CGR, Buenos Aires	12 Jul 2009
Belgium: University of Leuven	01 Dec 2008
Brazil: Centro de Reprodução Humana de Campinas	25 Jan 2009
Brazil: Clinica Medicina da Mulher, Sao Paulo	25 Jan 2009
China: Guangdong Provincial Hospital	20 Oct 2008
China: Shanghai Obstetrics and Gynaecology Hospital	03 May 2009
Ireland: National Maternity Hospital, Dublin	30 Apr 2009
Italy: Universita' Cattolica del Sacro Cuore, Rome	20 Oct 2008
Italy: University of Siena	12 Jan 2009
Nigeria: University of Ibadan	13 Oct 2008
Spain: University of Barcelona	06 Oct 2008
UK: University of Oxford	29 Sept 2008
USA: Univ. California San Francisco & Fertility Physicians Northern California, Palo Alto	20 Oct 2008
USA: Brigham & Women's Hospital, Boston	28 Apr 2009
USA: National Institutes of Health, Washington	03 Feb 2009

6.1 Sample size estimation

The calculation of power and required sample sizes to detect risk-factors for disease involved assumptions on (a) the likely prevalence rate of exposure variables of interest in controls; (b) the effect sizes to be detected; (c) the significance level with which the effect size is to be detected, and (d) minimum and maximum sample sizes likely to be achieved in the study.

As an illustration, Table 2 shows sample sizes required to detect associations between endometriosis and a number of putative risk factors with a power of 80% and at a significance level of 5%. For GSWH, the target sample size ~1,500 will enable the detection of a risk-factor with a prevalence of ~0.75 among controls, with relative risk down to 1.6 (e.g. oral contraceptive use).

Table 2 - Sample size calculation for GSWH based on risk estimates and prevalence in controls

Risk/Predictive factor	Relative risk of endometriosis *	Prevalence in controls	Required sample size per group	Total required sample size
Smoking	0.5 [79]	0.24	223	446
Long duration of menstrual flow	2.5 [80]	0.06	257	514
Short menstrual cycle length	2.1 [79]	0.06	376	752
History of oral contraception use	1.6 [100]	0.75	434	868

* References in parentheses

To calculate required sample sizes for the SF36v2 calculations, a standardised effect size of 0.2 was first derived based on intention to detect a 2-point mean difference in SF36v2 summary score between cases and controls and a standard deviation of 10. Using this standardised effect size with a two-sided 5% significance level and 80% power as in the equation below [161] gives the estimated required number of subjects per group as 394 (788 in total).

$$\frac{2[Z_{1-\alpha/2} + Z_{1-\beta}]^2}{\text{standardised effect size}}$$

7 Data collection methods

7.1 Design of patient questionnaire

To collect comprehensive exposure information, a sixty-seven item quantitative questionnaire was developed for GSWH. The questionnaire (appendix 3 and copy available at: <http://www.endometriosisfoundation.org/GSWH-questionnaire-English.pdf>) incorporates standardised questions and instruments previously validated in either women with pelvic pain or other clinical symptom groups. These instruments included:

- The Short Form 36 version 2 (SF36v2) to assess HRQoL [162]
- The Work Productivity and Activity Impairment (WPAI) questionnaire to assess the impact of symptoms on work productivity and general non-work-related activity [163]
- The IBS Rome III questionnaire to identify women with pelvic pain symptoms due to Irritable Bowel Syndrome [164]
- Standardised pelvic pain symptom assessment used in earlier research studies in Oxford [165,166]

The SF36 is probably the most widely evaluated generic patient-assessed health outcome measure [167]. It is a multi-purpose, generic health survey that includes one unscaled transition question and 35 questions on quality of life. It yields an 8-scale profile of functional health and well-being scores that fall into two psychometrically-based summary measures – the Physical Component Summary (PCS) and the Mental Component Summary (MCS). Scales included in the PCS include Physical Functioning, Role-Physical, Bodily Pain, and General Health; scales included in the MCS are Vitality, Social Functioning, Role-Emotional, and Mental Health. The SF36 has proved useful in comparing the relative burden of diseases in populations and assessing the relative impact of treatment interventions across time points. In 1996, improvements were introduced to the original version to: 1) correct for specific deficiencies around readability; 2) improve comparability with translations and cultural adaptations used widely, and 3) reduce the likelihood of missing responses. More specifically, minor modifications to the wording of six items on the sf36 were made to improve its acceptability in a British context. This yielded version 2 of the SF36, which is a direct descendant of the SF36 Developmental Form and the SF36 Mark 1 Standard Form. The SF36 version 2 comprised the first 11 questions in the questionnaire used in GSWH. Analysis of the SF36v2 in this study involved comparisons with population norms generated in a UK population study. This allowed comparison of the general health status of women in the study population with a reference average and also allowed comparisons of general health status and quality of life to be made by symptom and disease groups.

In addition to quantifying absenteeism from work due to illness or symptoms, the WPAI questionnaire measures the impact of illness or its symptoms on productivity while at work (presenteeism) and while doing non-work related activity. There are generally two versions of the WPAI available for use – the Specific Health Problem (SHP) version and the General Health (GH) version. While it is, in theory, possible to use the SHP version for any condition, its use is best

reserved for limited or local disease conditions, e.g., chronic hand dermatitis. More systemic diseases such as endometriosis are best assessed with the GH version, which was employed in this study. The six questions of the WPAI:GH questionnaire refer to work and activity in the previous seven days. Although women were asked to respond with respect to the last four weeks, analysis was based on the previous seven days – the rationale for the recall period employed in this study is further developed in chapter 8 (Endometriosis and work productivity impairment).

Functional gastrointestinal disorders (FGIDs) is an umbrella term for a broad group of gastrointestinal disorders in which symptoms cannot be explained by any structural or tissue abnormality. They include Irritable Bowel Syndrome (IBS), functional heartburn and functional faecal incontinence. The IBS Rome III criteria are included in a symptom-based system developed to classify these disorders. The diagnosis of IBS is made based on a person having had recurrent abdominal pain or discomfort for at least 3 days of each month in the last three months, associated with two or more of the following: improvement of pain or discomfort with defaecation; onset associated with change in frequency of stool, and onset associated with change in appearance of stool. The Rome IBS III questionnaire was incorporated to identify women with surgically diagnosed endometriosis who also met the symptom criteria for IBS.

Questionnaire items assessing educational background and ethnicity included comprehensive categories relevant to an international cohort of patients. The questionnaire was translated by native speakers into Mandarin, Dutch, French, German, Italian, Portuguese and Spanish, and translations were verified independently by clinical collaborators in the respective centres. For the SF36 version 2, validated language versions were used.

7.2 Design of surgical questionnaire

Collaborating gynaecologists recorded their findings using a standardised surgical sheet (appendix 4 and copy available at: <http://www.endometriosisfoundation.org/GSWH-surgical-sheet.pdf>). All surgeons involved in the GSWH in all participating hospitals were experienced in the diagnosis and surgical management of endometriosis. They were cognisant of all the different appearances of endometriotic lesions. The stage of the disease was defined according to the revised classification system of the American Society for Reproductive Medicine (rASRM) [33].

7.3 Validation of questionnaires

As highlighted above, only standardised instruments were incorporated into the GSWH questionnaire. The SF36v2 questionnaire has been assessed for internal consistency reliability of its dimensions as well as its construct validity in a large normative community sample in the UK [168]. The study reported a high internal consistency (items on each scale correlated well) and good construct validity for the SF36v2 survey. The study also generated UK population norms for the SF36v2 survey as well as algorithms for deriving the Physical and Mental Component Summaries.

The WPAI questionnaire has been validated in a variety of conditions. The discriminative validity and reproducibility of both versions of the questionnaire have been established but evaluative validity and responsiveness to clinically meaningful change for the SHP version has only been established in a limited set of conditions including inflammatory bowel syndrome, allergies, chronic hand dermatitis, Crohn's disease and gastroesophageal reflux disease [169,170]. Although the recall period in all WPAI validation studies is 7 days, a 4-week recall period was employed in this study as it was felt that the information would be better captured if women were asked to consider the previous 4 weeks.

The IBS Rome III questionnaire has been validated in two different survey studies commissioned by the Rome Foundation [171-173]. The first study identified the optimal scale for use in the Rome III questionnaire and the second assessed the reliability, sensitivity, and specificity of the questionnaire. Authors of the latter study concluded that the Rome III questionnaire was a valid and reliable instrument for provisionally diagnosing all FGIDs except unspecified functional bowel disorder.

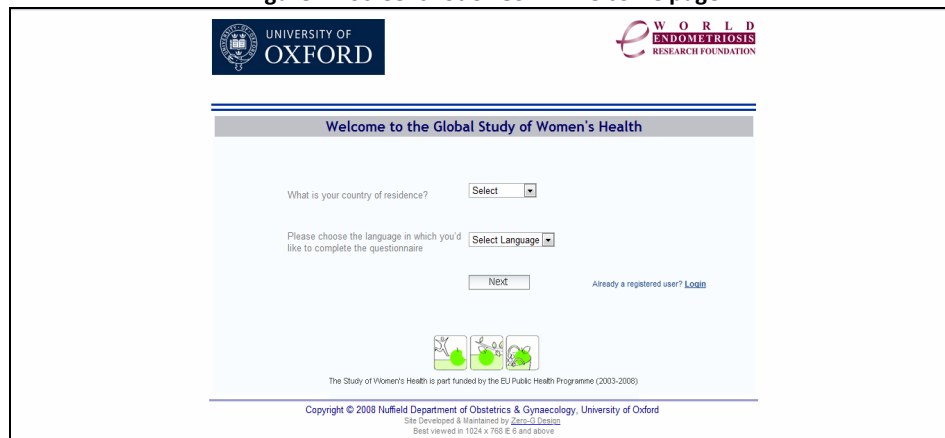
7.4 Online programming of questionnaires and database design

To ensure secure online data-collection, a three-tier internet-based network system was designed comprising (a) remote web browsers running on client computers; (b) a Web Enterprise application server (Microsoft.net), and (c) a secure database server (SQL server 2000) based at the Oxford University Computing Service. Key elements of online data collection are data security and confidentiality (information disclosed only to authorised users), integrity (information entered only by authorised users) and availability (information accessed only by authorised users) [174]. These were given careful consideration in the design of the online questionnaire and database. Data security and confidentiality were ensured through encrypted transmissions and firewall protection. Data integrity was ensured by respondents registering a username and password to access the questionnaire, allowing them to return to it as often as they wished until completion. Data availability was regulated by password protected access of centre-specific patient information (user ID, name, date of birth and status of questionnaires) only to local research assistants, after informed consent had been obtained. I had access to encrypted questionnaire information once completed, but no access to named patient information. Informed consent was provided electronically.

7.5 Administration of exposure questionnaire

The research assistant at each centre invited patients to participate and directed patients online if they chose to complete an online version of the questionnaire, or issued them a paper version if they preferred to complete the questionnaire that way. Research assistants were requested to keep a record of patients invited, for the purpose of calculating recruitment statistics. To complete the online questionnaire, patients used their web browsers to access the URL <http://womenstudy.obs-gyn.ox.ac.uk>. On the welcome page, they selected their country of residence and language of choice - the online tool was designed in such a way that a patient could select any of the available languages irrespective of their country of residence (Figure 2). The next page was an online consent page where a patient provided informed consent electronically to participate in GSWH. On the next page, they registered their details – name, date of birth, clinic attended. They then selected a password and answered a security question. Having registered, patients were directed onto the questionnaire itself.

Figure 2 - Screenshot of GSWH welcome page



The screenshot displays the 'Welcome to the Global Study of Women's Health' page. At the top, there are logos for the University of Oxford and the World Endometriosis Research Foundation. The main heading is 'Welcome to the Global Study of Women's Health'. Below this, there are two dropdown menus: 'What is your country of residence?' and 'Please choose the language in which you'd like to complete the questionnaire'. A 'Next' button is positioned below the language selection. To the right of the 'Next' button is a link that says 'Already a registered user? Login'. At the bottom, there is a small graphic of three green circles and text stating 'The Study of Women's Health is part funded by the EU Public Health Programme (2003-2008)'. The footer contains copyright information: 'Copyright © 2008 Nuffield Department of Obstetrics & Gynaecology, University of Oxford', 'Site Developed & Maintained by Zaira El Masri', and 'Best viewed in 1024 x 768 E & above'.

If a patient completed a paper version of the questionnaire, they could either post it or hand it to the research assistant when they came for their surgery. The research assistant then went

through similar procedures as above but used the research assistant portal to access the online questionnaire to enter the patient's responses.

Once entered, online questionnaire responses were neither accessible to, nor alterable by, patients or research staff.

7.6 Collation of responses

I accessed all the completed questionnaires in real time for download from the database as coded Excel spreadsheets. Completed exposure questionnaires and surgical sheets were periodically downloaded for data cleaning and routine checks of accuracy. Data collection ended in December 2009 and final data collation was carried out in early January 2010.

8 Surgical procedures

Participating clinicians at the collaborating centres were highly trained and experienced laparoscopic surgeons. They inspected the pelvis during laparoscopy and staged any endometriotic lesions found using the revised American Society of Reproductive Medicine (rASRM) classification: stage I (minimal), stage II (mild), stage III (moderate) or stage IV (severe) [33]. They were requested to complete on paper a standardised surgical form immediately after the operation. This included information on the presence and position of endometriomas or endometriotic nodules during pre-operative ultrasound scans, as well as staging of any endometriotic lesions found. If the surgeon did not complete the surgical form, the research assistant did so using the operation notes.

Figure 3 - Screenshot of research assistant administration page

UNIVERSITY OF OXFORD

WORLD ENDOMETRIOSIS RESEARCH FOUNDATION

Impact of Endometriosis Survey

ADMINISTRATOR VIEW PANEL FOR NURSE - OXFORD

HOME QUESTIONNAIRE TRACK CHANGE PASSWORD LOGOUT

ENE QUESTIONNAIRE

Select Year

Total No. of Patient Registrations : 227

Total No. of Completed Patient Questionnaires : 225

Total No. of Completed Surgical Questionnaires : 216

Firstname

Surname

Search

	Country	Patient Registration	Name	Date of Birth	Completed Patient Questionnaire	Completed Surgical Questionnaire
☐	UK	UK - Oxfr - 10031		14/01/77	Completed	Completed
☐	UK	UK - Oxfr - 10035		23/10/78	Completed	Completed
☐	UK	UK - Oxfr - 10036		20/12/60	Completed	Completed
☐	UK	UK - Oxfr - 10038		17/04/79	Completed	Completed
☐	UK	UK - Oxfr - 10042		03/06/75	Completed	Completed

The surgical form was available as an online version linked to the exposure questionnaire. To complete the data entry for each participant, the relevant surgical information from the earlier-completed paper version was entered online. To do this, the research assistant logged on to the research assistant administration page on <http://womenstudy.obs-gyn.ox.ac.uk/nurselogin.aspx> using the relevant clinic code, username and password. Using a questionnaire tracking function on the page, they accessed and completed the surgical form for each patient using the active link on their unique patient registration number. For each unique registration number, there was a corresponding patient name, date of birth and a way of noting whether the patient questionnaire and surgical form had been completed (Figure 3). Patients who had incomplete patient questionnaires or who had complete patient and surgical forms did not have active unique registration numbers.

Although women completed the online or paper version exposure questionnaire before their surgery, surgeons had no access to the information provided by the patients in the questionnaire.

CHAPTER 3

GSWH PILOT STUDY

9 Background and aims

A pilot or feasibility study is one designed on a smaller scale to test logistics and gather information prior to a larger study, in order to improve the latter's quality and efficiency [175]. The GSWH pilot study was carried out between 1st July and 8th August 2008, recruiting eligible women from the Nuffield Department of Obstetrics and Gynaecology (NDOG) clinics at the Women's Centre, John Radcliffe Hospital, in Oxford, to assess the feasibility of the agreed GSWH protocol. The pilot study was conducted principally to test the feasibility of the study protocol. It was also used to test the administration of the patient questionnaire and surgical form, specifically assessing comprehensibility, appropriateness and clearness of definitions in the questions. It also allowed initial assessment of consistency in the presentation and clarity in the understanding of questions asked. The consent forms and patient information leaflets were also assessed for similar characteristics in the pilot study. Understanding the rate of uptake of invitation in the pilot study provided information that guided planning for the length of recruitment. Reasons for declining invitation informed approaches to enhancing uptake rate in the main study.

The following sections summarise the method and key outcomes of the pilot study.

10 Methods

In the pilot study, 18-45 year old women were recruited who were scheduled for laparoscopy in Oxford either to investigate symptoms for which endometriosis could be a cause or for sterilisation. Eligible women were identified from the NDOG clinic waiting lists by the research assistant on a weekly basis and sent invitation letters to participate. This recruitment method had previously been shown to be highly successful in other studies conducted at NDOG, providing complete ascertainment of eligible women and maximum recruitment rates. Consenting women

had the option of either completing the online questionnaire or requesting a paper copy from the research assistant.

On every day of scheduled surgery, the research assistant checked the nurse administration database online to establish whether the woman about to undergo surgery had been invited to take part in the study and if she had completed an online questionnaire. If she had done so, her surgical sheet was completed first on paper by the surgeon and then online either by the surgeon or research assistant after the operation. If she consented to taking part but had not completed an online questionnaire, the research assistant invited her to complete the paper version before her surgery. After surgery, women were not invited to complete the questionnaire if they had not done so before the operation.

An episode of invitation to participate in the study was considered closed only when an eligible woman had undergone surgery without completing a questionnaire either online or on paper. Therefore, the denominator for response rates is the number of women who were sent invitation letters and had undergone their laparoscopy over the period of the pilot study.

10.1 Data Analysis

Basic data analysis was carried out after six weeks of recruitment. Response rate was calculated as the proportion of eligible invited women who agreed to participate. Reasons for non-participation were explored and documented by the research assistant via telephone conversations with the invitees who declined participation. The proportions of completed questionnaires entered either directly online or initially on paper were assessed to give an indication of how participants used either medium of response/participation.

The demographic and other characteristics of the pilot study population were described – principally age, marital status, education, ethnicity, reasons for investigation, age at menarche, duration of periods in last three months, cycle length and BMI. Although limited with respect to how much inference could be made from the results owing to the small sample size, comparisons in some of the above parameters were made between women with and without endometriosis.

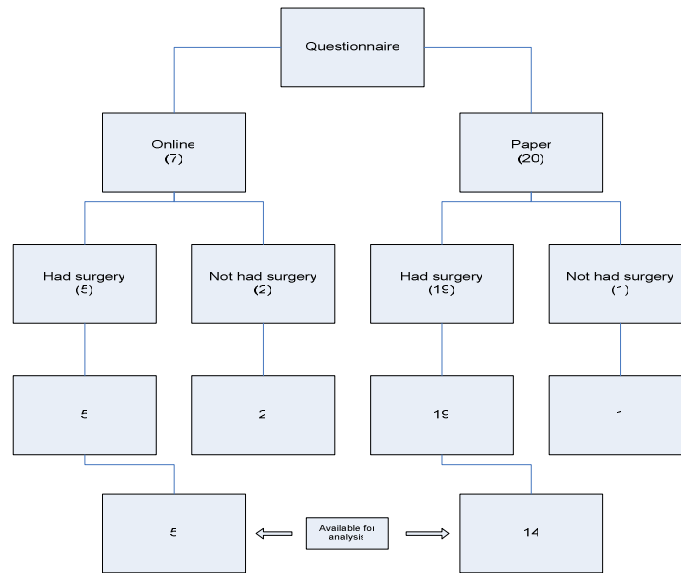
The SF36v2 questionnaire was also analysed. For the statistical analysis, the data were expressed as medians, as well as 25th and 75th percentiles (analyses of SF36v2 data in the main study is based on means and SD but the pilot data is analysed based on medians and interquartile ranges due to a relatively small sample size). Preliminary, basic descriptive statistics suggested that the distributions for 'health perception' and 'vitality' were normal in this population but the distributions of other scales were not normal. However, statistical analyses did not make any assumptions about normality for any of the scales owing to the very small sample size (n=19). The Mann-Whitney U test was used to assess the difference between scores of women with and without endometriosis on each of the scales.

11 Results

11.1 Response rates

Over the period of the pilot study, 32 eligible women who were invited to participate underwent laparoscopy. Of these women, 27 took part in the study, a response rate of 84.4%. Of the five women who did not take part, one did not speak English; the other four gave no specific reasons for their non-participation.

Figure 4 - Flow chart showing response to invitation in pilot study



As shown in Figure 4, only 7 of the 27 (26%) responses were online, as most women chose to complete the paper version of the questionnaire. Only records for which there were complete patient questionnaires and surgical forms were available for analysis. All five online responses eligible for analysis were included but only 14 of the 19 eligible paper responses were available.

Of the five questionnaires that were not available for analysis, two were complete paper questionnaires with no accompanying surgical forms; three were surgical forms unaccompanied by questionnaires. The latter were most likely to be the records of women who began completing paper questionnaires on the morning of their surgery but did not finish doing so before they went in for surgery.

Table 3 - Demographic characteristics of the pilot study population

Variable	n	%	Variable	n	%
Age			Reason for investigation		
25-29	2	10.5	Pelvic pain	6	31.6
30-34	11	57.9	Subfertility	11	57.9
35-39	4	21.1	Age at menarche		
40-44	0	0.0	<12	0	0.0
45-49	2	10.5	12 to 13	10	52.6
Ethnicity			14 to 15	6	31.6
Asian/oriental	1	5.3	≥16	3	15.8
Black African/American/Caribbean	1	5.3	Duration of periods in past 3		
White	15	78.9	≤2	2	11.8
Mixed race	1	5.3	3 to 5	9	52.9
Other	1	5.3	>5	3	17.6
Education			Too irregular to say	3	17.6
Primary	1	5.6	Cycle length		
Lower secondary	1	5.6	22-24 days	2	16.7
Upper secondary	0	0.0	25-28 days	5	41.7
Post-secondary not University	4	22.2	29-32 days	3	25.0
University	9	50.0	33 – 35 days	2	16.7
Postgraduate	3	16.7	BMI		
Marital status			<20	6	31.6
Single and living with partner	3	15.8	20-25	5	26.3
Married	11	57.9	26-30	6	31.6
Divorced/separated	5	26.3	>30	2	10.5

11.2 Characteristics of study sample

As shown in Table 3, most of the women enrolled in the pilot study were 30-34 year old, married, white women, the majority of whom were university educated. The commonest reasons for laparoscopy were to investigate pelvic pain and subfertility (nearly 60% of the women were subfertile). Out of the 19 women, 9 (47%) were diagnosed with endometriosis at surgery.

Although the small sample size did not allow meaningful statistical analyses, the results were nevertheless interesting. Women who underwent laparoscopy because of pelvic pain had 3.2 greater unadjusted odds of being diagnosed with endometriosis than those without pelvic pain (OR=3.2; 95% CI: 0.42 – 24.4). Women who underwent laparoscopy on account of subfertility had 1.3 greater unadjusted odds of being diagnosed with endometriosis than those who did not report subfertility (OR=1.3; 95% CI: 0.20 – 8.71).

11.3 Characteristics associated with endometriosis

The sample size was deemed too small to allow in-depth analysis of risk factors for endometriosis.

Table 4 - Median scores and 25% and 75% values for SF36v2 dimensions

SF36v2 dimension	Median	Variation (percentile 25-75)	
Physical function	90.0	90	90
Role limitation (physical)	100.0	84	100
Body Pain	90.0	78	100
Health perception	70.0	55	85
Vitality	56.3	50	63
Social functioning	100.0	69	100
Role limitation (mental)	100.0	79	100
Mental Health	75.0	70	83

11.4 Health-related Quality of Life impact of endometriosis

As shown in Table 4, compared to other dimensions of the sf36 survey of HRQoL, quality of life in general health perception and vitality were significantly impaired in the study population. Not surprisingly, owing to the very small sample size, there were no significant differences in dimension scores between women with endometriosis and those without (Table 5).

Table 5 - Comparison of SF36v2 HRQoL dimensions by endometriosis status

SF36 Dimension	n	Minimum	Maximum	25th	Percentile Median	75th	P value
Physical function							0.52
Endometriosis	9	15.0	95.0	90.0	90.0	90.0	
No endometriosis	10	90.0	90.0	90.0	90.0	90.0	
Role limitation (physical)							0.29
Endometriosis	9	68.8	100.0	93.8	100.0	100.0	
No endometriosis	10	62.5	100.0	82.8	90.6	100.0	
Body Pain							0.76
Endometriosis	9	35.0	100.0	77.5	80.0	100.0	
No endometriosis	10	45.0	100.0	70.0	95.0	100.0	
Health perception							0.14
Endometriosis	9	50.0	85.0	55.0	70.0	75.0	
No endometriosis	10	25.0	100.0	58.8	82.5	90.0	
Vitality							1
Endometriosis	9	37.5	68.8	50.0	56.3	62.5	
No endometriosis	10	37.5	68.8	50.0	56.3	62.5	
Social functioning							0.54
Endometriosis	9	50.0	100.0	75.0	100.0	100.0	
No endometriosis	10	37.5	100.0	62.5	93.8	100.0	
Role limitation (mental)							0.09
Endometriosis	9	75.0	100.0	100.0	100.0	100.0	
No endometriosis	10	41.7	100.0	68.8	91.7	100.0	
Mental Health							0.38
Endometriosis	9	70.0	85.0	70.0	75.0	80.0	
No endometriosis	10	30.0	90.0	51.3	70.0	83.8	

12 Discussion

The recruitment figures provided a first indication of recruitment number feasibility for the main study. Based on the power calculations presented in the protocol, the minimum target was to recruit at least 300 cases and 600 controls (at an estimated 30% endometriosis prevalence rate), from 15th September 2008 to 31st January 2010 (~60 weeks), across all 16 participating centres. Assuming similar recruitment potential across the centres, a target of 1,000 women would require recruitment of $1000/16 = 62.5$ women per centre.

The pilot study was successful and showed that the target recruitment of at least 1,000 women across all centres was feasible if results from Oxford could be extrapolated to the other centres. The response rate was high, at 84.4%, and the questionnaire well received by the women. Recruitment in other centres would need to be closely monitored when the main study started, in order to ensure the recruitment targets were reached. Only a few textual changes were made to the content of the exposure questionnaire.

MAIN STUDY RESULTS

CHAPTER 4

CHARACTERISTICS OF THE STUDY POPULATION AT RECRUITMENT

13 Introduction

The aim of this chapter is to describe 1) the diagnostic incidence of endometriosis, and 2) the characteristics of the study population, identifying those characteristics that are significantly associated with the risk of being diagnosed with endometriosis in the population. The literature review in chapter 1 had highlighted characteristics putatively associated with the risk of endometriosis. As these characteristics potentially confound associations between endometriosis and key outcomes – diagnostic delay, HRQoL and work productivity - the study population at recruitment is described on the basis of these characteristics.

More specifically, the analyses in this chapter address the following specific research questions:

- What is the study population size and recruitment rate at each centre?
- What are the diagnostic incidence rates for endometriosis across the different centres (including rates for stages of endometriosis)?
- What specific sociodemographic, gynaecological, reproductive, lifestyle and personal attributes are associated with endometriosis and how are they distributed across the study population?
- How does each centre compare with the remainder of the study population in respect of these characteristics?
- How do disease outcome groups - i.e. endometriosis, symptomatic and sterilisation controls - compare in respect of these characteristics?
- What variables are potential confounders of the relationship between endometriosis and key outcomes of interest in this research (diagnostic delay, HRQoL and work productivity impairment)?

14 Methods

14.1 Diagnostic incidence and stages of endometriosis

A woman was said to have endometriosis if the surgeon, having visualised endometriotic lesions during laparoscopy, entered a diagnosis of endometriosis on her surgical records. The group of women with endometriosis includes all women in the study population with endometriosis on laparoscopy, regardless of the indication for surgery (symptoms or sterilisation). For women in whom endometriosis was diagnosed at laparoscopy, disease severity is described as “minimal-mild endometriosis” (rASRM stages I+II) or “moderate-severe endometriosis” (rASRM stages III+IV) [33].

14.2 Comparison groups

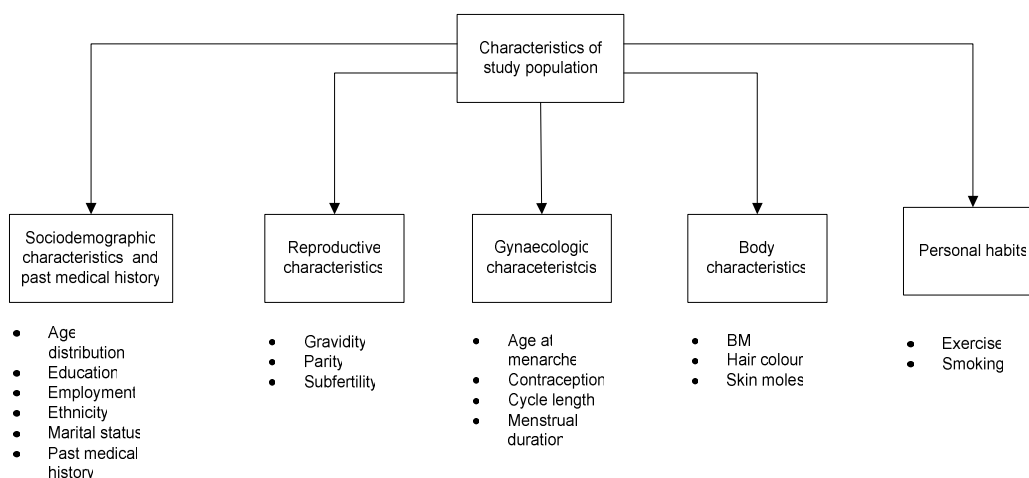
Analyses of all variables are conducted according to two main outcome groups: centre of recruitment and disease outcome groups. The variable ‘centre’ is re-categorised so that the centres at which fewer than 25 women were recruited (Buenos Aires, San Francisco, Palo Alto and Washington DC) are grouped together into an “Other” category. Disease outcome groups include: 1) women with endometriosis; 2) symptomatic controls without endometriosis; and 3) laparoscopic sterilisation controls without endometriosis.

As indicated earlier, the endometriosis group includes all women in the study population with endometriosis on laparoscopy, regardless of indication for surgery (symptoms or sterilisation); the symptomatic control group includes those without endometriosis on laparoscopy who were investigated for symptoms; the laparoscopic sterilisation group includes those without endometriosis on laparoscopy, who underwent laparoscopic sterilisation (and who may or may not have had symptoms).

14.3 Variable description

There are 5 broad groups of variables on which the characteristics of the study population at recruitment are analysed (Figure 5). These are described more fully in the following paragraphs.

Figure 5 - Characteristics on which population is described



14.3.1 Sociodemographic characteristics and past medical history

This includes a description of the rate of recruitment at participating centres and age, education, employment status, ethnicity, marital status and past medical history of women in the study population.

Age is analysed both as a continuous variable and a categorical variable with four categories (ages $18 \leq 24$, $25 \leq 31$, $32 \leq 38$ and $39 \leq 45$ years). Educational attainment is examined as a categorical variable with 6 categories: primary, lower secondary, upper secondary, post-secondary, university and post graduate levels. Further analysis of educational attainment is based on the proportion of women at each centre and in the disease outcome groups who reported achieving a post-secondary (i.e. post-secondary, university or postgraduate) qualification. Employment status is

presented as a categorical variable with 3 categories – self-employed, in paid employment and unemployed, with further analysis highlighting the reasons for not being in employment amongst women who reported that they did not work. Ethnicity data includes the categories White, Asian, Black and Others (includes ‘mixed’ race and Hispanics/Latinos). Marital status is analysed both as a categorical variable comprising 6 categories and as a binary variable of whether a woman was ‘married/co-habiting’ or not. Past medical history is analysed as a set of four binary variables which are aggregations of 30 conditions evaluated in women’s past medical histories. These are cancer, autoimmune/atopic conditions, ‘other’ and ‘any’. The specific conditions constituting these categories are specified in the footnotes on Appendix 1.

14.3.2 Reproductive characteristics

These include gravidity, parity and a history of subfertility. Gravidity and parity are assessed as continuous variables (minimum 0, maximum 6) while subfertility is a binary variable indicating whether or not a woman had ever attempted pregnancy for a period of 12 months or more without success.

14.3.3 Gynaecological characteristics

The group of gynaecologic characteristics includes age at menarche, contraception, menstrual cycle length and menstrual duration. Age at menarche and menstrual duration are analysed as continuous variables, with mean values compared across centres and disease outcome groups. Contraceptive use within the last three months was evaluated as a binary variable while menstrual cycle length had four categories - ≤ 24 , 25-32, ≥ 33 days and ‘irregular’.

14.3.4 Personal habits

This includes report of regular vigorous exercise in last three months - regular exercise means daily, often (few times a week) or regular (about once a week) exercise. It also includes smoking

habit, evaluated as the proportion of women who were current, former or never smokers. Current smokers were defined as women who reported smoking ≥ 100 cigarettes during their lifetime and who now smoke some days or every day. Former smokers were defined as women who reported having smoked ≥ 100 cigarettes during their lifetime but did not smoke at the time of the study. Never smokers were defined as persons who reported having smoked < 100 cigarettes during their lifetime [176].

14.3.5 Body characteristics

BMI is calculated as weight in kilograms divided by the square of height in meters and was classified according to the guidelines of the World Health Organisation [177]: BMI < 18.5 kg/m² is underweight, 18.5–24.9 kg/m² normal weight, 25–29.9 kg/m² overweight, and > 30 kg/m² is obesity. Obesity is further divided: class I is BMI 30–34.9 kg/m², class II 35–39.9 kg/m², and class III or extreme obesity is BMI > 40 kg/m². Hair colour is examined as a categorical variable comprising the following categories generated from the original variables in parentheses: Fair (Fair or Blonde, Light Brown), Red (Light Red or Ginger, Auburn or Dark Red), Brown (Medium Brown, Dark Brown) and Black.

14.3.6 Other key variables

Presenting complaints are characterised by the type and number of symptom groups for which women underwent laparoscopy, and severity of pelvic pain. Symptom types include: 1) pelvic pain without subfertility; 2) pelvic pain with subfertility; 3) subfertility without pelvic pain, and 4) no pelvic pain or subfertility. Since some symptoms (e.g. pelvic pain and dysmenorrhoea) are strongly correlated, principal component analysis is used to identify underlying patterns. Pelvic pain severity was defined as the mean numerical rating score (on a 1-10 scale) assigned by the women.

14.4 Statistical Methods

14.4.1 Descriptive statistics

Firstly, for each characteristic, the frequency in or distribution across the entire study population and for each centre is described. Secondly, centres are compared, each one to the remainder of the study population, on the frequency or distribution of those characteristics, using appropriate statistical testing methods. These statistical tests include principally 1) Pearson's χ^2 test for equality of proportions (for categorical variables) or the Fisher's exact test where the expected value of a categorical variable in any cell of a 2x2 contingency table is <5 , and 2) Student's t test of equality of means (for continuous variables) or the appropriate non-parametric equivalent if indicated by non-normality of the distribution, with p values. Thirdly, the disease outcome group categories (endometriosis, symptomatic and sterilisation controls) are compared (endometriosis vs. symptomatic controls; endometriosis vs. sterilisation controls), using appropriate statistical testing methods as above. Variables that are associated with endometriosis on univariate analysis (and those not related to endometriosis on univariate analysis but deemed clinically relevant) are then included in an unconditional multivariate logistic regression model. Variables that are significantly associated with endometriosis on multivariate analysis ($p < 0.05$) are then assessed for their independent association with the 3 key outcome themes of this study: diagnostic delay, HRQoL and work productivity impairment. For each outcome theme, variables that are associated with endometriosis after multivariate adjustment and with the outcome independently, are deemed important and are included in analyses of those outcomes subsequently.

Statistical methods are described more specifically in the following paragraphs.

14.4.2 Diagnostic incidence of endometriosis

The diagnostic incidence (with 95% confidence intervals) of endometriosis is calculated as the proportion of women recruited at each centre and in the study population who were diagnosed with endometriosis. The diagnostic incidence of endometriosis is similarly calculated for all symptomatic women and for those women who underwent sterilisation.

For those with endometriosis in the study population and at each centre, the proportions with minimal-mild and moderate-severe endometriosis are similarly calculated with 95% confidence intervals. The diagnostic incidence of endometriosis at each centre is statistically compared to that for the rest of the study population using Pearson's χ^2 test of equality of proportions. Similarly, the frequencies of minimal-mild and moderate-severe endometriosis at each centre is statistically compared to that for the remainder of the study population using Pearson's χ^2 test of equality of proportions.

14.4.3 Distribution of variables in the study population

To describe the characteristics of the study population at recruitment, the proportions of women with the characteristic of interest in the study population are calculated for categorical variables; means with standard deviations are calculated for continuous variables.

14.4.4 Centre-wise comparisons

To further describe the characteristics of the study population at recruitment, the proportions of women with the characteristic of interest at each centre are calculated for categorical variables; means with standard deviations are calculated for continuous variables. The Pearson's χ^2 test for differences in proportions or the Student's t-test of equality of means (or parametric equivalent, where indicated by non-normality of the relevant distribution) is used for

comparisons of proportions or mean values of variables between a centre and the remainder of the study population.

14.4.5 Comparisons across disease outcome groups

Disease outcome groups are compared for differences in the categorical variables using the Pearson's χ^2 test for heterogeneity and in the continuous variables using Student's t-test of equality of means (or the non-parametric Mann-Whitney U test as appropriate).

14.4.6 Principal component analysis

As some symptoms (e.g. pelvic pain and dysmenorrhoea) are strongly correlated, principal component analysis will identify underlying patterns. Using the principal axis method [178] with prior communality estimates of "1" and orthogonal rotation, factors (symptom patterns) are extracted and those with eigenvalues > 1 are retained. A symptom is deemed to load onto a factor if its component loading is > 0.40 for that pattern and ≤ 0.40 for the others. The mean number of individual symptoms within each factor is then compared across outcome groups; factors are used in multivariate models as necessary.

14.4.7 Unconditional logistic regression modelling

All variables that are deemed to be important are included in unconditional multivariate logistic regression models. These variables include: 1) those that are significantly associated with endometriosis ($p < 0.05$) on univariate analysis (see paragraph 14.4.1), and 2) those that are deemed clinically important but are not statistically associated significantly with endometriosis on univariate analysis. An unconditional multivariate logistic regression model is constructed, contrasting endometriosis cases vs. symptomatic controls. A regression model contrasting endometriosis cases and sterilisation controls is not constructed owing to the relatively small size

of the sterilisation group. For the regression model, goodness-of-fit is tested using the Hosmer-Lemeshow test for overall goodness of fit.

Variables that are associated significantly with endometriosis on multivariate regression are then assessed for independent association with key outcomes of the study - principally diagnostic delay, HRQoL (based on SF36v2 summary scores) and overall work productivity loss. Those variables that are associated with endometriosis on multivariate regression and with diagnostic delay, HRQoL and work productivity loss are considered potential confounders in analyses of the impact of endometriosis on HRQoL and work productivity in later chapters.

14.4.8 Missing values

Missing values are dealt with by listwise deletion in Stata 11, i.e. any observation missing a value for a specific variable is dropped completely in the analysis of that variable.

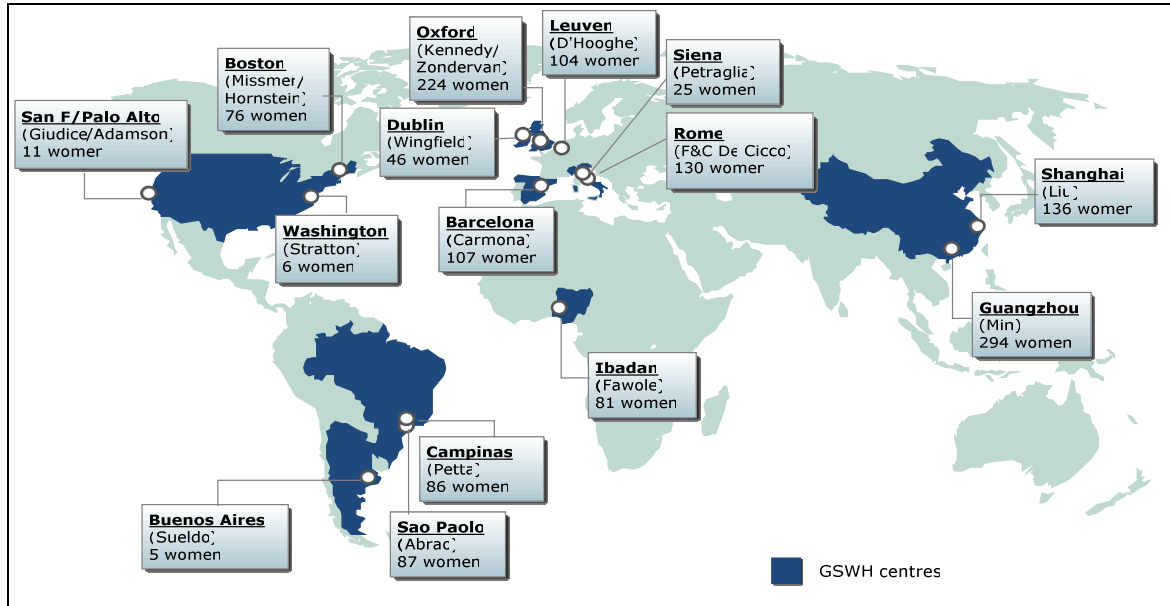
All analyses were done using Stata Release 11 (Stata Corporation, College Station, Texas, USA).

15 Results

15.1 Study population

A total of 1,669 eligible women were invited to take part in the study and 1,486 agreed (representing an 89% response rate). Sixteen women had been inappropriately included (based principally on their being outside the eligible age range of 18-45 years) and 52 had incomplete surgical records at close of recruitment (they had agreed to take part, completed the patient questionnaires, but had not had their surgery by then). These 68 women were excluded from analysis; thus complete data for 1,418 women from 16 centres in 10 countries across 5 continents (Figure 6) were available for analysis.

Figure 6 - Participating centres and numbers of women recruited in the GSWH



15.2 Diagnosis of endometriosis

15.2.1 Diagnostic incidence of endometriosis in study population and centres

Approximately 9 in 10 (90.8%) women in the study underwent laparoscopy on account of symptoms (1287/1418; 95% CI 89.3-92.3%); another 9.2% (130/1418; 95% CI 7.7-10.7%) underwent surgery to be sterilised, 40.8% (53/130; 95% CI 32.3-49.2%) of whom also had symptoms, even though those symptoms were not the reason they underwent laparoscopy (not shown). As shown in Table 6, a total of 745 women were diagnosed with endometriosis, representing a cumulative diagnostic incidence amongst all women in the study (those investigated for symptoms and those undergoing laparoscopy to be sterilised) of 52.5% (745/1418; 95% CI 49.0-56.1%). This diagnostic incidence ranged from 34.8% (146/224; 95% CI 24.2-45.4%) in Oxford to 100% in Siena.

Table 6 - Diagnostic incidence of endometriosis

Centre	Endometriosis		Symptomatic controls		Sterilisation controls		N
	n	%	n	%	n	%	
Barcelona	51	47.7%	11	10.3%	45	42.1%	107
Boston	44	57.9%	28	36.8%	4	5.3%	76
Campinas	43	50.0%	25	29.1%	18	20.9%	86
Dublin	29	63.0%	16	34.8%	1	2.2%	46
Guangzhou	105	35.7%	186	63.3%	3	1.0%	294
Ibadan	36	44.4%	45	55.6%	0	0.0%	81
Leuven	58	55.8%	46	44.2%	0	0.0%	104
Others	16	72.7%	6	27.3%	0	0.0%	22
Oxford	78	34.8%	134	59.8%	12	5.4%	224
Rome	61	46.9%	67	51.5%	2	1.5%	130
Sao Paolo	78	89.7%	9	10.3%	0	0.0%	87
Shanghai	121	89.0%	14	10.3%	1	0.7%	136
Siena	25	100.0%	0	0.0%	0	0.0%	25
Total	745	52.5%	587	41.4%	86	6.1%	1418

Amongst all women who were sterilised (with or without symptoms), the diagnostic incidence of endometriosis was 33.8% (44/130; 95% CI 25.7-42.0%); the diagnostic incidence of endometriosis was 14.3% (11/77; 95% CI 6.5-22.1%) in asymptomatic women who underwent sterilisation (not shown). As shown in Table 7, amongst all symptomatic women, the diagnostic incidence of endometriosis was 54.3% (699/1287; 95% CI 51.6-57.0%). Amongst subfertile women, the diagnostic incidence of endometriosis was 48.4% (95% CI 44-52.9%) and amongst women who had never been subfertile, it was 58.3% (95% CI 55.1-61.4%).

Table 7 - Diagnostic incidence of endometriosis in all symptomatic women

Centre	No endometriosis	Endometriosis	n	Diagnostic incidence (%)	95% LCL	95% UCL
Barcelona	16	50	66	75.8	65.4	86.1
Boston	31	41	72	56.9	45.5	68.4
Campinas	25	43	68	63.2	51.8	74.7
Dublin	16	28	44	63.6	49.4	77.9
Guangzhou	186	103	289	35.6	30.1	41.2
Ibadan	45	36	81	44.4	33.6	55.3
Leuven	46	58	104	55.8	46.2	65.3
Oxford	137	73	210	34.8	28.3	41.2
Rome	57	50	107	46.7	37.3	56.2
Sao Paolo	9	77	86	89.5	83.1	96.0
Shanghai	13	110	124	88.7	83.1	94.3
Siena	0	19	19	100.0	100.0	100.0
Others	6	11	17	64.7	42.0	87.4
Total	588	699	1,287	54.3	51.6	57.0

15.2.2 Centre-wise comparisons of diagnostic incidence

As shown in Table 8, Guangzhou (35.7 vs. 56.9%; $p<0.001$) and Oxford (34.8 vs. 55.8%; $p<0.001$) had a significantly lesser, and Sao Paolo (89.7 vs. 50.1%; $p<0.001$), Shanghai (89.0 vs. 48.6%; $p<0.001$) and Siena (100.0 vs. 51.7%; $p<0.001$) a significantly greater, diagnostic incidence of endometriosis than the remainder of the study population.

Table 8 - Centre-wise comparisons of the diagnostic incidence of endometriosis

Centre	Diagnostic incidence of endometriosis in centre	Diagnostic incidence of endometriosis in remainder of population	Pearson's χ^2 p value
Barcelona	47.7	52.9	0.30
Boston	57.9	52.2	0.33
Campinas	50.0	52.7	0.63
Dublin	63.0	52.2	0.15
Guangzhou	35.7	56.9	<0.001
Ibadan	44.4	53.0	0.14
Leuven	55.8	52.2	0.49
Oxford	34.8	55.8	<0.001
Rome	46.5	53.1	0.15
Sao Paolo	89.7	50.1	<0.001
Shanghai	89.0	48.6	<0.001
Siena	100.0	51.7	<0.001
Others	72.7	52.2	0.056

15.2.3 Severity of endometriosis disease

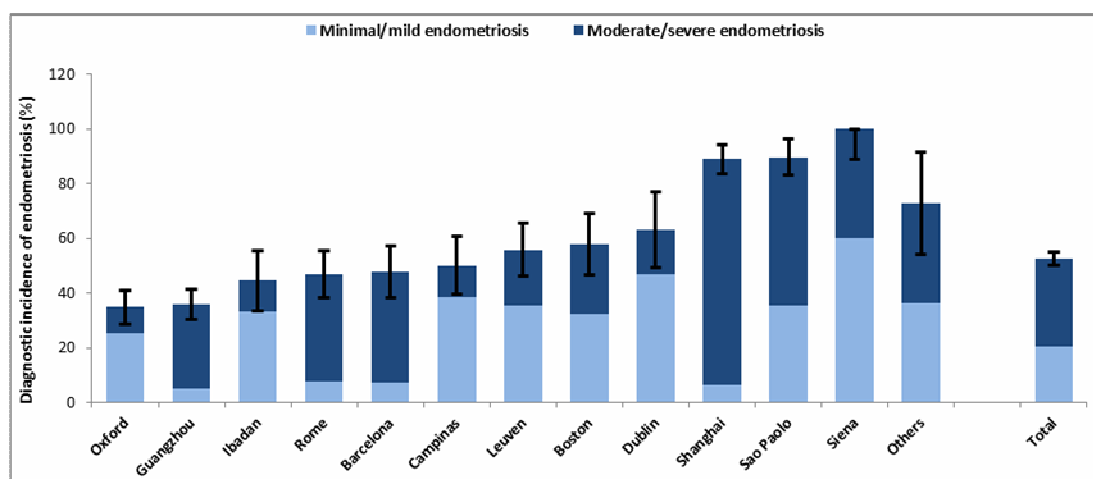
Most women with endometriosis in the study population had moderate (28.3%; 211/745) or severe (32.2%; 240/745) disease (Table 9). Notably, even amongst women who underwent laparoscopy to be sterilised but who also had endometriosis diagnosed at laparoscopy, 58.1% (25/43) had moderate-severe disease (not shown).

Amongst women with endometriosis, there was no correlation between endometriosis stage and the severity of pelvic pain ($r=0.003$; $p=0.95$).

Table 9 - Prevalence of stages of endometriosis in study population

Centre	Minimal		Mild		Moderate		Severe		Total
	n	%	n	%	n	%	n	%	
Barcelona	7	13.7	1	2.0	21	41.2	22	43.1	51
Boston	12	48.0	2	8.0	6	24.0	5	20.0	25
Campinas	24	53.3	11	24.4	8	17.8	2	4.4	45
Dublin	14	51.9	6	22.2	5	18.5	2	7.4	27
Guangzhou	14	13.3	1	1.0	43	41.0	47	44.8	105
Ibadan	28	47.5	9	15.3	10	16.9	12	20.3	59
Leuven	26	45.6	10	17.5	9	15.8	12	21.1	57
Oxford	40	51.9	16	20.8	14	18.2	7	9.1	77
Rome	7	11.9	3	5.1	25	42.4	24	40.7	59
Sao Paolo	17	21.8	14	17.9	14	17.9	33	42.3	78
Shanghai	2	1.7	7	5.8	43	35.5	69	57.0	121
Siena	3	12.0	12	48.0	9	36.0	1	4.0	25
Others	5	31.3	3	18.8	4	25.0	4	25.0	16
Total	199	26.7	95	12.8	211	28.3	240	32.2	745

Figure 7 - Diagnostic incidence of endometriosis and disease stage by Centre of recruitment



"Others" comprise Buenos Aires, Washington DC, San Francisco and Palo Alto

As shown in Table 10, Barcelona (84.3 vs. 58.8%; $p < 0.001$), Guangzhou (85.7 vs. 56.4%; $p < 0.001$), Rome (83.1 vs. 58.6%; $p < 0.001$) and Shanghai (92.6 vs. 54.3%; $p < 0.001$) had a significantly greater frequency of moderate-severe endometriosis than the remainder of the study population. On the other hand, women in Campinas (22.2 vs. 63.0%; $p < 0.001$), Dublin (25.9 vs. 61.8%; $p < 0.001$), Ibadan (37.3 vs. 62.5%; $p < 0.001$), Leuven (36.8 vs. 62.5%; $p < 0.001$), Oxford (27.3 vs. 64.4%; $p < 0.001$) and Siena (40.0 vs. 61.3%; $p = 0.033$) had a significantly lesser frequency of moderate-severe endometriosis than the remainder of the study population.

Table 10 - Centre-wise comparisons of prevalence of moderate-severe endometriosis

Centre	Proportion of women with moderate-severe endometriosis in centre	Proportion of women with moderate-severe endometriosis in remainder of population	Pearson's χ^2 p value
Barcelona	84.3	58.8	<0.001
Boston	44.0	61.1	0.085
Campinas	22.2	63.0	<0.001
Dublin	25.9	61.8	<0.001
Guangzhou	85.7	56.4	<0.001
Ibadan	37.3	62.5	<0.001
Leuven	36.8	62.5	<0.001
Oxford	27.3	64.4	<0.001
Rome	83.1	58.6	<0.001
Sao Paulo	60.3	60.6	0.96
Shanghai	92.6	54.3	<0.001
Siena	40.0	61.3	0.033
Others	50.0	60.8	0.38

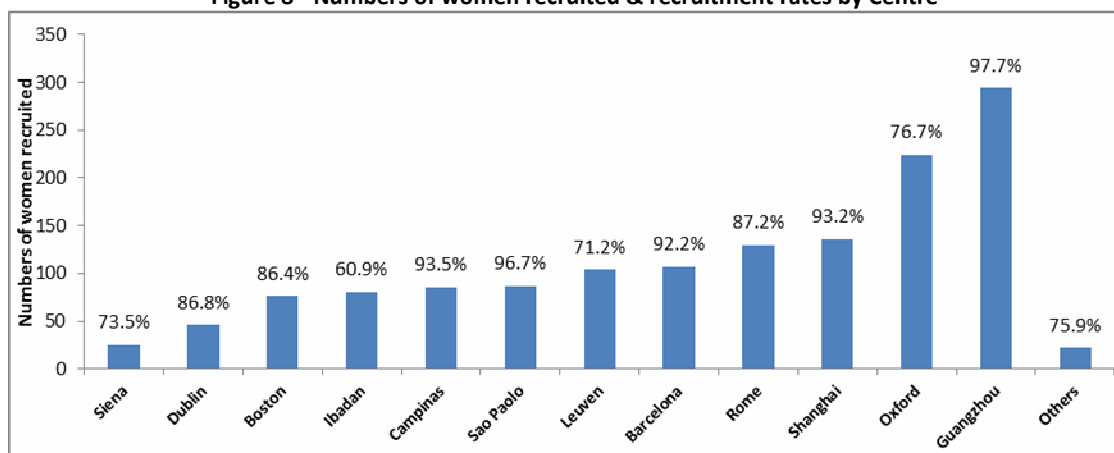
15.3 Characteristics of the study population

The study population is described in terms of the characteristics shown in Figure 6.

15.3.1 Sociodemographic characteristics and past medical history

15.3.1.1 Numbers of women recruited

Figure 8 - Numbers of women recruited & recruitment rates by Centre



Data labels above each bar are Centre-specific recruitment rates (%)

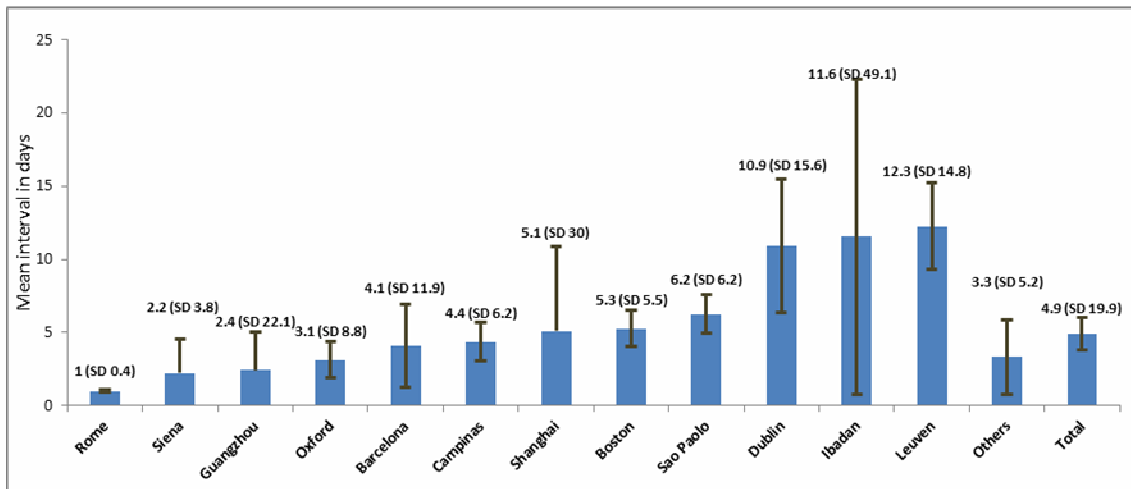
As shown in Figure 8, the numbers of women recruited at participating centres varied considerably, ranging from 22 women at 'Other' centres to 294 women at Guangzhou, this probably reflecting both differences in the rate of recruitment to the study as well as the general profile of the average patient seen at those centres.

The rate of recruitment (number of women who participated/number invited, expressed in percent) ranged from 60.9% in Ibadan to 97.7% in Guangzhou. Seven of the sixteen centres recruited above the median 87 women per centre, with Oxford, Rome, Guangzhou and Shanghai recruiting the most women (amongst them 55.3% of the study population).

15.3.1.2 Interval between date of surgery and completion of questionnaire

The mean interval between the dates of women's planned surgery and completion of the questionnaires was 4.9 days (SD 19.9) in the study population. As shown in Figure 9, this ranged from 1 day (SD 0.4) in Rome to 12.3 days (SD 14.8) in Leuven.

Figure 9 - Mean interval (SD) and 95% CIs between questionnaire completion and surgery (in days) by centre



Centre-wise comparisons (Table 11) showed that women in Dublin (10.9 vs. 4.7 days; $p=0.039$), Ibadan (11.6 vs. 4.4 days; $p=0.002$) and Leuven (12.3 vs. 4.3 days; $p<0.001$) had significantly longer intervals between questionnaire completion and planned surgery than the average woman in the remainder of the study population. On the other hand, women in Guangzhou (2.4 vs. 5.6 days; $p=0.02$) and Rome (1.0 vs. 5.3 days; $p=0.022$) had significantly shorter intervals.

Women with endometriosis had an interval of 5.9 days (SD 21.6) between questionnaire completion and planned surgery and this was not significantly different from 4.1 days (SD 19.3) for symptomatic, ($p=0.13$) and 2.8 days (SD 5.6) for sterilisation ($p=0.24$), controls.

Amongst women who had endometriosis, the interval between questionnaire completion and planned surgery was 8.0 days (SD 26.7) in women who had minimal-mild endometriosis and 4.6 days (SD 18.0) in those who had moderate-severe endometriosis ($p=0.061$).

Table 11 - Mean interval in days between questionnaire completion and surgery

Centre	Interval between date of completion of questionnaire and date of surgery (in days)		
	Centre	Remainder of study population	p value
Barcelona	4.1	4.9	0.73
Boston	5.3	4.9	0.87
Campinas	4.4	4.9	0.80
Dublin	10.9	4.7	0.039
Guangzhou	2.4	5.6	0.02
Ibadan	11.6	4.4	0.002
Leuven	12.3	4.3	<0.001
Oxford	3.1	5.2	0.17
Rome	1.0	5.3	0.022
Sao Paolo	6.2	4.8	0.51
Shanghai	5.1	4.9	0.92
Siena	2.2	4.9	0.67
Others	3.3	4.9	0.75

15.3.1.3 Age distribution of study population

The average age of women in the study population was 33.0 years (SD 6.3). As shown in Figure 10, most women were in the 25-31 and 32-38 year age bands. Women at Barcelona (35.4 vs. 32.8 yrs; $p<0.001$), Oxford (34.8 vs. 32.7 yrs; $p<0.001$), Rome (34.3 vs. 32.9 yrs; $p=0.013$), Sao Paolo (34.7 vs. 32.9 yrs; $p=0.009$) and Siena (36.4 vs. 33.0 yrs; $p=0.006$) were on average older than the average woman in the remainder of the study population. Those at Boston (31.4 vs. 33.1 yrs; $p=0.024$), Guangzhou (30.8 vs. 33.6 yrs; $p<0.001$) and Leuven (31.6 vs. 33.1 yrs; $p=0.019$) were younger than the average woman in the in the remainder of the study population.

Figure 10 - Age distribution of women in GSWH, by Centre

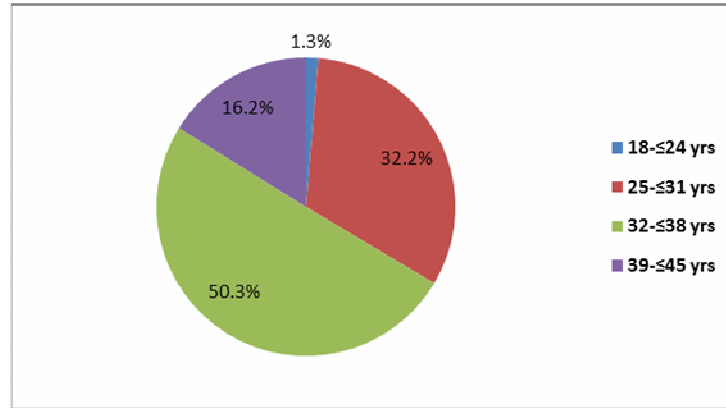
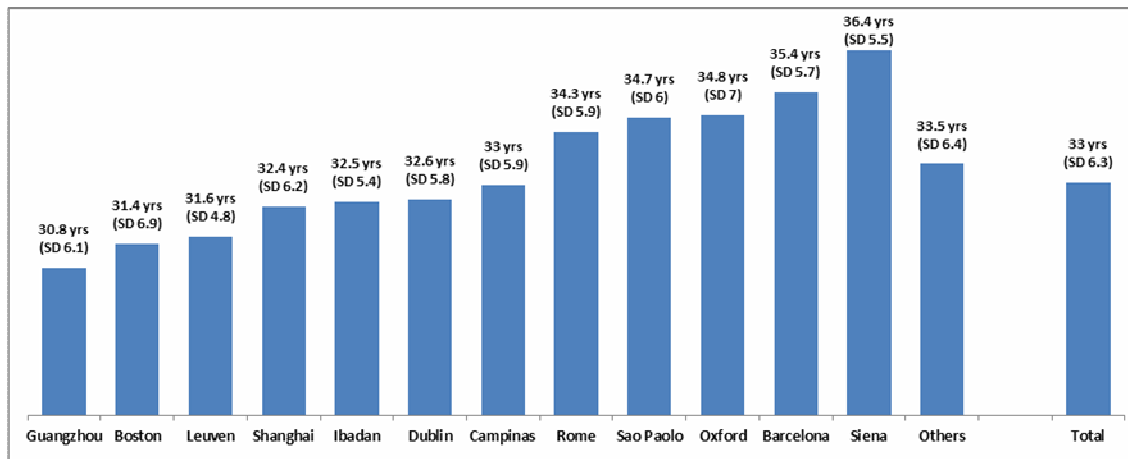


Figure 11 - Mean ages of women with standard deviations, by Centre



As shown in Appendix 1, the difference in age between women with endometriosis [32.5 years (SD 6.2)] and symptomatic controls [33.1 years (SD 6.4)] was not statistically significant ($p=0.10$) but sterilisation controls [37.2 years (SD 5.0)] were significantly older ($p<0.001$).

Women who had moderate-severe endometriosis were significantly older (mean age 33.1 years, SD 6.2) than those with minimal-mild endometriosis (mean age 32.2 years, SD 5.9) ($p=0.045$) (not shown).

15.3.1.4 Ethnicity

The study population comprised mainly women of White (48.2%; n=683) and Asian (32.1%; n=455) ethnic origins (Figure 12).

Figure 12- Ethnic origins of women in the GSWH study population

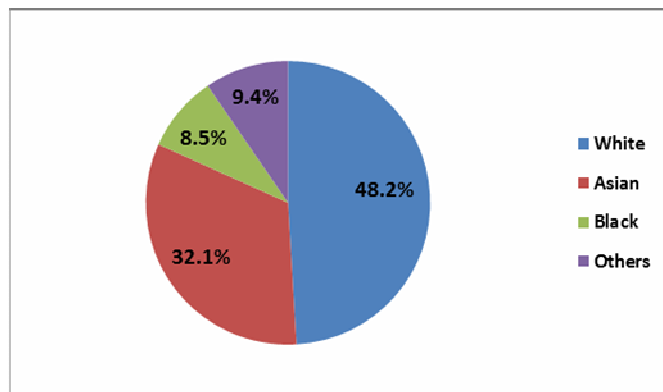
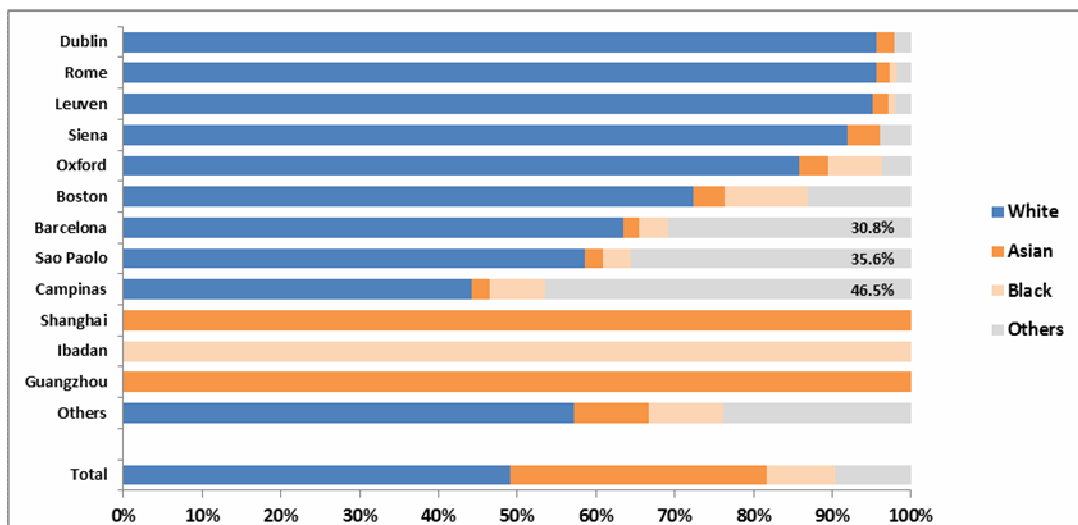


Figure 13 - Ethnic origins of women in GSWH by Centre



Women's ethnic origins broadly matched what would be expected given their countries of residence (Figure 13). The high proportion of people from 'other' ethnic group is notable in Campinas and Sao Paolo, where 46.5% (n=40) and 35.6% (n=31) of women, respectively, reported being of a 'mixed race' (data labelled in Figure 13). The similar high proportion of the 'other'

ethnic group in Barcelona (30.8%; n=33) is accounted for by a relatively high proportion of people reporting Hispanic or Latino ethnicity (27.1%; n=29) (not shown).

Centre-wise comparisons of the proportions of White women in each centre suggested all centres except Campinas (44.2 vs. 48.4%; p=0.45) and 'Others' (54.5 vs. 48.1%; p=0.55) had significantly greater proportions of white women compared to the remainder of the study population (Table 12).

Table 12 – Centre-wise comparison of proportions of White women in study population

Centre	Proportion of White women in centre (%)	Proportion of White women in remainder of study population (%)	Pearson's χ^2 p value
Barcelona	63.6	46.9	0.001
Boston	72.4	46.8	<0.001
Campinas	44.2	48.4	0.45
Dublin	95.7	46.6	<0.001
Guangzhou	0.0	60.8	<0.001
Ibadan	0.0	51.1	<0.001
Leuven	93.3	44.6	<0.001
Oxford	83.5	41.5	<0.001
Rome	83.1	44.6	<0.001
Sao Paolo	58.6	47.5	<0.001
Shanghai	0.0	53.3	<0.001
Siena	92.0	47.4	<0.001
Others	54.5	48.1	0.55

As shown in Appendix 1, there was a significant difference in the ethnic composition of women with endometriosis compared to symptomatic (p=0.005) and sterilisation controls (p<0.001). There was no difference in the proportion of White women in the endometriosis and symptomatic control groups (50.1 vs. 45.3%; p=0.14) but the endometriosis group had significantly fewer Black women (7.0 vs. 10.6%; p=0.015). Compared to the sterilisation control group, the endometriosis group had similar proportions of White (48.8 vs. 50.1%; p=0.83) and Black (8.1 vs. 7.0%; p=0.69) women. The proportions of women in the different ethnic groups differed significantly both between cases and symptomatic controls (Pearson's χ^2 for

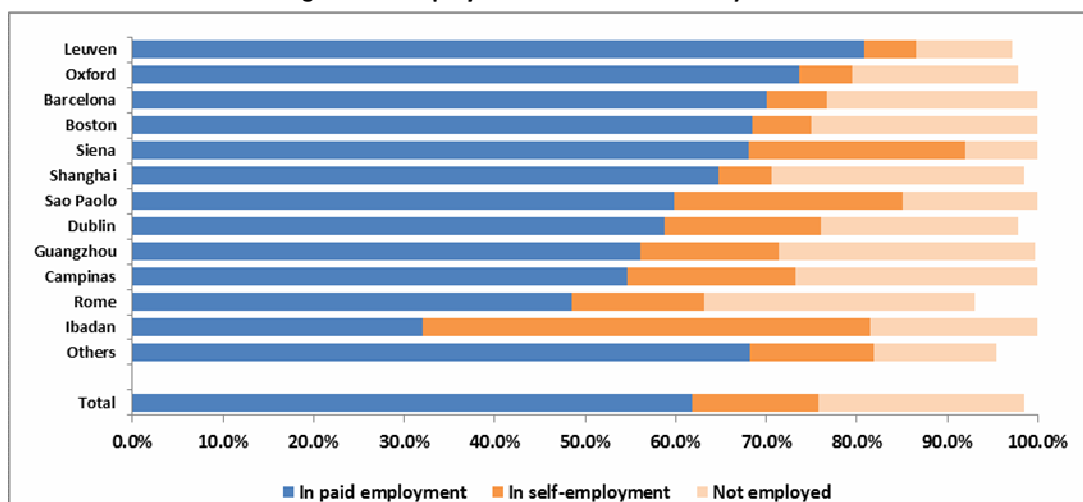
heterogeneity of proportions $p=0.005$) and cases and sterilisation controls (Pearson's χ^2 for heterogeneity of proportions $p<0.001$).

There were significantly greater proportions of White (62.2 vs. 37.3%; $p<0.001$) and Black (15.0 vs. 6.9%; $p<0.001$) women in the minimal-mild compared to the moderate-severe endometriosis groups. In contrast, a significantly greater proportion of Asian women had moderate-severe than minimal-mild endometriosis (46.8 vs. 9.2%; $p<0.001$). The proportions of women with minimal-mild vs. moderate-severe endometriosis differed significantly by ethnicity (Pearson's χ^2 for heterogeneity of proportions $p<0.001$).

15.3.1.5 Employment

Most women in the study population were either in paid (61.7%; 875/1418) or self-employment (14%; 198/1418); nearly a quarter of women (322/1418; 22.7%) were not in the paid workforce (Figure 14).

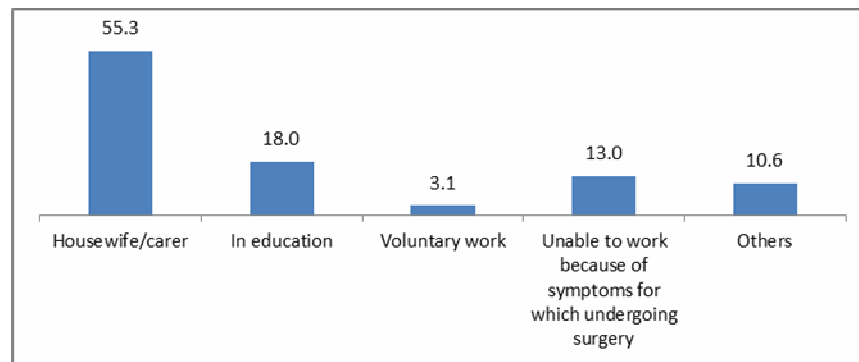
Figure 14 - Employment status of women by Centre



Some stacked bars do not total 100% because of missing values

Most women who were not in the paid workforce were housewives or carers (55.3%; 178/322) but about 13% of them (42/322) reported that they did not work because of the symptoms for which they underwent surgery (Figure 15).

Figure 15 - Percentages of women reporting specific reasons for not being in employment



Centre-wise comparisons (Figure 16) suggest there were proportionately more women in paid or self-employment in Leuven than in the remainder of the study population (89.1 vs. 76.0%; $p=0.003$). In contrast, there were proportionately fewer women in paid or self-employment in Guangzhou (71.7 vs. 78.3%; $p=0.016$) and Rome (67.8 vs. 77.8%; $p=0.012$) than in the remainder of the study population.

Figure 16 - Comparison of proportions of employed women in each centre vs. remainder of study population

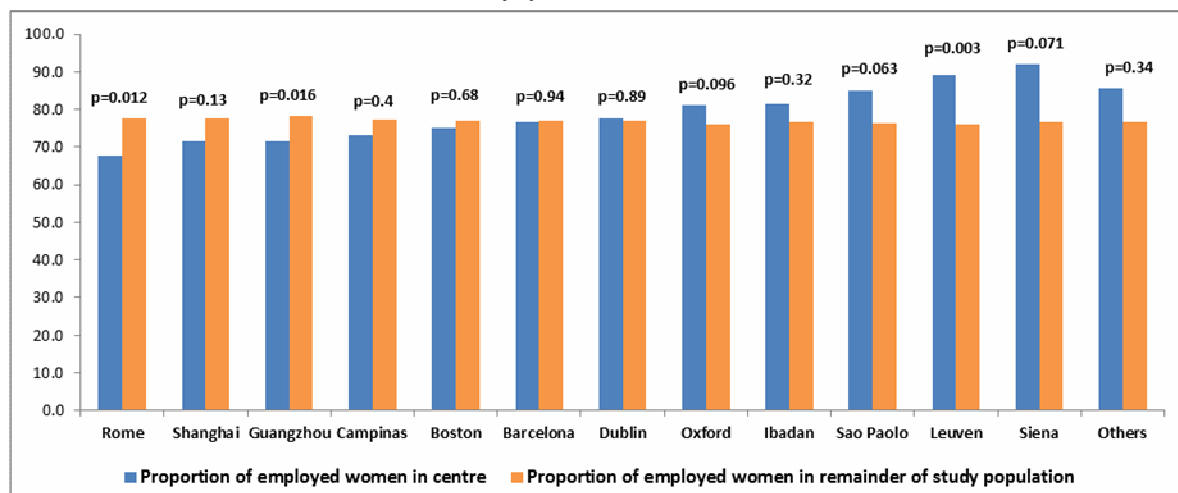
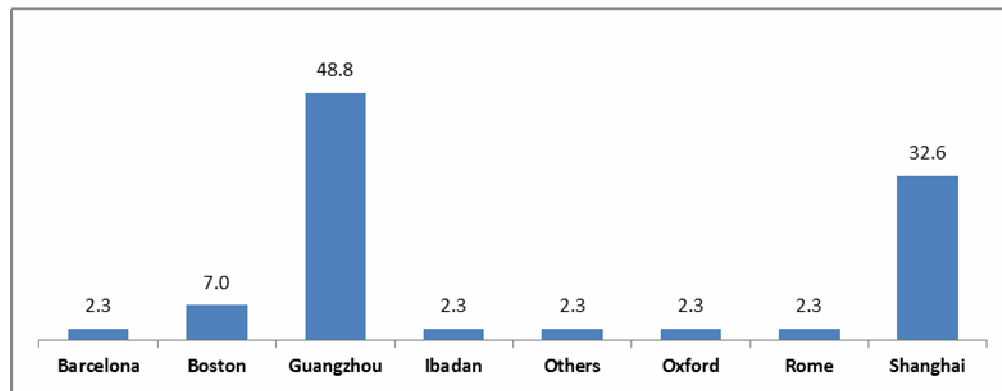


Figure 17 shows the percentages of unemployed women not working due to symptoms indicating surgery. The relatively high proportion of unemployed women in Guangzhou and Shanghai whose unemployment was due to the symptoms for which they underwent laparoscopy is notable.

Figure 17 - Percentages of unemployed women not working due to symptoms indicating surgery by centre



This data is shown only for centres where women reported not being in employment because of the symptoms for which they underwent surgery.

As shown in Appendix 1, the endometriosis group had a similar proportion of employed women as both symptomatic (78.5 vs. 73.6%; $p = 0.054$) and sterilisation controls. Similarly, compared to controls, the endometriosis group had a greater proportion of employed women (78.5% vs. 70.9%; $p = 0.067$).

Amongst women with endometriosis, there were no differences in the proportions of employed women in the minimal-mild compared to the moderate-severe endometriosis groups (79.3 vs. 78.3%; $p = 0.69$).

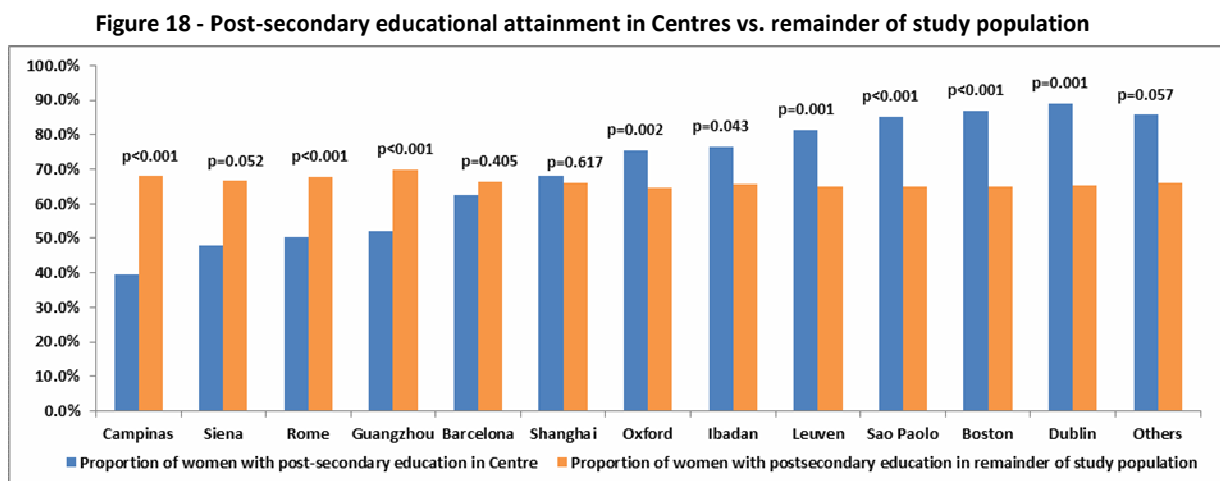
15.3.1.6 Education

The average woman in the study population was well educated: 65% of women ($n = 921$) had post-secondary, university or post-graduate education (Table 13).

Table 13 - Highest attained educational level in women by centre

Centre	Primary	%	Lower secondary	%	Upper secondary	%	Post-secondary	%	University	%	Post-graduate	%	Missing	N
Barcelona	10	9.3	6	5.6	23	21.5	26	24.3	32	29.9	7	6.5	3	107
Boston	5	6.6	1	1.3	4	5.3	12	15.8	33	43.4	21	27.6	0	76
Campinas	7	8.1	13	15.1	32	37.2	3	3.5	21	24.4	10	11.6	0	86
Dublin	0	0.0	0	0.0	5	10.9	10	21.7	14	30.4	17	37.0	0	46
Guangzhou	8	2.7	54	18.4	79	26.9	81	27.6	66	22.4	6	2.0	0	294
Ibadan	2	2.5	5	6.2	12	14.8	21	25.9	31	38.3	10	12.3	0	81
Leuven	0	0.0	0	0.0	19	18.3	12	11.5	60	57.7	11	10.6	2	104
Others	1	4.5	0	0.0	2	9.1	2	9.1	8	36.4	8	36.4	1	22
Oxford	0	0.0	10	4.5	42	18.8	62	27.7	56	25.0	41	18.3	13	224
Rome	1	0.8	17	13.1	43	33.1	18	13.8	36	27.7	8	6.2	7	130
Sao Paolo	1	1.1	1	1.1	11	12.6	4	4.6	33	37.9	37	42.5	0	87
Shanghai	5	3.7	18	13.2	20	14.7	37	27.2	45	33.1	10	7.4	1	136
Siena	0	0.0	4	16.0	9	36.0	3	12.0	7	28.0	2	8.0	0	25
Total	40	2.8	129	9.1	301	21.2	291	20.5	442	31.2	188	13.3	27	1,418

As shown in Figure 18, women at Boston (86.8% vs. 65.0%; $p<0.001$), Dublin (89.1% vs. 65.4%; $p<0.001$), Ibadan (76.5% vs. 65.6%; $p=0.043$) Leuven (81.4% vs. 65.0%; $p<0.001$), Oxford (75.4% vs. 64.6%; $p=0.002$) and Sao Paolo (85.1% vs. 65.0%; $p<0.001$) were more likely than the average woman in the remainder of the study population to have achieved a post-secondary educational qualification. Women at Campinas (39.5% vs. 68.0%; $p<0.001$), Guangzhou (52.0% vs. 70.0%; $p<0.001$) and Rome (50.4% vs. 67.7%; $p<0.001$) were less likely than the average woman in the remainder of the study population to have achieved similar qualification.



Data labelled with p values for chi² test of differences in the proportions of women achieving post-secondary educational qualification at each centre and remainder of study population.

As shown in Appendix 1, compared to symptomatic controls, the endometriosis group had a significantly greater proportion of women with post-secondary education (69.9 vs. 61.7%; $p=0.004$). Similarly, compared to sterilisation controls, the endometriosis group had a significantly greater proportion of women with post-secondary education (69.9 vs. 45.3%; $p<0.001$).

Amongst women who had endometriosis, a significantly greater proportion of the minimal-mild, compared to the moderate-severe, endometriosis group (73.1 vs. 66.7%; $p=0.047$) reported achieving a post-secondary educational qualification.

15.3.1.7 Marital status

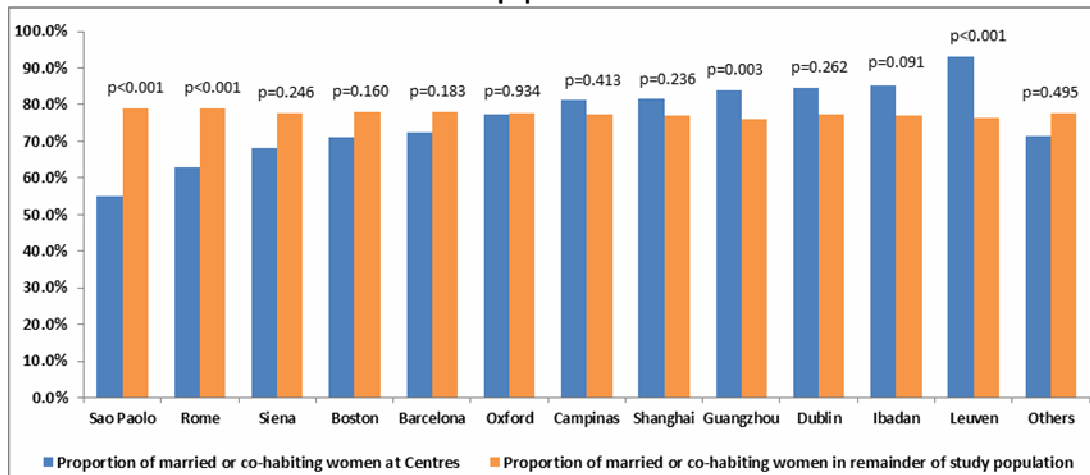
The marital status of women in the study population is shown for all centres in Table 14. Of the 1,418 women in the study population, 1,087 indicated they were either married or single and living with a partner (76.7%).

Table 14 - Marital status of women in GSHW by Centre

Centre	Single, living with partner	%	Married	%	Single, not living with partner	%	Divorced/ separated	%	Widowed	%	Missing	Total
Barcelona	22	20.6	54	50.5	16	15.0	12	11.2	1	0.9	2	107
Boston	14	18.4	40	52.6	22	28.9	0	0.0	0	0.0	0	76
Campinas	16	18.6	53	61.6	16	18.6	0	0.0	0	0.0	1	86
Dublin	4	8.7	34	73.9	7	15.2	0	0.0	0	0.0	1	46
Guangzhou	22	7.5	225	76.5	43	14.6	3	1.0	1	0.3	0	294
Ibadan	0	0.0	69	85.2	12	14.8	0	0.0	0	0.0	0	81
Leuven	41	39.4	53	51.0	5	4.8	2	1.9	0	0.0	3	104
Others	9	40.9	6	27.3	4	18.2	2	9.1	0	0.0	1	22
Oxford	59	26.3	112	50.0	33	14.7	17	7.6	0	0.0	3	224
Rome	20	15.4	58	44.6	40	30.8	6	4.6	0	0.0	6	130
Sao Paolo	6	6.9	42	48.3	31	35.6	8	9.2	0	0.0	0	87
Shanghai	5	3.7	106	77.9	23	16.9	2	1.5	0	0.0	0	136
Siena	3	12.0	14	56.0	5	20.0	3	12.0	0	0.0	0	25
Total	221	15.6	866	61.1	257	18.1	55	3.9	2	0.1	17	1,418

As shown in Figure 19, women in Guangzhou (84.0% vs. 75.9%; $p=0.003$) and Leuven (93.1% vs. 76.4%; $p<0.001$) were significantly more likely than the average woman in the remainder of the study population to be married or co-habiting while women in Rome (62.9% vs. 79.0%; $p<0.001$) and Sao Paolo (55.2% vs. 79.1%; $p<0.001$) were significantly less likely to be.

Figure 19 - Marital or co-habiting status of women in Centres, compared to remainder of study population



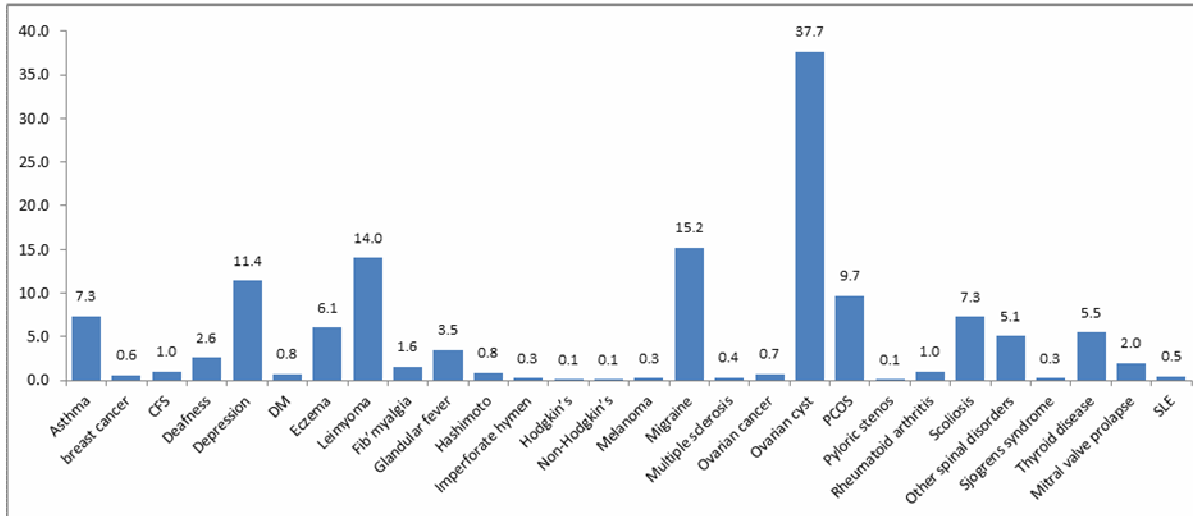
Data labelled with p values for χ^2 test of differences in the proportions of married or co-habiting women in each centre compared to those for the remainder of the study population

As shown in Appendix 1, compared to symptomatic controls, the endometriosis group had a significantly lower proportion of women who were married or co-habiting (73.3 vs. 80.2%; $p=0.002$). Similarly, compared to sterilisation controls, the endometriosis group had a significantly lower proportion of women who were married or single and co-habiting (73.3 vs. 84.9%; $p=0.017$).

15.3.1.8 Past medical history

As shown in the Figure 20 below, the most commonly reported conditions in the past medical history of women in the study population were ovarian cysts (37.7%; $n=534$), migraines (15.2%; $n=215$) and leiomyoma (14%; $n=199$). Others included depression (11.4%; $n=162$), polycystic ovarian syndrome (9.7%; $n=137$), asthma (7.3%; $n=104$) and scoliosis (7.3%; $n=103$).

Figure 20 - Frequency of reporting of conditions in the past medical history



When comparing between centres (Table 15), the relatively low frequency of a medical history of asthma, depression and migraines reported by women in Guangzhou (0.7%, 0.3% and 2% respectively), Shanghai (1.5%, 0 and 1.5% respectively) and Ibadan (3.7%, 2.5% and 3.7% respectively) were notable. Otherwise, no significant patterns were observed in how women reported specific conditions in their past medical history.

Table 15 - Percentage of women reporting a history of medical conditions, by Centre

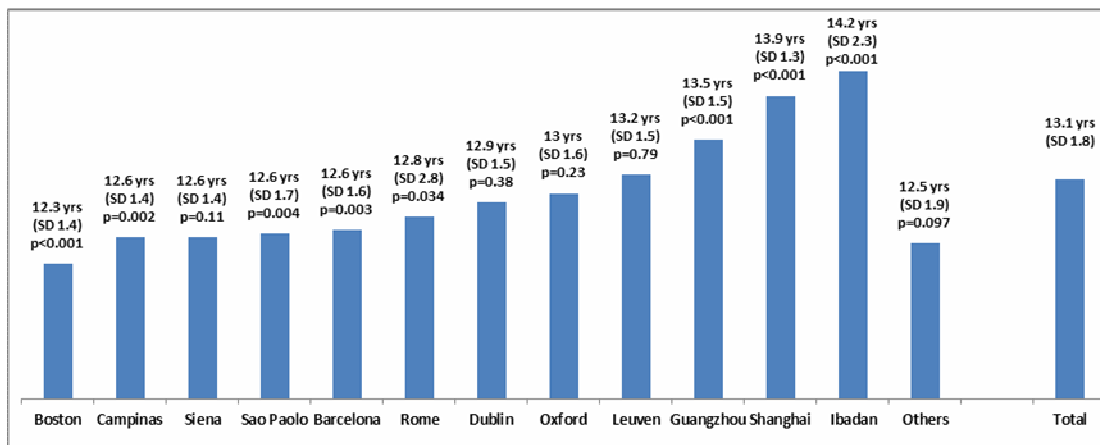
	Asthma	Breast cancer	Chronic Fatigue Syndrome	Deafness	Depression	DM	Eczema	Leiomyoma	Fibromyalgia	Glandular fever	Hashimoto's disease	Imperforate hymen	Hodgkin's disease	Non-Hodgkin's Lymphoma	Melanoma	Migraine	Multiple sclerosis	Ovarian cancer	Ovarian cyst	PCOS	Pyloric stenosis	Rheumatoid arthritis	Scoliosis	Other spinal disorders	Sjogrens disease	Thyroid disease	Mitral Valve Prolapse	SLE	n
Barcelona	8.4	0.9	0	3.7	15.9	1.9	1.9	10.3	0.9	0.9	0	0	0.9	0	0	25.2	0.9	0.9	26.2	7.5	0	2.8	12.1	8.4	0	3.7	0	0.9	107
Boston	18.4	1.3	1.3	2.6	26.3	0	14.5	36.8	3.9	0	0	2.6	0	0	0	38.2	0	3.9	40.8	3.9	0	1.3	14.5	3.9	0	9.2	3.9	0	76
Campanas	4.7	0	0	4.7	15.1	1.2	0	0	3.5	0	0	0	0	0	0	4.7	0	0	20.9	10.5	0	0	12.8	9.3	0	2.3	3.5	0	86
Dublin	6.5	0	0	2.2	21.7	2.2	13	4.3	2.2	10.9	0	0	0	0	0	21.7	0	0	30.4	15.2	2.2	2.2	0	0	0	0	0	0	46
Guangzhou	0.7	1	0	1.7	0.3	0.3	4.8	13.9	0	0	0	0	0	0	0	2	0	0.3	42.2	5.4	0	0.7	0	0.7	0.3	3.7	0	1	294
Ibadan	3.7	0	2.5	0	2.5	0	2.5	25.9	0	0	0	0	0	0	0	3.7	0	0	13.6	3.7	0	0	0	0	0	2.5	0	0	81
Leuven	4.8	0	1	3.8	12.5	0	10.6	5.8	1.9	2.9	0	0	1	0	1	26.9	1	0	19.2	12.5	0	1	12.5	6.7	0	6.7	2.9	0	104
Others	9.1	0	0	4.5	22.7	0	4.5	13.6	0	0	4.5	0	0	4.5	0	22.7	0	0	63.6	18.2	0	4.5	9.1	4.5	0	9.1	0	0	22
Oxford	17.4	0.4	2.7	4.9	20.5	2.2	12.1	12.9	0.4	10.7	0	0.9	0	0	1.3	19.6	0	0.4	23.7	11.2	0	0.4	1.8	2.7	0	2.7	0.4	1.3	224
Rome	10	0.8	0.8	0.8	8.5	0	1.5	21.5	3.1	12.3	3.1	0	0	0	0	16.2	0.8	0.8	40.8	20	0	0.8	20	10.8	0	8.5	5.4	0	130
Sao Paolo	5.7	1.1	2.3	2.3	25.3	1.1	1.1	2.3	2.3	0	6.9	0	0	0	0	34.5	2.3	1.1	48.3	17.2	0	3.4	19.5	19.5	0	18.4	10.3	0	87
Shanghai	1.5	0	0.7	1.5	0	0	5.1	14	2.9	0	0	0	0	0	0	1.5	0	1.5	82.4	2.2	0	0	0.7	2.2	1.5	5.9	0	0	136
Siena	12	0	0	0	8	0	8	36	4	0	4	0	0	0	0	24	0	0	56	20	0	0	20	8	4	8	8	0	35
Total	104	8	14	37	162	11	86	199	22	49	12	4	2	1	4	215	5	10	534	137	1	14	103	72	4	78	28	7	1,418

15.3.2 Gynaecological characteristics

15.3.2.1 Age at menarche

The average age at menarche of women in the study was 13.1 (SD 1.76) years. As shown in Figure 21, women in Ibadan (14.2 vs. 13.0 yrs; $p<0.001$), Guangzhou (13.5 vs. 13.0 yrs; $p<0.001$) and Shanghai (13.9 vs. 13.0 yrs; $p<0.001$) were significantly older at menarche than the average woman in the remainder of the study population. Women in Barcelona (12.6 vs. 13.2 yrs; $p=0.003$), Boston (12.3 vs. 13.2 yrs; $p<0.001$), Campinas (12.6 vs. 13.2 yrs; $p=0.002$), Rome (12.8 vs. 13.1 yrs; $p=0.034$) and Sao Paolo (12.6 vs. 13.2 yrs; $p=0.004$) were younger at menarche than the average woman in the remainder of the study population.

Figure 21 - Mean age (SD) at menarche by Centre with p values for comparison with the remainder of study population



Data labelled with mean age at menarche (SD) and p values for the t-test of equality of the mean age at menarche of women in each centre compared to that for the remainder of the study population

As shown in Appendix 1, compared to symptomatic controls, women in the endometriosis group were significantly younger at menarche (mean age at menarche in endometriosis group 13.0 years {SD 1.6} vs. 13.3 years {SD 1.7} in symptomatic controls) ($p=0.0043$). There was however no difference in age at menarche between women in the endometriosis group and those in the laparoscopic sterilisation group (mean age at menarche 12.8 years, SD 1.7; $p=0.20$).

Amongst women with endometriosis, those who had moderate-severe disease were significantly older at menarche (13.1 yrs, SD 1.6) compared to those who had minimal-mild disease (12.9 yrs, SD 1.7) ($p=0.040$).

15.3.2.2 Use of hormonal contraception

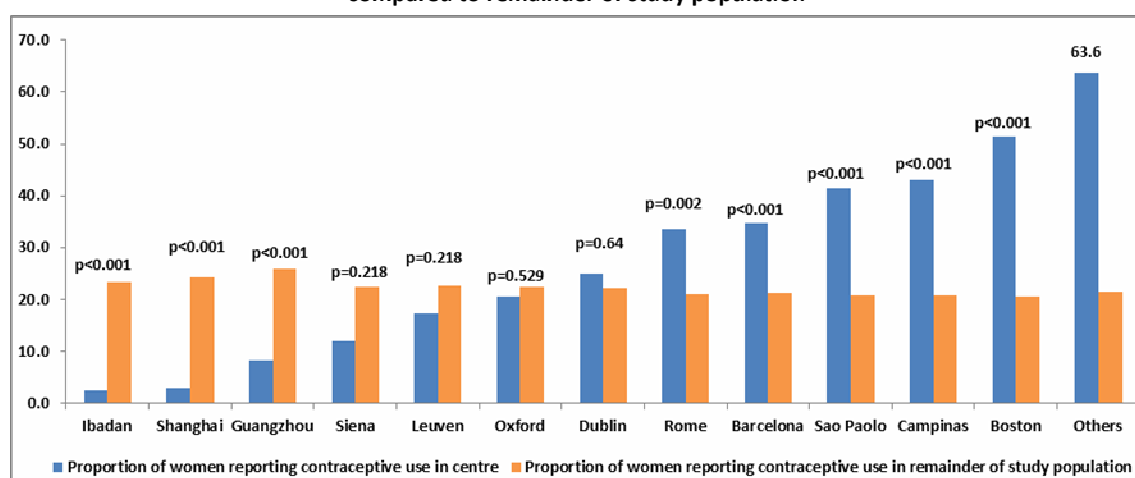
Over 1 in 5 women in the study population reported using hormonal contraception any time in the 3 months preceding participation in the study 21.9% ($n=311$) (Table 16).

Table 16 - Hormonal contraceptive use in past 3 months by Centre

Centre	No contraception	Contraception	n	Missing	Frequency (%)
Barcelona	70	37	107	0	34.6
Boston	37	39	76	0	51.3
Campinas	49	37	86	0	43.0
Dublin	33	11	44	2	23.9
Guangzhou	270	24	294	0	8.2
Ibadan	79	2	81	0	2.5
Leuven	86	18	104	0	17.3
Oxford	178	46	224	0	20.5
Rome	79	40	119	11	30.8
Sao Paolo	51	36	87	0	41.4
Shanghai	132	4	136	0	2.9
Siena	22	3	25	0	12.0
Others	8	14	22	0	63.6
Total	1,094	311	1,405	13	21.9

Notably, a relatively small proportion of women at Guangzhou (8.2%; $n=24$), Shanghai (2.9%; $n=4$) and Ibadan (2.5%; $n=2$), compared to the remainder of the study population, reported using hormonal contraception (Table 16). Centre-wise comparisons in Figure 22 demonstrate these differences in more detail.

Figure 22 – Proportions of women reporting hormonal contraceptive use in last 3 months in Centres, compared to remainder of study population



Data labelled with p values for chi² test of differences in the proportions of married or co-habiting women in each centre compared to those for the remainder of the study population

The most frequently reported reasons why women used hormonal contraception (Table 17) were for contraception (53.7%; n=167) and control of pelvic pain (19.9%; n=62). Amongst women who reported recently using hormonal contraception, the most common types used were the pill (77.5%; n=241); IUCD/coil (9%; n=28) or injections (7.7%; n=24). Those who reported using hormonal contraception had started doing so only in the last year in 48.2% of cases (n=150) or more than five years ago in 24.1% of cases (n=75).

Table 17 - Reasons for use of hormonal contraception in past 3 months by Centre

Centre	Contra- ception (n)	%	Pelvic pain (n)	%	Irregular menses (n)	%	Heavy periods (n)	%	Other (n)	%	Missing (n)	%	Total
Barcelona	23	62.2	11	29.7	1	2.7	0	0.0	1	2.7	1	2.7	37
Boston	21	53.8	9	23.1	2	5.1	4	10.3	3	7.7	0	0.0	39
Campinas	27	73.0	6	16.2	2	5.4	1	2.7	1	2.7	0	0.0	37
Dublin	8	72.7	2	18.2	0	0.0	1	9.1	0	0.0	0	0.0	11
Guangzhou	13	54.2	1	4.2	6	25.0	0	0.0	4	16.7	0	0.0	24
Ibadan	0	0.0	1	50.0	1	50.0	0	0.0	0	0.0	0	0.0	2
Leuven	8	44.4	4	22.2	2	11.1	0	0.0	4	22.2	0	0.0	18
Oxford	32	69.6	8	17.4	2	4.3	2	4.3	2	4.3	0	0.0	46
Rome	10	25.0	10	25.0	4	10.0	5	12.5	9	22.5	2	5.0	40
Sao Paolo	21	58.3	6	16.7	3	8.3	3	8.3	3	8.3	0	0.0	36
Shanghai	0	0.0	0	0.0	0	0.0	1	25.0	3	75.0	0	0.0	4
Siena	1	33.3	0	0.0	2	66.7	0	0.0	0	0.0	0	0.0	3
Others	3	21.4	4	28.6	2	14.3	1	7.1	4	28.6	0	0.0	14
Total	167	53.7	62	19.9	27	8.7	18	5.8	34	10.9	3	1.0	311

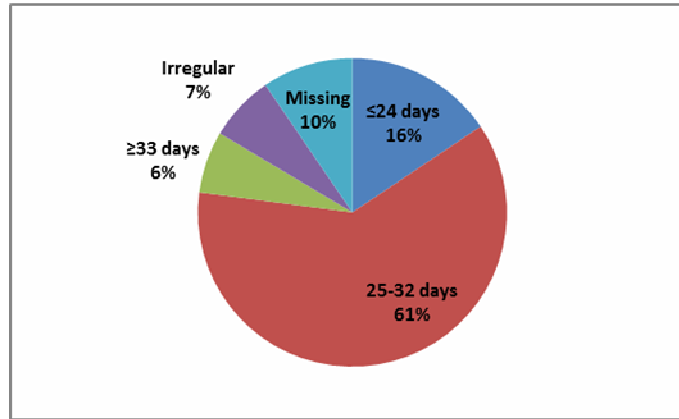
As shown in Appendix 1, compared to symptomatic controls, a greater proportion of women in the endometriosis group reported using hormonal contraception in the previous three months (23.4 vs. 16.9%; $p=0.004$). A greater proportion of women in the sterilisation group (23.4 vs. 45.3%; $p<0.001$) reported using hormonal contraception than in the endometriosis group. There were no differences in the proportion of endometriosis and symptomatic control women who reported using hormonal contraception for contraception or on account of pelvic pain, irregular or heavy menses ($p=0.42$). Sterilisation controls were, however, significantly more likely to use hormonal contraceptives for contraception and less so for symptoms than women with endometriosis ($p<0.001$).

Amongst women who had endometriosis, there was no difference in the proportion of the minimal-mild (23.1%; $n=68$), compared to the moderate-severe (19.7%; $n=89$), endometriosis group (73.1 vs. 66.7%; $p=0.047$) who reported using hormonal contraception in the past three months.

15.3.2.3 Menstrual cycle length

Most women in the study population who had had a period in the last three months described their periods as regular (79.0%; $n=1,022$).

Figure 23 - Proportions of women in GSWH study population reporting different cycle lengths



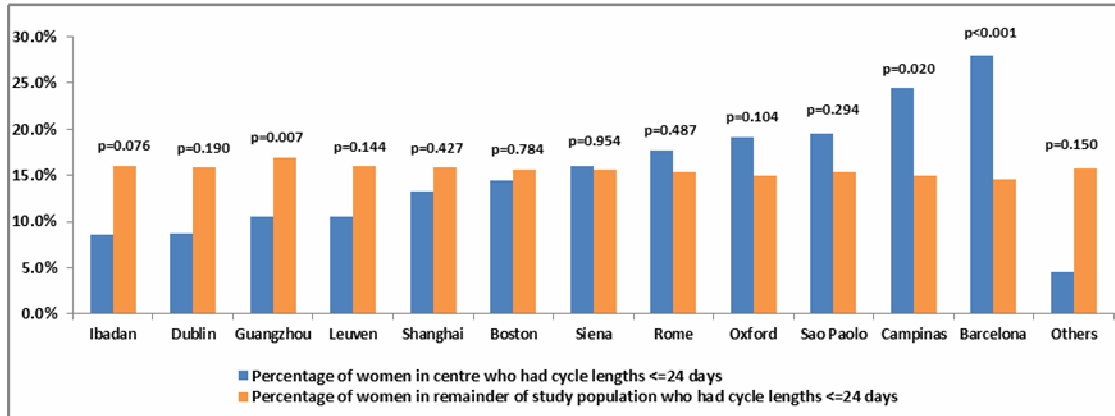
As shown in Figure 23 & Table 18, most women had menstrual cycles of 25-32 days (61.5%; n=872) or ≤24 days in length (15.6%; n=221).

Table 18 – Percentages of women who reported menstrual cycles of specific lengths by Centre

Centre	≤24 days		25-32 days		≥33 days		Irregular		Missing		n
	n	%	n	%	n	%	n	%	n	%	
Barcelona	30	28.0%	60	56.1%	5	4.7%	2	1.9%	10	9.3%	107
Boston	11	14.5%	32	42.1%	5	6.6%	8	10.5%	20	26.3%	76
Campinas	21	24.4%	51	59.3%	2	2.3%	7	8.1%	5	5.8%	86
Dublin	4	8.7%	30	65.2%	3	6.5%	6	13.0%	3	6.5%	46
Guangzhou	31	10.5%	196	66.7%	33	11.2%	30	10.2%	4	1.4%	294
Ibadan	7	8.6%	68	84.0%	3	3.7%	0	0.0%	3	3.7%	81
Leuven	11	10.6%	61	58.7%	10	9.6%	14	13.5%	8	7.7%	104
Oxford	43	19.2%	114	50.9%	14	6.3%	19	8.5%	34	15.2%	224
Rome	23	17.7%	76	58.5%	3	2.3%	3	2.3%	25	19.2%	130
Sao Paolo	17	19.5%	51	58.6%	4	4.6%	1	1.1%	14	16.1%	87
Shanghai	18	13.2%	101	74.3%	6	4.4%	6	4.4%	5	3.7%	136
Siena	4	16.0%	19	76.0%	1	4.0%	1	4.0%	0	0.0%	25
Others	1	4.5%	13	59.1%	3	13.6%	1	4.5%	4	18.2%	22
Total	221	15.6%	872	61.5%	92	6.5%	98	6.9%	135	9.5%	1,418

As shown in Figure 24, a significantly lesser proportion of women at Guangzhou reported menstrual cycle lengths of ≤24 days compared to the remainder of the study population (10.5% vs. 16.9%; p=0.007). On the other hand, significantly greater proportions of women at Campinas (24.4% vs. 15.0%; p=0.020) and Barcelona (28.0% vs. 14.6%; p<0.001) reported menstrual cycle lengths of ≤24 days compared to the remainder of the study population.

Figure 24 - Percentages of women who had menstrual cycle length of ≤ 24 days



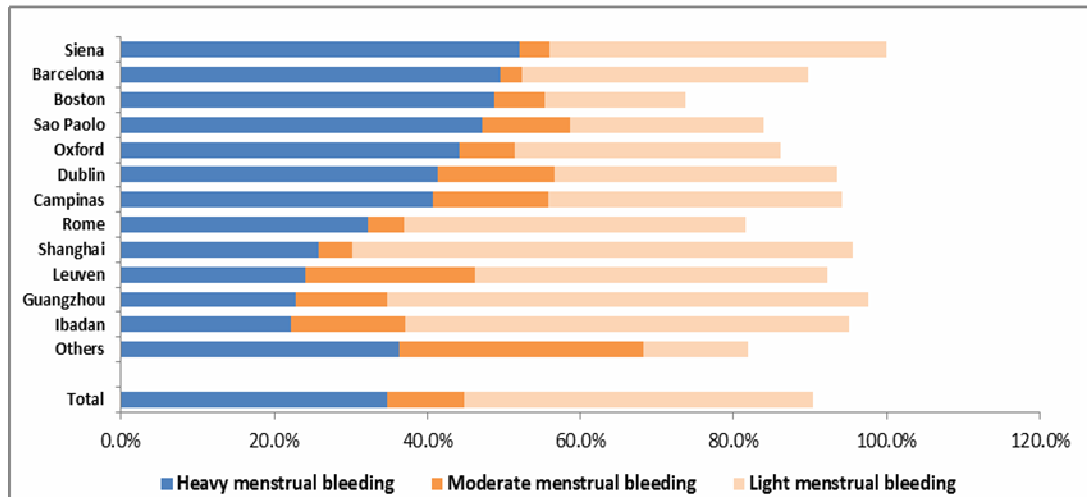
Data labelled with p values for χ^2 test of differences in the proportions of women in each centre with menstrual cycle lengths ≤ 24 days compared to those for the remainder of the study population

As shown in Appendix 1, compared to symptomatic controls, a greater proportion of women in the endometriosis group reported shorter cycle lengths of ≤ 24 days and fewer reported cycle lengths of ≥ 33 days ($p=0.041$). There was however no difference in reported menstrual cycle lengths between women in the sterilisation and endometriosis groups ($p=0.23$).

Amongst women with endometriosis, women who had moderate-severe disease did not differ from those who had minimal-mild disease in the proportions represented in the categories of menstrual cycle length (Pearson's χ^2 $p=0.307$).

15.3.2.4 Menstrual duration

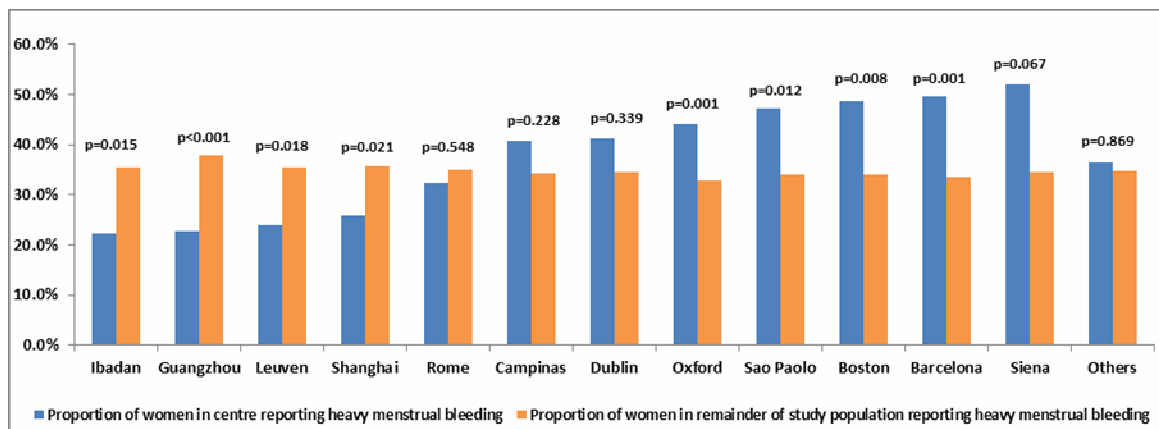
Figure 25 - Percentages of women reporting heavy menstrual flow by Centre



Stacked bars do not total 100% because of missing values

Generally, women in the study population reported heavy or moderate menstrual periods (Figure 25). Significantly greater proportions of women in Barcelona (49.5% vs. 33.5%; $p=0.001$), Boston (48.7% vs. 33.9%; $p=0.008$), Oxford (44.2% vs. 32.9%; $p<0.001$) and Sao Paolo (47.1% vs. 33.9%; $p=0.012$), compared to the remainder of the study population, reported having heavy menstrual bleeding. Conversely, significantly lesser proportions of women in Guangzhou (22.8% vs. 37.8%; $p<0.001$), Ibadan (22.2% vs. 35.5%; $p=0.015$), Leuven (24.0% vs. 35.5%; $p=0.018$) and Shanghai (25.7% vs. 35.6%; $p=0.021$), compared to the remainder of the study population, reported having heavy menstrual bleeding (Figure 26).

Figure 26 - Percentage of women who reported heavy menstrual bleeding by Centre



Data labelled with p values for χ^2 test of differences in the proportions of women in each centre, compared to those for the remainder of the study population, who reported heavy menstrual cycles.

Reported mean menstrual duration ranged from 4.0 days in women at Ibadan to 5.8 days in women at Shanghai (Table 19). On average, women at Barcelona (4.3 vs. 5.0 days; $p<0.001$), Campinas (4.5 vs. 4.9 days; $p=0.020$), Dublin (4.3 vs. 4.9 days; $p=0.032$), Leuven (4.5 vs. 4.9 days; $p=0.007$), Ibadan (4.0 vs. 5.0 days; $p<0.001$) and Rome (4.5 vs. 5.0 days; $p=0.003$) had shorter menstrual durations than the average woman in the remainder of the study population. Those in Boston (5.5 vs. 4.9 days; $p=0.025$), Guangzhou (5.4 vs. 4.8 days; $p<0.001$) and Shanghai (5.6 vs. 4.8 days; $p<0.001$) had longer mean menstrual durations than the average woman in the remainder of the study population (not shown).

Table 19 - Reported menstrual duration by Centre

Centre	Mean (days)	SD	n	Missing
Barcelona	4.2	2.0	97	10
Boston	5.4	4.2	56	20
Campinas	4.6	2.1	81	5
Dublin	4.8	4.8	43	3
Guangzhou	5.3	1.7	290	4
Ibadan	4.0	1.2	78	3
Leuven	4.2	1.7	96	8
Oxford	5.0	3.2	195	29
Rome	4.5	1.9	106	24
Sao Paolo	4.5	2.3	73	14
Shanghai	5.8	3.2	130	6
Siena	4.9	1.7	25	0
Others	4.5	2.0	18	4
Total	4.9	2.6	1,288	130

As shown in Appendix 1, there were no statistically significant differences between women with endometriosis and symptomatic controls on the one hand ($p=0.99$) and between women with endometriosis and sterilisation controls on the other in the mean reported duration of menstruation ($p=0.63$).

Amongst women with endometriosis in the study population, those who had moderate-severe endometriosis reported longer menstrual durations (mean 5.1 days; SD 1.73) than those who had minimal-mild endometriosis (mean 4.7 days; SD 1.56) ($p=0.017$).

15.3.3 Reproductive characteristics

15.3.3.1 Gravidity

Five hundred and eighty-five women in the study population reported a previous pregnancy (41.3%). Progressively fewer reported higher gravidity, with 19.0% ($n=269$) reporting one previous pregnancy and 0.8% ($n=11$) reporting six previous pregnancies (not shown). As shown in Table 20, the mean gravidity of women in the study population was 0.87 (SD 1.3)

Table 20 - Gravidity of women in study population who reported a previous pregnancy

Centre	Mean Gravidity	SD	n	Missing
Barcelona	1.34	1.4	98	9
Boston	0.47	1.0	73	3
Campinas	0.86	1.4	86	0
Dublin	0.47	0.9	43	3
Guangzhou	0.94	1.2	258	36
Ibadan	1.21	1.5	81	0
Leuven	0.55	0.9	103	1
Oxford	1.27	1.6	215	9
Rome	0.57	1.0	122	8
Sao Paolo	0.43	0.7	87	0
Shanghai	0.84	1.2	125	11
Siena	0.24	0.4	25	0
Others	0.67	1.1	21	1
Total	0.87	1.3	1337	81

Women in Boston (0.46 vs. 0.89; $p=0.006$), Leuven (0.55 vs. 0.90; $p=0.009$), Dublin (0.47 vs. 0.88; $p=0.035$), Rome (0.57 vs. 0.90; $p=0.006$), Sao Paolo (0.43 vs. 0.90; $p<0.001$) and Siena (0.24 vs. 0.88; $p=0.013$) reported significantly lower gravidity compared to the average woman in the remainder of the study population but those in Ibadan (1.21 vs. 0.85; $p=0.013$), Oxford (1.27 vs. 0.79; $p<0.001$) and Barcelona (1.34 vs. 0.83; $p<0.001$) had higher gravidity (not shown).

As shown in Appendix 1, women with endometriosis reported a lower average gravidity (mean 0.5, SD 0.9) than both symptomatic (mean 1.0, SD 1.4) and sterilisation (mean 2.3, SD 1.6) controls (both $p < 0.001$).

15.3.3.2 History of subfertility

As shown in Table 21, 608 women (42.9%) reported that they had tried to get pregnant for more than 12 months without success and 71.7% ($n=436$) of these women were currently being investigated for fertility difficulties.

Table 21 - Subfertility in the GSWH study population by Centre

Centre	No Subfertility	Subfertility	N	Missing	%
Barcelona	74	33	107	0	30.8
Boston	57	19	76	0	25.0
Campinas	43	43	86	0	50.0
Dublin	15	29	44	2	63.0
Guangzhou	167	127	294	0	43.2
Ibadan	17	64	81	0	79.0
Leuven	24	78	102	2	75.0
Oxford	111	109	220	4	48.7
Rome	76	41	117	13	31.5
Sao Paolo	66	21	87	0	24.1
Shanghai	116	20	136	0	14.7
Siena	13	12	25	0	48.0
Others	10	12	22	0	54.5
Total	789	608	1,397	21	42.9

Most women (87.8%; $n=534$) who reported a history of subfertility indicated that they (or their partners) had had one or more tests to discover the cause of the problem (not shown). Amongst those women, the most common condition identified on diagnostic testing was blocked tubes (21.9%; $n=117$) and endometriosis was clinically suspected in 19.1% ($n=102$) of them. Of the women who reported subfertility, 42.1% ($n=256$) had had some form of treatment, the most common being Clomiphene (69.1%; $n=177$) (not shown).

As shown in Appendix 1, compared to the endometriosis group, there was a significantly greater proportion of women in the symptomatic control group who reported a history of subfertility (51.8 vs. 39.6%; $p<0.001$). Compared to the endometriosis group, there was however a significantly lesser proportion of women in the sterilisation control group who reported a history of subfertility (18.6 vs. 39.6%; $p<0.001$).

15.3.3.3 Parity

Amongst the 585 women who had had a previous pregnancy, 304 reported having carried one or more pregnancies up to or beyond 24 weeks gestation in the past (52.0%) (not shown). Progressively fewer women who had had at least 1 pregnancy reported higher parity, with 23.6% (n=138) reporting one previous pregnancy, and 1.0% (n=6) reporting six previous pregnancies, carried beyond the 24th week of gestation.

As shown in Table 22, the mean parity of women in the study population was 0.48 (SD 1.05; range 0 to 6).

Table 22 - Parity of women by Centre

Centre	Mean Parity	SD	n	Missing
Barcelona	1.07	1.42	102	5
Boston	0.15	0.68	73	3
Campinas	0.59	1.18	78	8
Dublin	0.37	0.85	46	0
Guangzhou	0.30	0.79	246	48
Ibadan	0.59	1.38	66	15
Leuven	0.27	0.66	95	9
Oxford	0.90	1.45	201	23
Rome	0.34	0.81	121	9
Sao Paolo	0.30	0.62	84	3
Shanghai	0.32	0.76	115	21
Siena	0.16	0.37	25	0
Others	0.11	0.32	19	3
Total	0.48	1.05	1271	147

As shown in Appendix 1, women with endometriosis reported a lower average parity (mean 0.2; SD 0.5) than symptomatic controls (mean 0.5; SD 1.0) ($p<0.001$). Similarly, sterilisation controls reported a higher average gravidity (mean 1.8, SD 1.4) than women with endometriosis ($p<0.001$).

15.3.4 Body characteristics

15.3.4.1 Body Mass Index (BMI)

Most women in the study population (61.9%; $n=878$) had a normal BMI and 13.9% ($n=197$) were obese (Figure 27). As shown in Table 19, the mean BMI of the study population was 23.0 ± 4.4 kg/m^2 (range 11.75–66.60 kg/m^2).

Figure 27 - Proportions of women in study population in BMI categories, with 95% confidence intervals

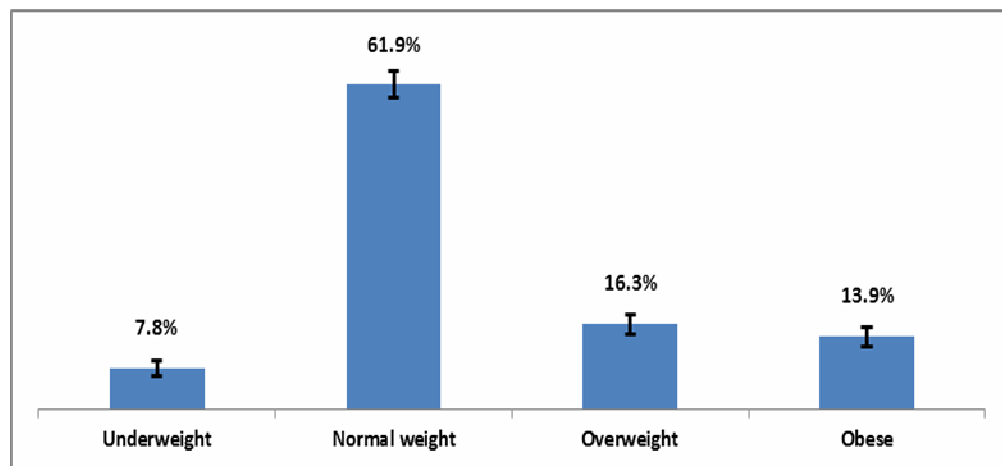
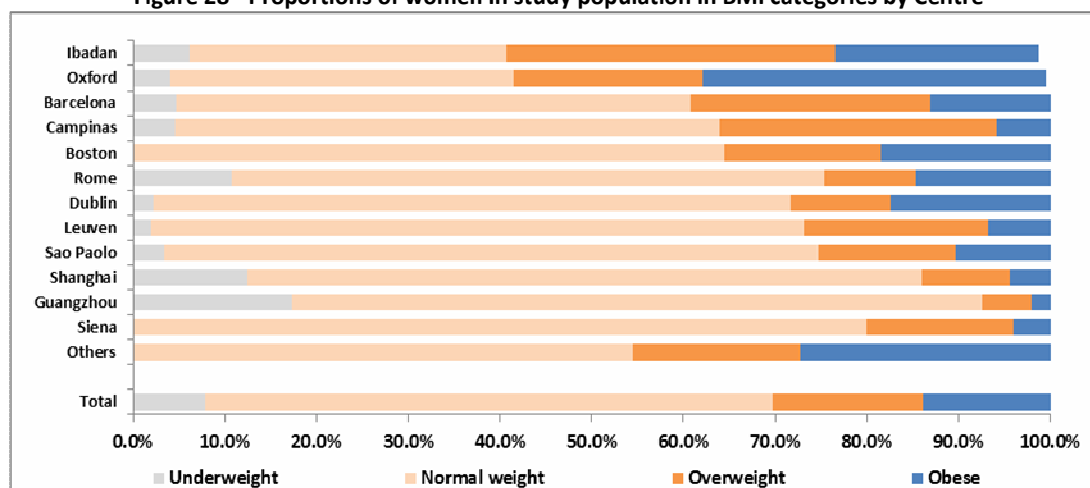


Figure 28 - Proportions of women in study population in BMI categories by Centre



Stacked bars for Ibadan and Oxford do not total 100% because of 1 missing value each

Compared to the average for the remainder of the study population, women at Boston (25.1 vs. 22.9 kg/m²; $p < 0.001$), Campinas (24.2 vs. 22.9 kg/m²; $p = 0.013$), Ibadan (26.8 vs. 22.8 kg/m²; $p < 0.001$) and Oxford (24.8 vs. 22.8 kg/m²; $p < 0.001$) had significantly higher BMI. Those at Guangzhou (20.7 vs. 23.7 kg/m²; $p < 0.001$), Rome (22.0 vs. 23.1 kg/m²; $p = 0.013$) and Shanghai (21.6 vs. 23.2 kg/m²; $p < 0.001$) had lower average BMI. Birth weight was reported only by an average of 30% of women (ranging from 4% at Ibadan to 76% at Siena). Where birth weight, current weight and height were reported, heavier weight at birth was associated with higher BMI in the study population (Spearman's $\rho = 0.1480$; $p = 0.0045$).

Table 23 - Mean Body Mass Index (BMI) of women by Centre

Centre	Mean	SD	n	Missing
Barcelona	23.8	4.4	100	7
Boston	25.1	5.2	74	2
Campinas	24.2	3.9	86	0
Dublin	22.5	2.7	39	7
Guangzhou	20.8	2.9	292	2
Ibadan	26.8	6.3	81	0
Leuven	23.0	3.5	101	3
Oxford	24.8	4.5	164	60
Rome	22.0	3.4	114	16
Sao Paolo	23.5	4.3	86	1
Shanghai	21.6	4.8	132	4
Siena	22.5	3.1	25	0
Others	23.9	4.5	18	4
Total	23.0	4.4	1312	106

As shown in Appendix 1, BMI was significantly lower in women with endometriosis (22.5 ± 4.1 kg/m²) than in symptomatic (23.4 ± 4.8 kg/m²) and sterilisation (25.2 ± 4.4 kg/m²) controls (both $p < 0.001$). Further analyses (not shown) found that the percentage of overweight subjects was similar among women with endometriosis and symptomatic controls (14.2 vs. 15.8%; $p = 0.27$) but compared to the endometriosis group, there was a significantly higher proportion of overweight women in the sterilisation control group (14.2 vs. 30.2%; $p < 0.001$). There were significantly more obese women amongst both symptomatic (17.7 vs. 10.1%; $p < 0.001$) and sterilisation controls (17.4 vs. 10.1%; $p = 0.038$) compared to the endometriosis group. The percentage of underweight subjects did not significantly differ in the endometriosis, compared to both the symptomatic (9.1 vs 6.5%; $p = 0.087$) and sterilisation (9.1 vs. 3.5%; $p = 0.076$) control groups.

The mean BMI in minimal-mild endometriosis (rASRM I–II; $n = 294$) was 23.3 ± 4.1 kg/m² and 22.2 ± 4.2 kg/m² in moderate-severe endometriosis (rASRM III–IV; $n = 451$) (p value for t test of difference of means < 0.001).

15.3.4.2 Natural hair colour

The most commonly reported natural hair colours in the study population were black (32.3%; $n = 458$) and light, medium or dark shades of brown (58.6%; $n = 831$). Only 2.6% (95% CI 1.8–3.4%) of women reported having natural light red or dark red hair (Table 20). The predominant natural hair colours of women reflected what would be expected, i.e. black hair in Black and Asian women and predominantly brown or fair/blonde hair in White women (Table 24).

Table 24 - Frequency of natural hair colours in women by Centre

Centre	%								Total N
	Fair/ Blonde	Light brown	Light red/ginger	Auburn/ dark red	Medium brown	Dark brown	Black	Missing	
Barcelona	5.6	15.0	0.0	1.9	21.5	39.3	15.0	1.9	107
Boston	7.9	25.0	0.0	5.3	27.6	25.0	9.2	0.0	76
Campinas	10.5	23.3	0.0	0.0	19.8	27.9	18.6	0.0	86
Dublin	4.3	17.4	2.2	4.3	34.8	34.8	2.2	0.0	46
Guangzhou	0.0	7.5	1.0	0.0	3.1	12.2	76.2	0.0	294
Ibadan	0.0	6.2	0.0	0.0	6.2	16.0	71.6	0.0	81
Leuven	18.3	20.2	2.9	1.0	30.8	23.1	2.9	1.0	104
Oxford	12.5	24.1	1.3	4.9	28.6	22.8	5.4	0.4	224
Rome	5.4	20.0	0.0	0.0	37.7	29.2	3.8	3.8	130
Sao Paolo	2.3	31.0	0.0	0.0	29.9	29.9	6.9	0.0	87
Shanghai	1.5	2.9	2.2	0.7	1.5	13.2	77.9	0.0	136
Siena	4.0	20.0	0.0	0.0	24.0	44.0	8.0	0.0	25
Others	4.5	27.3	4.5	9.1	9.1	36.4	9.1	0.0	22
Total	5.9	16.4	1.0	1.6	19.2	23.0	32.3	0.6	1,418

Table 25 - Hair colour by ethnicity and Centre

Centre	Race/ethnicity															
	Others				Black				Asian				White			
	Hair Colour															
	Fair	Red	Brown	Black	Fair	Red	Brown	Black	Fair	Red	Brown	Black	Fair	Red	Brown	Black
Barcelona	7	1	18	6	0	0	2	2	0	0	1	1	15	1	44	7
Boston	0	0	8	2	1	1	4	2	0	0	0	3	24	3	28	0
Campinas	11	0	20	9	0	0	0	6	1	0	1	0	17		20	1
Dublin	0	0	1	0	0	0	0	0	0	0	1	0	10	3	30	1
Guangzhou	0	0	0	0	0	0	0	0	22	3	45	224	0	0	0	0
Ibadan	0	0	0	0	5	0	18	58	0	0	0	0	0	0	0	0
Leuven	0	1	0	0	0	0	0	1	0	0	1	1	39	3	54	1
Others	2	0	3	0	0	0	1	1	0	0	1	1	5	3	4	0
Oxford	1	0	4	3	5	1	6	3	0	0	5	3	74	11	99	2
Rome	0	0	2	0	0	0	1	0	0	0	1	1	28	0	74	4
Sao Paolo	6	0	21	4	1	0	2	0	0	0	1	1	22	0	28	1
Shanghai	0	0	0	0	0	0	0	0	6	4	20	106	0	0	0	0
Siena	0	0	0	1	0	0	0	0	0	0	0	1	6	0	17	0
Total	27	2	77	25	12	2	34	73	29	7	77	342	240	24	398	17
%	20.6	1.5	58.8	19.1	9.9	1.7	28.1	60.3	6.4	1.5	16.9	75.2	35.3	3.5	58.6	2.5

15.3.4.3 Skin moles

Most women in the study population reported having 1-10 (51.0%; n=723) or 11-50 (25.7%; n=363) skin moles (Table 26). Compared to the remainder of the study population, a significantly greater proportion of women in Leuven (22.4 vs. 9.7%; p=0.002), Rome (26.2 vs. 9.2%, p<0.001), Sao Paolo (33.8 vs. 9.3%; p<0.001) and Siena (47.1 vs. 10.0%; p<0.001) reported having more than

50 skin moles. A significantly lesser proportion of women at Guangzhou (0 vs. 13.7%; $p<0.001$), Ibadan (0 vs. 11.2%; $p=0.003$) and Shanghai (0.7 vs. 11.7%; $p<0.001$), compared to the remainder of the study population, reported having more than 50 skin moles.

Table 26 – Proportions of women reporting skin moles by Centre

Centre	%					Total N
	No moles	1-10 moles	11-50 moles	>50 moles	Missing	
Barcelona	0.9	16.8	46.7	29.9	5.6	107
Boston	0.0	17.1	53.9	21.1	7.9	76
Campinas	0.0	1.2	36.0	47.7	15.1	86
Dublin	2.2	13.0	56.5	26.1	2.2	46
Guangzhou	0.0	17.7	69.7	12.6	0.0	294
Ibadan	0.0	43.2	55.6	1.2	0.0	81
Leuven	2.9	15.4	40.4	23.1	18.3	104
Oxford	3.1	7.6	42.0	34.4	12.9	224
Rome	7.7	2.3	30.0	39.2	20.8	130
Sao Paolo	0.0	0.0	42.5	32.2	25.3	87
Shanghai	0.7	7.4	72.1	19.1	0.7	136
Siena	0.0	0.0	24.0	44.0	32.0	25
Others	0.0	9.1	40.9	36.4	13.6	22
Total	12.2	51.0	25.7	9.5	1.6	1,418

Compared to symptomatic controls, a significantly greater proportion of women with endometriosis reported having >50 skin moles (11.5 vs. 7.7%; $p=0.001$). There was however no difference in the proportions of endometriosis cases and sterilisation controls who reported having >50 skin moles (11.5 vs. 4.7%; $p=0.066$).

15.3.5 Personal habits

15.3.5.1 Smoking

As shown in Table 27, 12.9% (183/1418; 95% CI 11.2-14.7%) and 13.6% (193/1418; 95% CI 11.8-15.4%) of women in the study population were current and former smokers respectively.

Table 27 - Smoking status of women in the study population by Centre

Centre	Current smokers		Former smokers		Never smokers		N
	N	%	n	%	n	%	
Barcelona	41	38.3%	18	16.8%	48	44.9%	107
Boston	10	13.2%	12	15.8%	54	71.1%	76
Campinas	12	14.0%	9	10.5%	65	75.6%	86
Dublin	7	15.2%	15	32.6%	19	42.2%	46
Guangzhou	7	2.4%	5	1.7%	282	95.9%	294
Ibadan	0	0.0%	0	0.0%	81	100.0%	81
Leuven	13	12.5%	21	20.2%	69	66.3%	104
Oxford	36	16.1%	74	33.0%	106	48.8%	224
Rome	36	27.7%	17	13.1%	69	55.2%	130
Sao Paolo	10	11.5%	16	18.4%	61	70.1%	87
Shanghai	0	0.0%	2	1.5%	134	98.5%	136
Siena	6	24.0%	2	8.0%	17	68.0%	25
Others	5	22.7%	2	9.1%	15	68.2%	22
Total	183	12.9%	193	13.6%	1,020	72.6%	1418

There were 13 missing values for 'never smokers' - 1 for Dublin, 7 for Oxford and 5 for Rome. There were no missing values for current and former smokers

Centre-wise comparisons (Table 28) show that compared to the remainder of the study population, significantly greater proportions of women in Barcelona (38.3 vs. 10.8%; $p<0.001$) and Rome (27.7 vs. 11.4%; $p<0.001$) and significantly lesser proportions in Guangzhou (2.4 vs. 15.7%; $p<0.001$), Shanghai (0 vs. 14.3%; $p<0.001$) and Ibadan (0 vs. 13.7%; $p<0.001$) were current smokers. Compared to the remainder of the study population, significantly greater proportions of women in Dublin (32.6 vs. 13.0%; $p<0.001$), Leuven (20.2 vs. 13.1%; $p=0.042$) and Oxford (33.0 vs. 10.0%; $p<0.001$) and significantly lesser proportions in Guangzhou (1.7 vs. 16.7%; $p<0.001$), Shanghai (1.5 vs. 14.9%; $p<0.001$) and Ibadan (0 vs. 14.4%; $p<0.001$) were former smokers. Finally, compared to the remainder of the study population, significantly greater proportions of women in Guangzhou (95.5 vs. 66.5%; $p<0.001$), Ibadan (100.0 vs. 71.0%; $p<0.001$) and Shanghai (98.5 vs. 69.9%; $p<0.001$) and significantly lesser proportions in Barcelona (44.9 vs. 74.9%; $p<0.001$), Dublin (42.2 vs. 73.79%; $p<0.001$), Oxford (48.8 vs. 77.0%; $p<0.001$) and Rome (55.6 vs. 74.3%; $p<0.001$) reported having never smoked.

Table 28 - Centre-wise comparisons for smoking history

Centre	'Current' smoking			'Former' smoking			'Never' smoking		
	Proportion of in Centre	Proportion in remainder population	Pearson's chi ² p-value	Proportion of in Centre	Proportion in remainder population	Pearson's chi ² p-value	Proportion of in Centre	Proportion in remainder population	Pearson's chi ² p-value
Barcelona	38.3	10.8	<0.001	16.8	13.4	0.32	44.9	74.9	<0.001
Boston	13.2	12.8	0.93	15.8	13.5	0.57	71.1	72.7	0.75
Campinas	14.0	12.8	0.75	10.5	13.8	0.38	75.6	72.5	0.53
Dublin	15.2	12.8	0.63	32.6	13.0	<0.001	42.2	73.7	<0.001
Guangzhou	2.4	15.6	<0.001	1.7	16.7	<0.001	95.9	66.5	<0.001
Ibadan	0.0	13.6	<0.001	0.0	14.4	<0.001	100.0	71.0	<0.001
Leuven	12.5	12.9	0.91	20.2	13.1	0.042	66.3	73.2	0.13
Oxford	16.1	12.2	0.12	33.0	10.0	<0.001	48.8	77.0	<0.001
Rome	27.1	11.4	<0.001	13.2	13.7	0.88	55.6	74.3	<0.001
Sao Paolo	11.5	12.9	0.70	18.4	13.3	0.18	70.1	72.8	0.58
Shanghai	0.0	14.2	<0.001	1.5	14.9	<0.001	98.5	69.9	<0.001
Siena	24.0	12.6	0.093	8.0	13.7	0.41	68.0	72.7	0.6
Others	22.7	12.7	0.16	9.1	13.7	0.53	68.2	72.7	0.64

The endometriosis group did not differ from the symptomatic control group in the proportions of current (12.9 vs. 10.4%; $p=0.25$), former (13.8 vs. 14.1%; $p=0.66$) or never (72.2 vs. 69.7%; $p=0.74$) smokers. Compared to endometriosis cases however, sterilisation controls had a significantly greater proportion of women who were current smokers (26.7 vs. 12.9%; $p=0.001$) and a significantly lesser proportion who were never smokers (58.1 vs. 72.2%; $p=0.012$) (Appendix 1).

On average, both current and former smokers started smoking at age 16.8 years (SD 4.0); this ranged from 16.0 years (SD 3.5) at Campinas to 24.5 years (SD 7.8) at Shanghai (not shown). Women with endometriosis who were current smokers did not differ in age at smoking debut from both symptomatic (mean age 17.1 vs. 16.6 years; $p=0.36$) and sterilisation (mean age 17.1 vs. 15.7 years; $p=0.067$) controls. Similarly, women with endometriosis who were former smokers did not differ in age at smoking debut from both symptomatic (mean age 16.8 vs. 17.1 years; $p=0.71$) and sterilisation (mean age 16.8 vs. 18.1 years; $p=0.33$) controls.

15.3.5.2 Exercise

Table 29 – History of any vigorous exercise by Centre

Centre	No vigorous exercise	Some vigorous exercise	n	Missing	Frequency (%)
Barcelona	33	74	107	0	69.2
Boston	9	67	76	0	88.2
Campinas	28	58	86	0	67.4
Dublin	4	41	45	1	89.1
Guangzhou	145	149	294	0	50.7
Ibadan	39	42	81	0	51.9
Leuven	10	94	104	0	90.4
Oxford	36	186	222	2	83.0
Rome	30	90	120	10	69.2
Sao Paolo	10	77	87	0	88.5
Shanghai	93	43	136	0	31.6
Siena	19	6	25	0	24.0
Others	2	20	22	0	90.9
Total	458	947	1,405	13	66.8

On average, 66.8% (95% CI 64.3-69.2%) had done some vigorous exercise in the past (Table 30). In the three months preceding participation in the study, however, only 25.9% (n=367) of women did regular ('once a week', 'few times a week' or daily) vigorous exercise. Amongst these women, 34.8% (95% CI 29.9-39.8%) reported that at certain times, they had avoided vigorous exercise because of pelvic pain and 46.9% (95% CI 41.7-52.1%) because of having a period (not shown).

Table 30 - Centre-wise comparisons for proportions of women who reported regular exercise

Centre	Proportion of women reporting regular vigorous exercise in Centre	Proportion of women reporting regular vigorous exercise in remainder population	Pearson's χ^2 p-value
Barcelona	36.1	39.6	0.57
Boston	55.4	38.1	0.006
Campinas	40.7	39.2	0.82
Dublin	48.7	38.9	0.22
Guangzhou	24.7	42.0	<0.001
Ibadan	22.0	40.1	0.020
Leuven	45.7	38.6	0.18
Oxford	49.5	36.8	0.002
Rome	40.9	39.1	0.74
Sao Paolo	35.5	39.6	0.48
Shanghai	22.7	40.1	0.021
Siena	0.0	39.6	0.033
Others	52.6	39.0	0.23

Women with endometriosis (27.0%; n=201) were not more or less likely than symptomatic controls (25.2%; n=148) to have reported doing regular vigorous exercise in the last three months ($p=0.86$). Similarly, they were not more or less likely than sterilisation controls (20.9%; n=18) to have reported doing regular vigorous exercise in the last three months ($p=0.54$).

15.4 Principal component analysis

The first four components on principal component analysis displayed eigenvalues greater than 1. Therefore, only these components were retained for rotation. Combined, components 1-4 accounted for 52% of the total variance. Questionnaire items and corresponding factor loadings are presented in Table 31 below.

Table 31 - Rotated factor pattern for reasons for undergoing surgery in GSWH

Variable	Factor 1	Factor 2	Factor 3	Factor 4	Uniqueness
Pelvic pain	0.6765	0.3161	0.1043	0.0638	0.4275
Pelvic mass	-0.1207	0.3684	0.0792	0.4185	0.6683
Dysmenorrhoea	0.8306	0.1335	0.0478	0.0491	0.2876
Menorrhagia	0.7961	0.0274	0.0706	0.0307	0.3596
No subfertility	-0.0496	0.0697	0.0139	-0.7892	0.3697
Ovarian cyst	0.1757	0.1443	0.0476	0.596	0.5908
Dyspareunia	0.6016	0.3009	0.1581	0.053	0.5197
Painful bowel opening	0.3297	0.6991	0.1566	0.0214	0.3776
Bloody bowel opening	0.1319	0.7545	0.0296	-0.0058	0.4124
Bowel upset	0.4729	0.5414	0.1874	0.0257	0.4475
Painful urination	0.2185	0.2415	0.6385	-0.0315	0.4853
Bloody urine	0.0294	0.0773	0.6685	0.0488	0.5439
Other urinary problems	0.0982	0.077	0.6912	-0.0111	0.5066
Other problems	0.1254	-0.2605	0.412	0.1837	0.7129

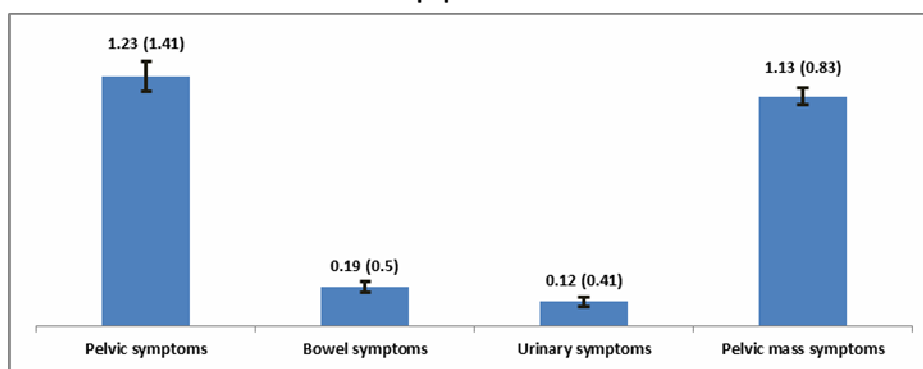
Using these criteria, four items were found to load onto the first component, which was labelled the “pelvic symptoms” factor. Two items also loaded onto the second component, which was labelled the “bowel symptoms” factor. Three items loaded onto the third component, which was labelled the “urinary symptoms” factor and three items loaded onto the fourth component, which was labelled the “pelvic mass” factor (Table 32).

Table 32 - Selected factors and loading variables

Factor 1 ("pelvic symptoms" factor)	Factor 2 ("bowel symptoms" factor)	Factor 3 ("urinary symptoms" factor)	Factor 4 ("pelvic mass" factor)
Pelvic pain	Painful bowel opening	Pain on passing urine	Pelvic mass
Dysmenorrhoea	Bloody bowel opening	Blood in urine	Ovarian cyst
Menorrhagia		Other urinary problems	Not subfertile
Dyspareunia			

As shown in Figure 29, women in the study population presented with an average of 1.2 (SD 1.4) pelvic, 0.19 (SD 0.5) bowel, 0.12 (SD 0.4) urinary and 1.1 (SD 0.83) pelvic mass symptoms.

Figure 29 - Mean (SD) number of symptoms in symptom groups reported by women in the study population



As shown in Table 33, women in Boston (2.4 vs. 1.2 symptoms; $p<0.001$), Oxford (1.7 vs. 1.1 symptoms; $p<0.001$), Sao Paolo (2.5 vs. 1.1 symptoms; $p<0.001$) and Siena (2.2 vs. 1.2 symptoms; $p=0.002$) presented with significantly more 'pelvic' symptoms than the average woman in the remainder of the study population; women in Guangzhou (0.5 vs. 1.4 symptoms; $p<0.001$), Ibadan (0.7 vs. 1.3 symptoms; $p=0.001$) and Shanghai (0.6 vs. 1.3 symptoms; $p<0.001$) presented with significantly fewer 'pelvic' symptoms. Women in Boston (0.4 vs. 0.2 symptoms; $p<0.001$), Dublin (0.4 vs. 0.2 symptoms; $p<0.001$), Leuven (0.3 vs. 0.2 symptoms; $p=0.024$), Rome (0.3 vs. 0.2 symptoms; $p=0.037$) and Sao Paolo (0.4 vs. 0.2 symptoms; $p<0.001$) presented with significantly more 'bowel' symptoms than the average woman in the remainder of the study population; women in Campinas (0.1 vs. 0.2 symptoms; $p=0.033$), Guangzhou (0.1 vs. 0.2 symptoms;

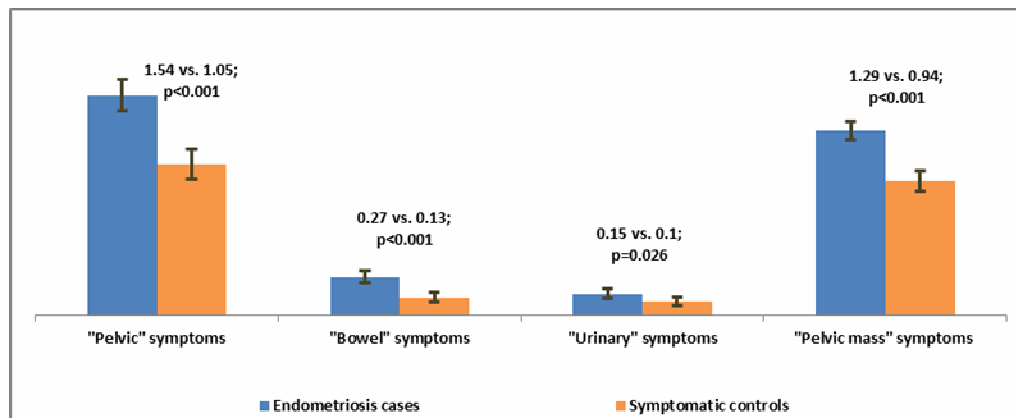
p<0.001), Ibadan (0.0 vs. 0.2 symptoms; p=0.001) and Shanghai (0.1 vs. 0.2 symptoms; p=0.006) presented with significantly fewer 'bowel' symptoms. Women in Boston and Sao Paolo (both 0.3 vs. 0.1 symptoms; p<0.001) presented with significantly more 'urinary' symptoms than the average woman in the remainder of the study population; women in Guangzhou (0.0 vs. 0.1 symptoms; p<0.001), Ibadan (0.0 vs. 0.1 symptoms; p=0.036) and Shanghai (0.0 vs. 0.1 symptoms; p=0.028) presented with significantly fewer 'urinary' symptoms. Finally, women in Boston (1.4 vs. 1.1 symptoms; p<0.001), Rome (1.3 vs. 1.1 symptoms; p=0.002), Sao Paolo (1.4 vs. 1.1 symptoms; p<0.001), Shanghai (1.6 vs. 1.1 symptoms; p<0.001) and Siena (1.6 vs. 1.1 symptoms; p=0.002) presented with significantly more 'pelvic mass' symptoms than the average woman in the remainder of the study population; women in Campinas (0.8 vs. 1.1 symptoms; p<0.001), Leuven (0.7 vs. 1.2 symptoms; p<0.001), Ibadan (0.3 vs. 1.2 symptoms; p<0.001) and Oxford (1.0 vs. 1.2 symptoms; p=0.028) presented with significantly fewer 'pelvic mass' symptoms.

Table 33 - Centre-wise comparisons of number of symptoms in symptom groups

Centre	Mean (SD) number of Pelvic symptoms			Mean (SD) number of Bowel symptoms			Mean (SD) number of Urinary symptoms			Mean (SD) number of Pelvic mass symptoms		
	Centre	Remainder population	p-value	Centre	Remainder population	p-value	Centre	Remainder population	p-value	Centre	Remainder population	p-value
Barcelona	1.3	1.2	0.85	0.2	0.2	0.76	0.1	0.1	0.41	1.3	1.1	0.065
Boston	2.4	1.2	<0.001	0.4	0.2	<0.001	0.3	0.1	<0.001	1.4	1.1	0.01
Campinas	1.2	1.2	0.84	0.1	0.2	0.033	0.1	0.1	0.82	0.8	1.1	<0.001
Dublin	1.5	1.2	0.18	0.4	0.2	<0.001	0.1	0.1	0.88	0.9	1.1	0.11
Guangzhou	0.5	1.4	<0.001	0.1	0.2	<0.001	0.0	0.1	<0.001	1.1	1.1	0.88
Ibadan	0.7	1.3	0.001	0.0	0.2	<0.001	0.0	0.1	0.036	0.3	1.2	<0.001
Leuven	1.4	1.2	0.16	0.3	0.2	0.024	0.1	0.1	0.95	0.7	1.2	<0.001
Oxford	1.7	1.1	<0.001	0.2	0.2	0.079	0.1	0.1	0.42	1.0	1.2	0.028
Rome	1.2	1.2	0.82	0.3	0.2	0.037	0.2	0.1	0.081	1.3	1.1	0.002
Sao Paolo	2.5	1.1	<0.001	0.4	0.2	<0.001	0.3	0.1	<0.001	1.4	1.1	<0.001
Shanghai	0.6	1.3	<0.001	0.1	0.2	0.006	0.0	0.1	0.028	1.6	1.1	<0.001
Siena	2.1	1.2	0.002	0.4	0.2	0.088	0.1	0.1	0.64	1.6	1.1	0.002
Others	1.4	1.2	0.55	0.3	0.2	0.23	0.0	0.1	0.41	1.2	1.1	0.76

As shown below in Figure 30, compared to symptomatic controls, women who were diagnosed with endometriosis at laparoscopy presented with significantly more symptoms in all symptom categories.

Figure 30 - Mean number of symptoms presented by women by endometriosis status



15.5 Unconditional multivariate logistic regression

Age and menstrual duration were not associated with endometriosis on univariate analysis but were included in the model as they were deemed to be clinically relevant. Owing to important centre-wise differences in the distribution of most variables, 'site' (specified as a categorical variable with the 13 centres as the categories - *see paragraph 14.1*) was considered an important covariate and included in the multivariate regression model. The Hosmer-Lemeshow test (p=0.8218) suggests a good model fit (Figure 31).

Figure 31 - Hosmer-Lemeshow test of goodness of fit

Logistic model for endo_surgsy. goodness-of-fit test						
(Table collapsed on quantiles of estimated probabilities)						
Group	Prob	obs_1	Exp_1	Obs_0	Exp_0	Total
1	0.1527	3	2.7	24	24.3	27
2	0.2547	6	5.5	20	20.5	26
3	0.3646	8	7.9	18	18.1	26
4	0.4444	13	10.6	13	15.4	26
5	0.5300	11	12.8	15	13.2	26
6	0.6108	12	15.6	15	11.4	27
7	0.6817	17	16.9	9	9.1	26
8	0.7625	19	18.9	7	7.1	26
9	0.8458	23	21.1	3	4.9	26
10	0.9551	23	23.1	3	2.9	26

number of observations =	262
number of groups =	10
Hosmer-Lemeshow chi2(8) =	4.38
Prob > chi2 =	0.8218

As shown in Appendix 2, unconditional multiple logistic regression with endometriosis status as binary outcome variable suggested that the following characteristics were significantly associated with endometriosis: gravidity (adjusted OR 0.36; $p=0.01$), pelvic pain severity (adjusted OR 1.19; $p=0.04$) and non-endometriotic adhesions (adjusted OR 0.30; $p=0.001$).

As shown in Table 34, only pelvic pain severity was independently associated with diagnostic delay in addition to its association with endometriosis in multivariate analysis. Pelvic pain severity was independently associated with physical HRQoL while gravidity and pelvic pain severity were independently associated with the mental aspect of HRQoL. Finally, only pelvic pain severity was independently associated with overall work productivity impairment. These variables will subsequently be treated as potential confounders of the association between endometriosis and the key outcomes and included in further analyses as appropriate.

Table 34 - Univariate association of key variables with key study outcomes

Characteristics associated with endometriosis on multivariate analysis	Diagnostic delay		Health-related Quality of Life (HRQoL)				Work productivity impairment	
			Physical HRQoL		Mental HRQoL			
	Regression coefficient	P value	Regression coefficient	P value	Regression coefficient	P value	Regression coefficient	P value
Gravidity	0.19	0.42	-0.19	0.37	0.73	0.002	-1.03	0.36
Pelvic pain severity	1.09	<0.001	-1.4	<0.001	-1.14	<0.001	5.9	<0.001
Non-endometriotic adhesions	-0.42	0.58	0.11	0.88	-0.6	0.49	-5.0	0.11

16 Discussion

This study found a diagnostic incidence of endometriosis in all women of 52.5% (95% CI 49.0-56.1%); in asymptomatic women who underwent sterilisation, the diagnostic incidence was 14.3% (95% CI 6.5-22.1%). The incidence or prevalence of endometriosis reported in any population depends largely on its characteristics, with rates being generally higher in symptomatic and lower in asymptomatic women. The rate of 52.9% reported in this study for women with dysmenorrhoea is consistent with the range of 40-60% reported in the literature;

similarly for the rate of 14.3% (95% CI 6.5-22.1%) in subfertile women with the 4-43% reported in the literature [179,180]. There are a number of reasons adduced for the observed variations in diagnostic rates or prevalence of endometriosis across studies and populations. These include differences in diagnostic thresholds and methods, differences in child bearing age across populations, surgeon's training, and completeness or thoroughness of investigation [181]. This study, however, found a wide range of diagnostic incidence rates despite a uniform set of entry criteria into the study and participation of experienced clinicians; this possibly reflecting a residual influence of varying thresholds for, and paths leading to diagnostic laparoscopy across the participating centres.

As reported in the majority of previous studies [182,183], there was no correlation between disease stage and the severity of dysmenorrhoea, CPP or dyspareunia, reflecting the position that rASRM staging of endometriosis does not correspond well with interference with physiological processes in the disease [183]. Although the study by Vercellini et al. [185] found an association between disease stage and severity of dysmenorrhoea and non-menstrual pain, the point estimates of the odds ratios were very close to unity and thus do not significantly alter the position that endometriosis symptoms do not reflect disease stage. Although the reason for the lack of correlation between symptom severity and disease stage is not very clearly established, it is thought that deep implant location and the presence of pelvic adhesions may be more important determinants of symptom severity than disease stage judged using conventional criteria [186]. In this study, deep endometriosis (peritoneal or ovarian), but not adhesions, predicted average severity of dysmenorrhoea and dyspareunia. Another possible explanation which has been offered for the lack of correlation between symptom severity and disease stage is the variation in metabolic activity of endometriotic implants, as those that produce large amounts of prostaglandins may be early implants with increased numbers of functional glands present in them [187].

Most women in the study population were in the 32-38 years age group and the average age of the study population was 33.0 years (SD 6.3), ranging from an average of 30.8 years (SD 6.1) for women in Guangzhou to 36.4 years (SD 5.5) for those in Siena. Although women with endometriosis were not different in age to symptomatic controls, they were significantly younger than sterilisation controls (32.5 vs. 37.2 years; $p < 0.001$). The older age of sterilisation controls is almost certainly due to the fact that most women are being sterilised after childbearing, most likely later in life. Amongst women who had endometriosis, those who had moderate-severe endometriosis were significantly older than those with minimal-mild endometriosis (33.1 vs. 32.2 years; $p = 0.045$). The finding in this study of a lack of association of between endometriosis and age is consistent with those of some previous studies. More specifically, in one study of 206 symptom-free parous Norwegian women (average age 37 years), there was no association between age of women and risk of endometriosis [188].

Ethnicity was associated with the risk of endometriosis after multivariate adjustment for key demographic and clinical variables including site, age, education and marital status ($p = 0.020$). There was no difference in the proportion of White women in the endometriosis and control groups but the endometriosis group had significantly fewer Black women (7.0 vs. 10.6%; $p = 0.015$). Other studies that have reported an association of ethnicity with endometriosis have either suggested a higher risk in White women compared to Black and Asian women [12] or reported a higher rate of occurrence in Asian compared to White women [69,189,190]. The study by Miyazawa [190] was a retrospective analysis of all hospital admissions and was unadjusted for age and socioeconomic status, while Arumugam & Templeton [189] in their study compared subfertile women undergoing diagnostic laparoscopy in Malaysia and Scotland; neither had an appropriate control group nor controlled for the effect of relevant potential confounders. Adjustment for potential confounders such as age, socioeconomic status, co-morbidity, infertility

and parity is crucial in determining if ethnicity/race has a genuine influence on endometriosis risk. Indeed a strong argument has been put forward that socioeconomic status and differential access to healthcare by Caucasian and Asian or Black women largely account for observations of any association between race/ethnicity and endometriosis risk observed in some studies [71]. This study takes account of socioeconomic status by proxy of educational attainment and confirms an association between endometriosis and ethnicity.

Certain occupational exposures associated with being in some form of employment are linked with increased endometriosis risk in the literature but it is not clear that occupational exposure, measured directly or by proxy of employment status, increases endometriosis risk. In this study, employment status was not associated with the risk of endometriosis. In one case-control study of Lebanese women, occupational status (classified as homemaker vs outside employment) was not associated with endometriosis risk when educational attainment (proxy for socioeconomic status) was adjusted for [191]. Where an increased risk of endometriosis with employment status is reported in the literature, it is theoretically based on occupational exposure to certain substances, principally dioxins and organochlorine compounds. This association however remains controversial because most of those studies measure body burdens of these substances simultaneously with disease status and are thus unable to make genuine causal inferences [192-194]. Other compounds or factors that have been implicated in the reported increased risk of endometriosis associated with occupational exposure include formaldehyde, chemical dusts, organic solvents, video display units and the circadian rhythm disruptions associated with night- or evening-shift work [195-198]. This study suggests there is no association between endometriosis risk and employment status, but it is not possible to draw any reliable conclusions on the relationship between endometriosis risk and specific occupational exposures, although the latter is itself not convincingly associated with endometriosis risk [81]. It is worth noting however that this study only represents a snapshot in time of the association between employment and

endometriosis. Consequently, it is unable to determine the longitudinal relationships vital to interpreting the association between employment and endometriosis, these principally being whether women were unable to work because of chronic symptoms or whether specific occupational exposures amongst those who worked contributed to their developing endometriosis.

As reported in a number of other studies, this study found on univariate analysis that the endometriosis group had attained higher educational qualifications compared to symptomatic and sterilisation controls [39,82,109] but on multivariate adjustment, there was no association between endometriosis and educational attainment. Without controlling for factors that could explain univariate associations between endometriosis and education (such as factors related to onset of childbearing), it is impossible to establish reliably a relationship between educational attainment and endometriosis risk. In the study by Hemmings et al. [40], the association of educational attainment and endometriosis risk was assessed after adjustment for subfertility, age at first pregnancy and interval between menarche and first pregnancy. The authors found an association between higher educational attainment and endometriosis risk, which they attributed to socioeconomically determined differential access to health care. In this study however, after adjusting for parity, gravidity, subfertility and age at menarche in addition to other key variables, this association could not be confirmed. Furthermore, when this analysis was restricted to centres where healthcare was predominantly government-funded and where differential access by socioeconomic status would thus have been minimal (Barcelona, Oxford, Rome and Siena), there was no statistically significant association between endometriosis and educational attainment (unadjusted OR 0.92; $p=0.68$), suggesting that factors related to childbearing (such as delayed childbearing associated with educational attainment) may explain the association between education and endometriosis risk reported elsewhere.

As in a number of other studies [73,74,77,101], there was no association between marital status and endometriosis risk after multivariate adjustment for other relevant covariates. Most previous studies do not control for important characteristics that may confound the relationship. For example, it is conceivable that amongst women who suffer endometriosis, pelvic pain associated with sexual intercourse may interfere with establishing marital relationships. Furthermore, in addition to subfertility clearly affecting childbearing in established marital relationships, the fear of subfertility itself may hinder a woman's self-efficacy in establishing such a relationship. Consequently, any attempt to describe or quantify the association of endometriosis with marital status should ideally account for the influence of the nature and severity of presenting symptoms (or reason for diagnostic investigation) as well as for factors such as parity. In this study, after accounting for parity, symptoms for which women underwent laparoscopy, number of symptoms and severity of pelvic pain, marital status was not associated with endometriosis risk.

Younger age at menarche was not associated with an increased risk of endometriosis after multivariate adjustment. The theory suggests that the occurrence of endometriosis is related to both retrograde menstruation and oestrogen exposure. A woman with earlier menarche would presumably have a greater likelihood of retrograde menstruation and more ovulations and menstruations over her reproductive lifespan [199]. The literature evidence on the relationship between menarche age and endometriosis risk is however inconclusive. For example, while some authors suggest there is no relationship [68,200,201] or even a lesser risk with younger age at menarche [39], other more recent studies suggest that endometriosis is associated with younger age at menarche [8,43,202]. Most of these studies are however limited by sample size and fail to control for important potential confounders. For example, women with earlier age at menarche are more likely to have dysmenorrhoea. When account was taken of the presence and severity of pelvic pain (chronic pelvic pain, dysmenorrhoea and dyspareunia) in this study, the putative relationship between endometriosis and early age at menarche could not be confirmed.

Moreover, the clinical significance of any association between earlier age at menarche and endometriosis risk is uncertain although it has been suggested that later age at menarche may be used to guide diagnostic and therapeutic strategies if other symptoms point to endometriosis as a possible diagnosis [202].

In this study, after accounting for key covariates including parity, cycle length, menstrual duration, symptom type and pelvic pain severity, there was no association between use of hormonal contraception in the past three months and endometriosis. The literature on the influence of hormonal contraceptive use on endometriosis risk suggests that current and recent use of hormonal contraceptives are protective, but past or ever use are not and may indeed increase the risk [70,109,203]. The explanation for this observation may be that hormonal contraceptives reduce oestrogen production, induce endometrial atrophy and reduce menstrual flow, all of which are factors that should reduce the risk of endometriosis. It has also been suggested that hormonal contraceptive use suppresses the symptoms of endometriosis, which then emerge after use has been stopped. The difficulty with establishing the relationship conclusively lies in the fact that many women with symptoms suggestive of endometriosis are placed on oral contraceptives early in their care-seeking journey to control their symptoms; consequently without applying rigorous study methods, it is difficult to establish temporality and causality. In this study, when analysis was restricted to asymptomatic women who were being sterilised, there was no association between hormonal contraceptive use and endometriosis risk (unadjusted OR 0.74; $p=0.64$ – *not shown in main results*). The small size of the group of asymptomatic women undergoing sterilisation ($n=77$; *more detail in chapter 5*) may however have affected the power of the analysis to detect an association.

Menstrual cycle length was not associated with endometriosis risk in multivariate analysis. Increasing menstrual cycle length might imply that a woman is exposed to fewer ovulations and

menstrual cycles over her reproductive lifespan, thus reducing her risk of endometriosis. A positive relationship between endometriosis and shorter cycle lengths (usually <27 days) has been reported previously [8,72,78] but an important difficulty with firmly establishing the relationship lies in the fact that these studies have assessed short cycle lengths reported after the onset of symptoms of endometriosis. In their discussion, Arumugam & Lim [78] consider the growing body of evidence suggesting that short menstrual cycle lengths may actually be a consequence rather than a precursor of endometriosis. They cite abnormal luteal function resulting from an insensitivity of the ovary to the midcycle LH surge. Consequently, to firmly establish the temporality which should underpin a valid relationship between shorter cycle lengths and endometriosis risk, pre-symptom onset cycle length should be ascertained. Indeed, Treloar et al. [202] in a case-control study of 268 Australian women with moderate-severe endometriosis and 244 women without endometriosis found no relationship between pre-symptom onset menstrual cycle length and endometriosis. Similar to the findings on cycle length and endometriosis risk, this study did not confirm the conclusion in other reports [2,69] that endometriosis risk may be increased by longer duration of menstrual periods. Again, the reported association may reflect a consequential rather than a causal effect, i.e. endometriosis leading to longer duration of menstrual periods, rather than longer menstrual duration leading to endometriosis. There is, however, little support in the literature for this view.

This study reports a significant inverse relationship between endometriosis and gravidity after multivariate adjustment (adjusted OR 0.35; $p=0.001$). This finding has been consistently reported in a number of previous studies [43,69,203,204] and is in keeping with the concept that reduced exposure to oestrogens would reduce endometriosis risk. A common limitation of a number of these studies, however, is their lack of adjustment for subfertility since subfertile women, by definition, are less likely to achieve pregnancy and are independently more likely to have endometriosis. This study takes account of subfertility, parity and other key covariates and

confirms that there is a valid inverse relationship between gravidity and reduced endometriosis risk. However, when account was taken of gravidity, subfertility and other key covariates, parity was not found to be associated with endometriosis risk. Theoretically, low parity might be expected to increase endometriosis risk since menstruating women with cervical os diameters less than 2.0mm have an increased risk for developing endometriosis [48,205]. Further, nulliparous women may not have the benefit of cervical dilation associated with labour and delivery and may therefore be prone to retrograde menstruation compared to parous women [4]. Indeed, in a previous case-control study of multiparous women diagnosed with endometriosis during sterilisation, higher parity was associated with reduced endometriosis risk [69]. Another case-control study in Italy comparing surgically-confirmed endometriosis cases with women admitted for acute conditions at the same hospital found a similar protective effect of parity on endometriosis risk but the authors only adjusted for age and not for other key variables such as gravidity [84]. However, any observed association between endometriosis risk and parity may be explained by the long periods of amenorrhoea and consequent reduced exposure to oestrogen associated with gravidity, rather than any intrinsic protective effect offered by factors specifically associated with parity. Indeed in this analysis, we found that gravidity principally accounted for the univariate association of parity with endometriosis risk.

This study shows that women with endometriosis have lower average BMI than symptomatic (22.5 vs. 23.4 kg/m²; p<0.001) and sterilisation (22.5 vs. 25.2 kg/m²; p<0.001) controls, are less frequently obese than symptomatic (10.1 vs. 17.7%; p<0.001) and sterilisation (10.1 vs. 17.4%; p=0.038) controls, and are less frequently overweight than sterilisation controls (14.2 vs. 30.2%; p<0.001). After multivariate adjustment for relevant covariates, this study found that for every unit increase in BMI (kg/m²), there was an approximate 3-12% decrease in the likelihood of being diagnosed with endometriosis. BMI was also significantly associated with endometriosis disease severity (OR 0.94; p<0.001). A number of earlier studies on endometriosis and BMI did not

identify this inverse relationship between BMI and endometriosis [43,69,101,122] but they may have been limited by sample size. Later studies which examined the relationship with relatively larger sample sizes have reported conflicting findings: one large epidemiological study of women in Montreal [40] found no significant association between endometriosis and BMI but Parazzini et al. [107] found a similar inverse association as reported in this study. The Montreal study by Hemmings et al. only adjusted for the effect of age and it is possible that substantial underestimation of effect could have occurred as a result of incomplete adjustment for relevant covariates. For example, assuming that BMI was inversely related to endometriosis risk, failure to adjust for a variable that was either positively (such as age) or negatively associated (such as physical exercise and fertility) with both BMI and endometriosis would result in negative confounding significant enough to nullify an association between the two [205]. In this study, careful attention is given to adjusting for the variables that are potential confounders of the relationship. More specifically, age was adjusted for since BMI increases with age, as does endometriosis risk. Although physical exercise is reported in the literature to be inversely associated both with endometriosis risk [66,79,81,109] and BMI, it was not included in the main multivariate regression model as the association with endometriosis risk was not evident in univariate analysis. However, its inclusion as a covariate in the main model did not alter the significant inverse association between BMI and endometriosis. Severe pelvic pain, a feature of endometriosis, can cause loss of appetite and failure to account for its effect may result in positive confounding of the BMI-endometriosis relationship. Subfertility could negatively confound the BMI-endometriosis relationship as it is (independently) inversely related with BMI [207] as well as endometriosis risk. Finally, women tend to gain weight in association with childbearing and adjustment for parity is important in defining the relationship between BMI and endometriosis risk. Having accounted for the above factors, it is clear that low BMI is significantly associated with increased endometriosis risk. It is however possible that the temporal relationship between low BMI and endometriosis is the reverse, such that women with

endometriosis become less obese or overweight as a result of their illness. Although this is possible as women's symptoms may cause a loss of appetite resulting in reduced BMI (assuming other variables are held constant), the direction of effect is difficult to predict since their pain may similarly limit physical activity and result in increased BMI (assuming other variables are held constant). Hediger et al. [39] further confirmed that this inverse relationship between BMI and endometriosis risk was present not only at the time of diagnosis but also historically. Furthermore, Missmer et al (12) in a large prospective study of premenopausal women who were part of the Nurses' Health Study II cohort found an inverse association between BMI at age 18 years and diagnostic incidence of endometriosis after adjusting for age, race and parity. The explanation for the lower BMI seen in endometriosis is not immediately obvious but as hinted earlier, it could be a result of dietary habits - one study [107] found a positive correlation between beef or ham intake and the risk of endometriosis but no investigation has estimated total caloric intake in women with endometriosis. Some authors have postulated that genetic factors determining endometriosis are linked to those determining BMI [121] but this remains to be proven.

In addition to body size, endometriosis has been linked with a number of other personal physical characteristics including natural red hair colour and skin moles. The reported link between natural red hair colour and endometriosis in previous studies [126] was not confirmed in this study. Missmer et al. similarly found no such association but suggested that the relationship if present, might differ by infertility status [123]. As Kvaskoff et al. [208] noted in their population, it is possible that the small proportion of women with natural red-hair colour in this study (37 out of 1,418 women - 2.6%, cf. 1.7% in Kvaskoff's study) may have restricted the ability to observe this effect. In 2009, Kvaskoff et al. [208] reported a positive association between the number of naevi (skin moles) and endometriosis risk in a large nested case-control study of over 90,000 French women who self-reported endometriosis. This study confirms their findings after adjusting for

age, body mass index, menarche, menstrual cycle length, hair colour and ethnicity. It is thought that a strong genetic basis explains the association, particularly specific susceptibility genes (specifically tumour suppressor genes) associated with melanoma. Furthermore, moles result from multiplication of skin melanocytes, a process which is under the influence of sex hormones including oestrogens [209].

In summary, this study recruited 1,418 women out of an eligible 1,669 and found 52.5% of them to have endometriosis. The presence of characteristics putatively associated with, as well as the diagnostic incidence of, endometriosis varied across the centres although a distinct pattern was not evident. Gravity, pelvic pain severity and non-endometriotic adhesions were the key variables that emerged as potential confounders of an association between endometriosis and key outcomes of interest in this study. Consequently, they will be adjusted for, as appropriate, in analyses of the impact of endometriosis in subsequent chapters of this thesis.

CHAPTER 5

**SYMPTOMS ASSOCIATED WITH
ENDOMETRIOSIS**

17 Introduction

In chapter 4, the study population was described in some detail in respect of the diagnostic incidence of endometriosis and the distribution of key sociodemographic, clinical, physical and lifestyle attributes known or thought to be associated with endometriosis. There were 2 key sets of comparison groups on which those characteristics were described: 1) centres - comprising 13 centres, including an 'other' centre derived from combining all 4 of the original 16 centres where less than 25 women were recruited); and 2) disease outcome groups - endometriosis, symptomatic controls and sterilisation controls.

The frequency or distribution of characteristics across the study population and for each centre was described. Next, centres were compared, each one to the remainder of the study population, on the frequency or distribution of characteristics, using appropriate statistical testing methods. The disease outcome group categories were then compared using appropriate statistical testing methods. Variables associated with endometriosis on univariate analysis were included in an unconditional logistic regression model. Variables significantly associated with endometriosis on multivariate analysis ($p < 0.05$) were then assessed for independent association with diagnostic delay, HRQoL and work productivity impairment. Variables associated with endometriosis after multivariate adjustment and with the outcome independently were deemed important and included in subsequent analyses of that outcome.

This chapter builds on the analyses in chapter 4 and focuses on a detailed description of the symptoms that led to women's laparoscopy. More specifically, there are two focused research questions that are answered in the analyses in this chapter:

- How are the symptoms for which women underwent laparoscopy distributed across the study population?

- How does each centre compare to the remainder of the study population in respect of the frequency of each symptom?

18 Methods

18.1 Comparison groups

As in chapter 4, analyses of the symptoms for which women underwent laparoscopy are conducted according to two main outcome groups: centre of recruitment and disease outcome groups. The variable 'centre' is re-categorised so that the centres at which fewer than 25 women were recruited (Buenos Aires, San Francisco, Palo Alto and Washington DC) are grouped together into an "Other" category. Disease outcome groups include: 1) women with endometriosis; 2) symptomatic controls; and 3) laparoscopic sterilisation controls. The endometriosis group includes all women, regardless of indication for surgery, with endometriosis on laparoscopy; the symptomatic control group includes those without endometriosis who were investigated for symptoms; the laparoscopic sterilisation group includes those without endometriosis, who underwent sterilisation (who may or may not have had symptoms). For women with endometriosis, disease severity is described as "minimal-mild endometriosis" (rASRM stages I+II) or "moderate-severe endometriosis" (rASRM stages III+IV) [33].

18.2 Variable description

18.2.1 General

All women recruited in the study underwent laparoscopic surgery either on account of symptoms or for sterilisation. Some women who underwent sterilisation may also have reported one or more symptoms. If such women had endometriosis on laparoscopy, they are included in the endometriosis group, and if not, in the sterilisation control group.

For each symptom, the mean age of women at onset is reported. The age of each woman at symptom onset is defined as the earliest age at onset of any of the symptoms for which she underwent surgery. The mean of the ages at symptom onset for all women in the study population and in each centre is presented.

18.2.2 Pelvic pain with/without subfertility

Pelvic pain and subfertility are considered major symptoms of clinical importance and the study population is thus described by the frequency of these symptoms, both in mutual exclusion, and in combination. Pelvic pain refers to any or a combination of chronic pelvic pain (CPP), dysmenorrhoea (painful periods) and dyspareunia (pain during or in the 24 hours after sexual intercourse). The categories in this analysis thus includes: 1) pelvic pain without subfertility; 2) pelvic pain with subfertility; 3) subfertility without pelvic pain, and 4) no pelvic pain or subfertility.

18.2.3 Pelvic pain severity

Pelvic pain severity was defined as the mean numerical rating score (on a 1-10 scale) assigned by the women to the severity of their pelvic pain. The study population mean pelvic pain severity rating is described for each of chronic pelvic pain, dysmenorrhoea and dyspareunia (during and in the 24 hours after intercourse). An average pelvic pain severity rating is then obtained as the average of the reported 'average pain severity' scores for each woman on the following: 1) dysmenorrhoea, 2) CPP, and 3) dyspareunia during and in the 24 hours after intercourse.

18.2.4 Number of symptoms

The description of presenting complaints or reasons for undergoing laparoscopy in the study population is also based on the number of symptoms for which women underwent laparoscopy. As described in chapter 4, some symptoms (e.g. pelvic pain and dysmenorrhoea) are strongly

correlated and for this reason, principal component analysis is used to identify underlying patterns.

18.3 Statistical Methods

18.3.1 Frequency of symptoms

The proportions of women with symptoms (including pelvic pain $\pm$ subfertility and other individual symptoms) are calculated for the study population and for each centre

18.3.2 Centre-wise comparisons

To further describe the presenting symptoms for which women underwent laparoscopy, the proportions of women with those symptoms at each centre are compared with the proportions for the remainder of the study population, with Pearson's χ^2 test for differences in proportions presented.

18.3.3 Comparisons across disease outcome groups

Disease outcome groups are compared for differences in the proportions of women reporting specific symptoms using the Pearson's χ^2 test for differences in proportions.

18.3.4 Principal component analysis

As some symptoms (e.g. pelvic pain and dysmenorrhoea) are strongly correlated, principal component analysis will identify underlying patterns. Using the principal axis method [178] with prior communality estimates of "1" and orthogonal rotation, factors (symptom patterns) are extracted and those with eigenvalues > 1 are retained. A symptom is deemed to load onto a factor if its component loading is > 0.40 for that pattern and ≤ 0.40 for the others. The mean

number of individual symptoms within each factor is then compared across outcome groups; factors are used in multivariate models as necessary.

All analyses were done using Stata Release 11 (Stata Corporation, College Station, Texas, USA).

19 Results

19.1 Pelvic pain and subfertility

Table 35 below shows that 40.8% (n=578) of women in the study population underwent laparoscopy on account of pelvic pain (CPP, dysmenorrhoea or dyspareunia) without subfertility. One in 5 women (20.0%; n=284) underwent laparoscopy on account of having both pelvic pain and subfertility, while 14% (n=198) of women underwent laparoscopy because of subfertility without pelvic pain.

Table 35 - Pelvic pain and subfertility as reasons for laparoscopy

Centre	Pelvic pain, no subfertility		Pelvic pain and subfertility		Subfertility, no pelvic pain		N
	N	%	N	%	n	%	
Barcelona	58	54.2%	13	12.1%	2	1.9%	107
Boston	51	67.1%	15	19.7%	4	5.3%	76
Campinas	37	43.0%	17	19.8%	13	15.1%	86
Dublin	18	39.1%	14	30.4%	8	17.4%	46
Guangzhou	81	27.6%	35	11.9%	77	26.2%	294
Ibadan	12	14.8%	32	39.5%	31	38.3%	81
Leuven	27	26.0%	43	41.3%	21	20.2%	104
Others	10	45.5%	4	18.2%	3	13.6%	22
Oxford	101	45.1%	59	26.3%	25	11.2%	224
Rome	57	43.8%	18	13.8%	5	3.8%	130
Sao Paulo	60	69.0%	18	20.7%	1	1.1%	87
Shanghai	55	40.4%	9	6.6%	6	4.4%	136
Siena	11	44.0%	7	28.0%	2	8.0%	25
Total	578	40.8%	284	20.0%	198	14.0%	1,418

Centre-wise comparisons (Table 36) suggested that the distributions of the proportion of women who reported 'pelvic pain $\pm$ subfertility', 'subfertility without pelvic pain' and 'neither pelvic pain nor subfertility' differed between specific centres and the remainder of the study population in all

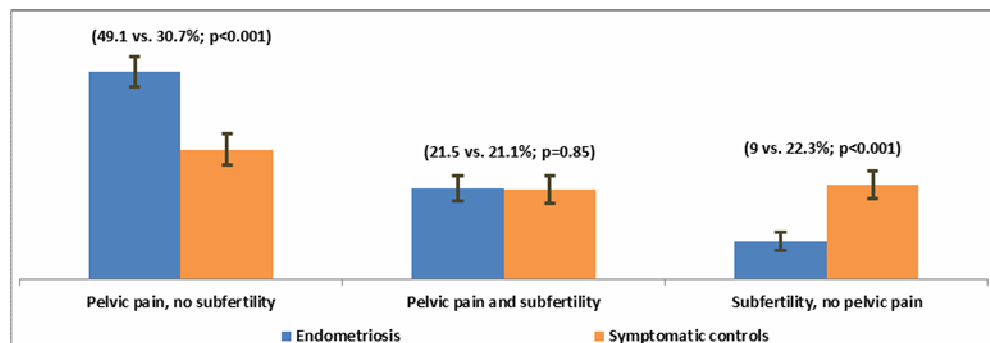
centres except Campinas (χ^2 $p=0.95$), Dublin (χ^2 $p=0.15$), Siena (χ^2 $p=0.64$) and 'Others' (χ^2 $p=0.93$).

Table 36 - Centre-wise comparisons for nature of symptoms presented by women

Centre	Proportion in centre (%)				χ^2 p value (centre vs. remainder of study population)
	Pelvic pain, no subfertility	Pelvic pain and subfertility	Subfertility, no pelvic pain	No pelvic pain, no subfertility	
Barcelona	54.2	12.2	1.9	31.8	<0.001
Boston	67.1	19.7	5.3	7.9	<0.001
Campinas	43.0	19.8	15.1	22.1	0.95
Dublin	39.1	30.4	17.4	13.0	0.15
Guangzhou	27.6	11.9	26.2	34.4	<0.001
Ibadan	14.8	39.5	38.3	7.4	<0.001
Leuven	26.2	41.8	20.4	11.7	<0.001
Oxford	45.3	26.5	11.2	17.0	0.004
Rome	49.1	15.5	4.3	31.0	0.003
Sao Paolo	69.0	20.7	1.2	9.2	<0.001
Shanghai	40.4	6.6	4.4	48.5	<0.001
Siena	44.0	28.0	8.0	20.0	0.64
Others	47.6	19.0	14.3	19.0	0.93

As shown in Figure 32, of the 745 women in whom endometriosis was diagnosed, 49.1% ($n=366$) underwent laparoscopy on account of pelvic pain without subfertility, compared to 30.7% ($n=180$) of symptomatic controls. Of those with endometriosis, (21.5%; $n=160$) underwent laparoscopy on account of having both pelvic pain and subfertility, compared to 21.1% ($n=124$) of symptomatic controls. Almost 1 in 10 (9.0%; $n=67$) women with endometriosis were investigated on account of subfertility without pelvic pain and this compared to 22.3% ($n=131$) of symptomatic controls.

Figure 32 – Comparison of pelvic pain and subfertility as reasons for laparoscopy by endometriosis status, with Pearson's χ^2 test p values for test of equality of the proportions



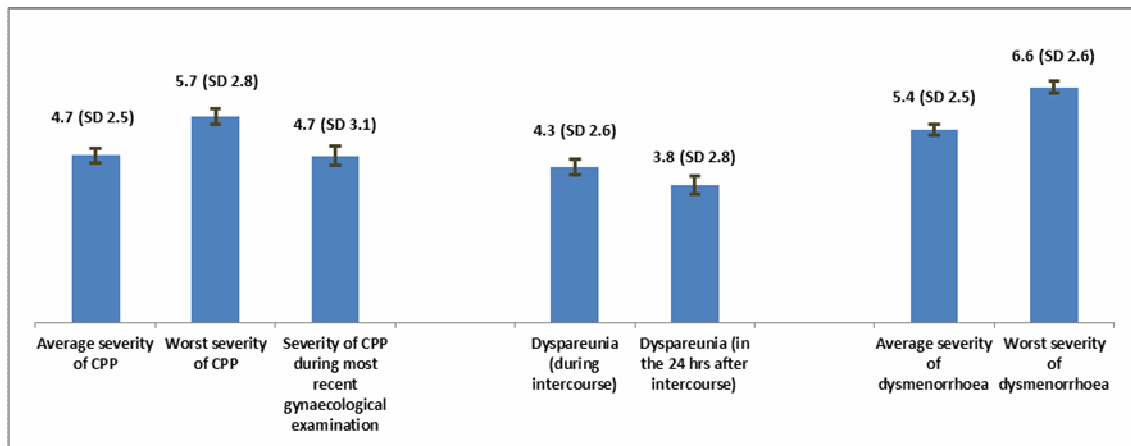
Amongst women with moderate-severe endometriosis, a significantly greater proportion presented with pelvic pain without subfertility than did so amongst those with minimal-mild endometriosis (50.6 vs. 40.8 %; $p=0.009$). Amongst women with moderate-severe endometriosis, a significantly lesser proportion however presented with pelvic pain and subfertility than did so amongst those with minimal-mild endometriosis (15.7 vs. 32.3 %; $p<0.001$). Similarly, amongst women with moderate-severe endometriosis, a significantly lesser proportion presented with subfertility without pelvic pain than did so amongst those with minimal-mild endometriosis (6.9 vs. 16.3 %; $p<0.001$) (not shown).

In unconditional logistic regression (including all symptom groups, i.e. pelvic pain without subfertility, pelvic pain and subfertility, subfertility without pelvic pain, and no pelvic pain nor subfertility), the adjusted odds of being diagnosed with endometriosis were greatest in women who underwent laparoscopy for pelvic pain without subfertility (OR 2.3; 95% CI 1.8-3.1) and for pelvic pain with subfertility (OR 1.8; 95% CI 1.3-2.4). Being investigated for subfertility without pelvic pain was not significantly associated with a diagnosis of endometriosis at laparoscopy (OR 0.7; 95% CI 0.5-1.0).

19.1.1 Severity of pelvic pain (dysmenorrhoea, dyspareunia and CPP)

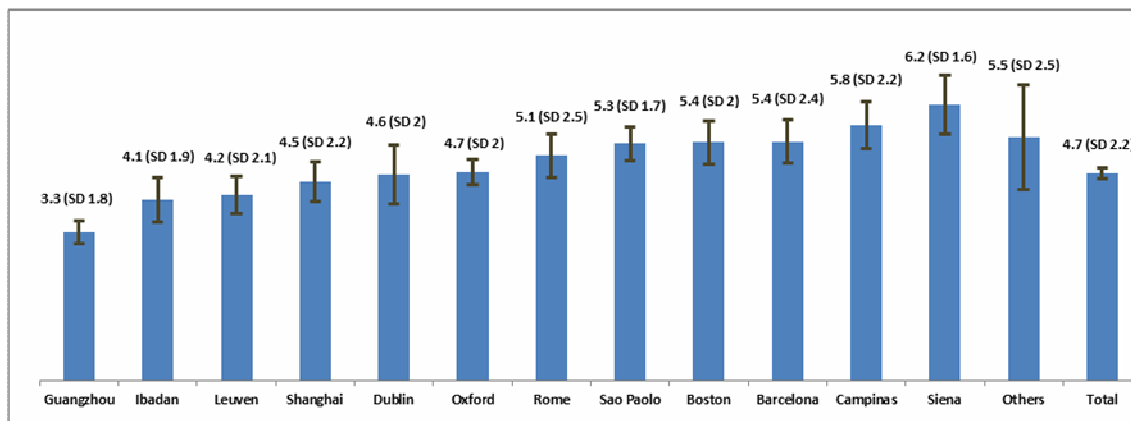
Figure 33 shows the subjective severity of forms of pelvic pain reported by women, suggesting that women rated dysmenorrhoea at its worst a mean 6.6 (SD 2.6) on the numerical rating scale.

Figure 33 - Mean severity (SD) of different types of pelvic pain reported by women in the study population



The mean subjective rating of the average severity of all pelvic pain in the study population was 4.7 (SD 2.2) and ranged from 3.3 (SD 1.8) in women at Guangzhou to 6.2 (SD 1.6) in women at Siena (Figure 34).

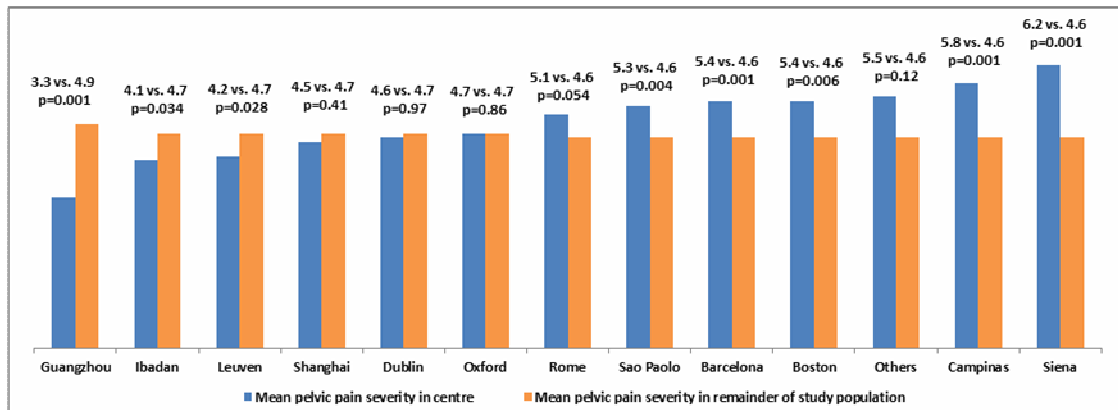
Figure 34 - Mean severity (SD) of pelvic pain (CPP, dysmenorrhoea and dyspareunia) by centre



Centre-wise comparisons (Figure 35) showed that women at Sao Paolo (5.3 vs. 4.6; $p=0.004$), Barcelona (5.4 vs. 4.6; $p<0.001$), Boston (5.4 vs. 4.6; $p=0.006$), Campinas (5.8 vs. 4.6; $p=0.001$) and Siena (6.2 vs. 4.6; $p=0.001$) had significantly more severe pelvic pain on average compared to the remainder of the study population. In contrast, women at Guangzhou (3.3 vs. 4.9; $p=0.001$),

Ibadan (4.1 vs. 4.7; $p=0.034$) and Leuven (4.2 vs. 4.7; $p=0.028$) had significantly less severe pelvic pain on average compared to the remainder of the study population.

Figure 35 - Centre-wise comparisons for mean severity of pelvic pain, with p values for t-test of difference mean in centre vs. remainder of study population



The average severity of pelvic pain was significantly worse in women with endometriosis than in symptomatic controls (mean 5.0 vs. 4.2; $p<0.001$) but did not differ between women with endometriosis and sterilisation controls (mean 5.0 vs. 4.6; $p=0.17$).

19.2 Description of individual symptoms presented by women

Figure 36 displays the frequency of the individual symptoms for which women underwent laparoscopy. The most frequently reported symptoms that led to laparoscopy were chronic pelvic pain (42.8%; $n=605$), painful periods (40.8%; $n=581$), ovarian cysts (34.9%; $n=495$) and subfertility (34.5%; $n=489$). Generally, urinary symptoms were the least frequently reported symptoms. The proportions of women at participating centres reporting individual symptoms as the indication for their laparoscopy are presented in Table 37.

Figure 36 - Frequency of symptoms for which women underwent laparoscopy

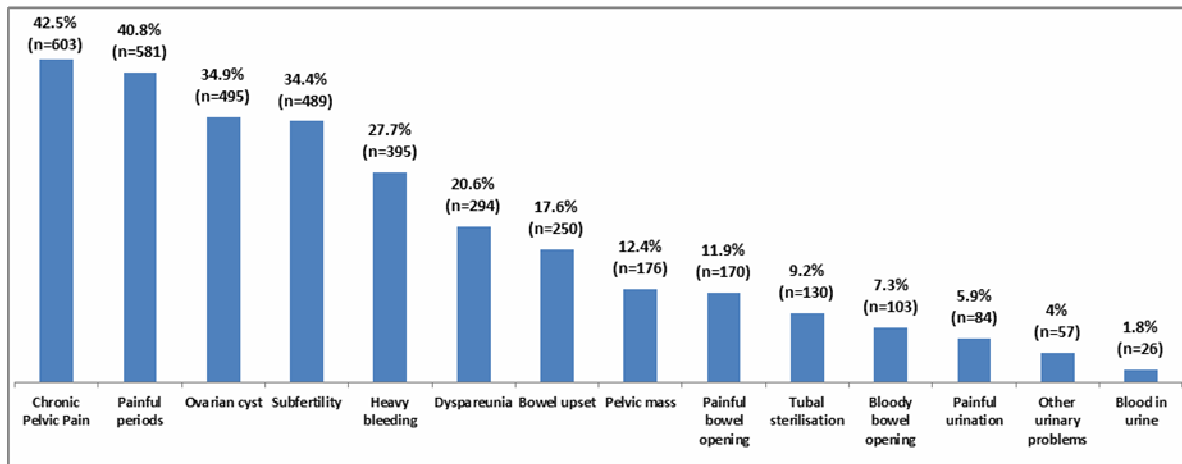


Table 37 - Reasons for undergoing laparoscopy

Centre	Tubal sterilisation		Chronic Pelvic Pain		Pelvic mass		Dysmenorrhoea		Heavy bleeding		Subfertility		Ovarian cyst		Dyspareunia		Painful bowel opening		Bloody bowel opening		Bowel upset		Painful urination		Blood in urine		Other urinary problems		N
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	
Barcelona	56	52.3	56	52.3	5	4.7	49	45.8	28	26.2	15	14.0	39	36.4	19	17.8	11	10.3	8	7.5	18	16.8	8	7.5	2	1.9	6	5.6	107
Boston	4	5.3	51	67.1	19	25.0	54	71.1	50	65.8	20	26.3	30	39.5	33	43.4	19	25.0	11	14.5	29	38.2	11	14.5	4	5.3	10	13.2	76
Camplinas	18	20.9	42	48.8	3	3.5	36	41.9	23	26.7	31	36.0	14	16.3	17	19.8	5	5.8	2	2.3	10	11.6	6	7.0	1	1.2	4	4.7	86
Dublin	2	4.3	28	60.9	2	4.3	20	43.5	17	37.0	22	47.8	17	37.0	12	26.1	12	26.1	8	17.4	13	28.3	2	4.3	0	0.0	3	6.5	46
Guangzhou	4	1.4	67	22.8	58	19.7	63	21.4	26	8.8	112	38.1	90	30.6	16	5.4	8	2.7	7	2.4	13	4.4	3	1.0	2	0.7	4	1.4	294
Ibadan	0	0.0	35	43.2	2	2.5	19	23.5	10	12.3	63	77.8	7	8.6	8	9.9	1	1.2	0	0.0	5	6.2	2	2.5	0	0.0	0	0.0	81
Leuven	0	0.0	48	46.2	12	11.5	51	49.0	24	23.1	66	63.5	24	23.1	27	26.0	20	19.2	11	10.6	27	26.0	8	7.7	1	1.0	3	2.9	104
Oxford	19	8.5	108	48.2	22	9.8	118	52.7	102	45.5	84	37.5	66	29.5	51	22.8	35	15.6	20	8.9	40	17.9	14	6.3	6	2.7	11	4.9	224
Rome	7	5.4	52	40.0	13	10.0	47	36.2	31	23.8	25	19.2	57	43.8	38	29.2	20	15.4	16	12.3	37	28.5	12	9.2	4	3.1	7	5.4	130
Sao Paolo	1	1.1	52	59.8	10	11.5	64	73.6	45	51.7	19	21.8	47	54.0	48	55.2	22	25.3	10	11.5	30	34.5	13	14.9	4	4.6	7	8.0	87
Shanghai	7	5.1	39	28.7	17	12.5	37	27.2	18	13.2	16	11.8	81	59.6	10	7.4	7	5.1	4	2.9	9	6.6	3	2.2	2	1.5	1	0.7	136
Siena	12	48.0	12	48.0	10	40.0	15	60.0	12	48.0	9	36.0	15	60.0	8	32.0	6	24.0	3	12.0	12	48.0	1	4.0	0	0.0	1	4.0	25
Others	0	0.0	13	59.1	3	13.6	8	36.4	9	40.9	7	31.8	8	36.4	7	31.8	4	18.2	3	13.6	7	31.8	1	4.5	0	0.0	0	0.0	22
Total	130	9.2	603	42.5	176	12.4	581	40.8	395	27.7	489	34.4	495	34.9	294	20.6	170	11.9	103	7.3	250	17.6	84	5.9	26	1.8	57	4.0	1418

19.2.1 Centre-wise comparisons on key individual symptoms presented by women

Table 38 shows centre-wise comparisons for proportions of women in each centre vs. remainder of the study population who reported the 4 most common symptoms (see Figure 36) that led to women's laparoscopic surgery (CPP, painful periods, ovarian cysts and subfertility). Women in Barcelona (52.3 vs. 42.4%; $p=0.047$), Boston (67.1 vs. 41.8%; $p<0.001$), Dublin (62.2 vs. 42.6%; $p=0.009$) and Sao Paolo (59.8 vs. 42.1%; $p<0.001$) were significantly more, and those in Guangzhou (22.8 vs. 48.6%; $p<0.001$) and Shanghai (28.7 vs. 44.8%; $p<0.001$) significantly less, likely to report CPP than the remainder of the study population. Women in Boston (69.7 vs. 39.3%; $p<0.001$), Oxford (52.7 vs. 38.7%; $p<0.001$) and Sao Paolo (73.6 vs. 38.8%; $p<0.001$) were significantly more, and those in Guangzhou (21.4 vs. 46.0%; $p<0.001$), Ibadan (23.5 vs. 42%; $p=0.001$) and Shanghai (27.9 vs. 42.3%; $p=0.001$) significantly less, likely to report painful periods than the remainder of the study population. Other significant centre differences are displayed in Table 38.

Table 38 - Centre-wise comparisons of proportions of women who presented with symptoms at centre vs. remainder of study population

Centre	Chronic Pelvic Pain			Painful periods			Ovarian cysts			Subfertility		
	% in centre	% in remainder of study population	Pearson's χ^2 p value	% in centre	% in remainder of study population	Pearson's χ^2 p value	% in centre	% in remainder of study population	Pearson's χ^2 p value	% in centre	% in remainder of study population	Pearson's χ^2 p value
Barcelona	52.3	42.4	0.047	45.8	40.5	0.29	36.4	34.7	0.71	14.0	35.9	<0.001
Boston	67.1	41.8	<0.001	69.7	39.3	<0.001	38.2	34.6	0.53	25.0	34.8	0.081
Campinas	48.8	42.8	0.28	40.7	40.9	0.96	15.1	36.1	<0.001	34.9	34.2	0.9
Dublin	62.2	42.6	0.009	43.5	40.8	0.72	37.0	34.7	0.75	47.8	33.8	0.048
Guangzhou	22.8	48.6	<0.001	21.4	46.0	<0.001	30.6	35.9	0.091	38.1	33.2	0.12
Ibadan	43.2	43.2	0.99	23.5	42.0	0.001	8.6	36.4	<0.001	77.8	31.6	<0.001
Leuven	46.6	42.9	0.47	49.0	40.3	0.081	22.1	35.8	0.005	62.5	32.0	<0.001
Oxford	48.4	42.2	0.085	52.7	38.7	<0.001	29.5	35.8	0.068	37.5	33.6	0.26
Rome	46.4	42.9	0.47	36.4	41.4	0.28	44.2	33.9	0.019	19.4	35.7	<0.001
Sao Paolo	59.8	42.1	0.001	73.6	38.8	<0.001	54.0	33.5	<0.001	21.8	35.0	0.012
Shanghai	28.7	44.8	<0.001	27.9	42.3	0.001	60.3	32.1	<0.001	11.0	36.7	<0.001
Siena	48.0	43.1	0.63	60.0	40.6	0.05	60.0	34.3	0.008	36.0	34.2	0.85
Others	61.9	42.9	0.081	36.4	41.0	0.66	36.4	34.8	0.88	31.8	34.3	0.81

As shown in Figure 37, women who had endometriosis were significantly more likely than both symptomatic and sterilisation controls to report CPP (49.3% vs. 34.8% vs. 30.2%), painful periods

(52.9% vs. 31.7% vs. 9.3%) and ovarian cysts (45.5% vs. 26.2% vs. 7.0%). They were however only more likely to have undergone surgery on account of subfertility compared to sterilisation controls (30.7% vs. 7.0%), a greater proportion of symptomatic controls reporting subfertility (43.6% vs. 30.7%). Table 39 shows the frequency of other symptoms in disease outcome groups.

Figure 37 - Comparisons of proportions of women in disease outcome groups who reported key symptoms (p values are for chi² test of equality of proportions for endometriosis vs. symptomatic controls and endometriosis vs. sterilisation controls)

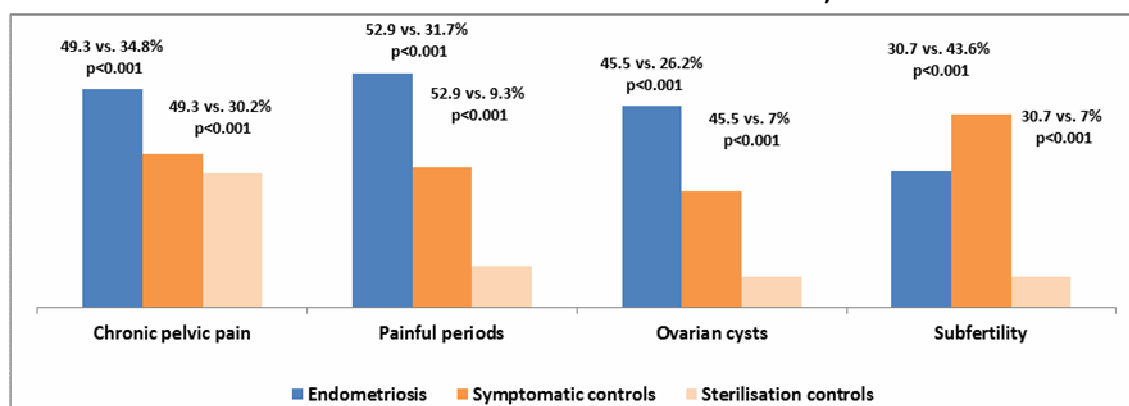


Table 39 - Proportions of women in disease outcome groups who reported other symptoms

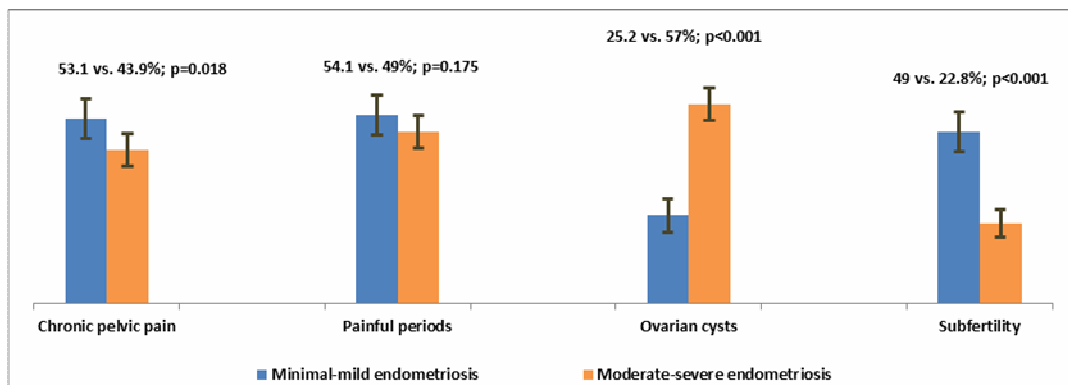
Symptom	Overall sample prevalence (%)	Endometriosis (n=745)		Symptomatic controls (n=587)		Chi ² p values ^a	Sterilisation controls (n=86)		Chi ² p values ^b
		n	%	N	%		n	%	
Menorrhagia	27.7	243	32.6	150	25.6	0.017	6	7	<0.001
Dyspareunia	20.6	206	27.7	86	14.7	<0.001	3	3.5	<0.001
Bowel upset	17.6	174	23.4	75	12.8	<0.001	4	4.7	<0.001
Dyschezia	11.9	131	17.6	38	6.5	<0.001	2	2.3	<0.001
Cyclical rectal bleeding	7.3	71	9.5	32	5.5	0.010	1	1.2	0.009
Painful urination	5.9	62	8.3	21	3.6	0.001	0	0	0.005
Haematuria	1.8	17	2.3	8	1.4	0.37	1	1.2	0.50

^a - p value for chi² test of equality of proportions for endometriosis vs. symptomatic controls; ^b - p value for chi² test of equality of proportions for endometriosis vs. sterilisation controls

In multivariate analysis adjusting for individual presenting symptoms, dysmenorrhoea (adjusted OR 2.7; 95% CI 2.0-3.7), dyspareunia (adjusted OR 1.4; 95% CI 1.0-2.0) and dyschezia (adjusted OR 2.0; 95% CI 1.2-3.2) were all associated with increased odds of endometriosis diagnosis at laparoscopy (not shown).

As shown in Figure 38, significantly greater proportions of women with minimal-mild, compared to moderate-severe, endometriosis reported CPP (53.1 vs. 43.9%; $p=0.018$) and subfertility (49.0 vs. 22.8%; $p<0.001$). A significantly greater proportion of women with moderate-severe endometriosis (57.0 vs. 25.2%; $p<0.001$) however underwent laparoscopy because of ovarian cysts.

Figure 38 – Comparison of proportions of women with minimal-mild vs. moderate-severe endometriosis who presented with key symptoms (p values are for χ^2 test of equality of proportions)



19.2.2 Age of women at onset of symptoms

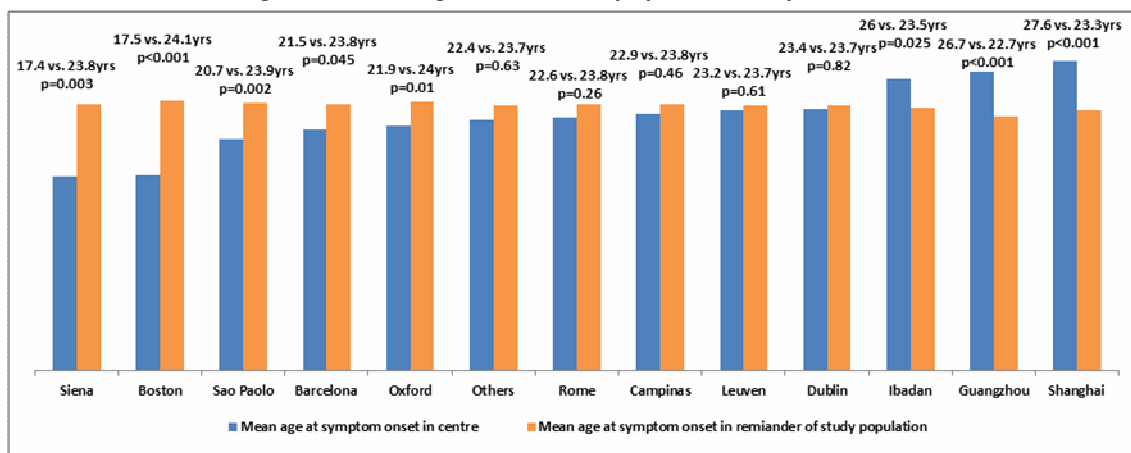
As shown in Table 40, dysmenorrhoea was the earliest-onset symptom reported by women, who were on average 20.2 years old (SD 8.4) when they first noted the onset of the pains that eventually led to a laparoscopy. On the other hand, the latest-onset symptom for which women underwent surgical investigation was ovarian cyst, which was identified at an average age of 28.9 years (SD 8.9). Generally, women were 23.7 years old (SD 9.2) when they first noted the symptoms which led to a laparoscopy.

Table 40 – Mean (SD) age of onset of specific symptoms

Symptom	N	Mean age (years)	SD
Dysmenorrhoea	532	20.2	8.4
Pelvic mass	167	28.9	8.9
Menorrhagia	357	21.8	9.7
Subfertility	438	28.7	5.7
Ovarian cyst	457	28.5	7.7
Dyspareunia	266	26.5	7.6
Painful bowel opening	159	25.8	8.5
Bleeding on bowel opening	93	26.3	9.1
Bowel upset	216	22.8	9.6
Painful urination	76	26.1	7.8
Blood in urine	23	27.4	9.7
Other urinary problems	52	26.0	8.6
All symptoms	1,137	23.7	9.2

Centre-wise comparisons showed that women at Siena (17.4 vs. 23.8yrs; $p=0.003$), Boston (17.5 vs. 24.1yrs; $p<0.001$), Sao Paolo (20.7 vs. 23.9yrs; $p=0.002$), Barcelona (21.5 vs. 23.8yrs; $p=0.045$) and Oxford (21.9 vs. 24.0yrs; $p=0.010$) were significantly younger at symptom onset than the average woman in the remainder of the study population. Women at Ibadan (26.0 vs. 23.5yrs; $p=0.025$), Guangzhou (26.7 vs. 22.7yrs; $p<0.001$) and Shanghai (27.6 vs. 23.3yrs; $p<0.001$) were significantly older than the average woman in the remainder of the study population at symptom onset (Figure 39).

Figure 39 - Mean age of women at symptom onset by Centre



Women who had endometriosis diagnosed at laparoscopy were significantly younger at symptom onset than symptomatic controls (22.9 vs. 24.8 years; Student's t test $p < 0.001$) but were not different to sterilisation controls in average age at symptom onset (22.9 vs. 21.8 years; Student's t test $p = 0.63$).

19.2.3 Mean number of individual symptoms presented by women

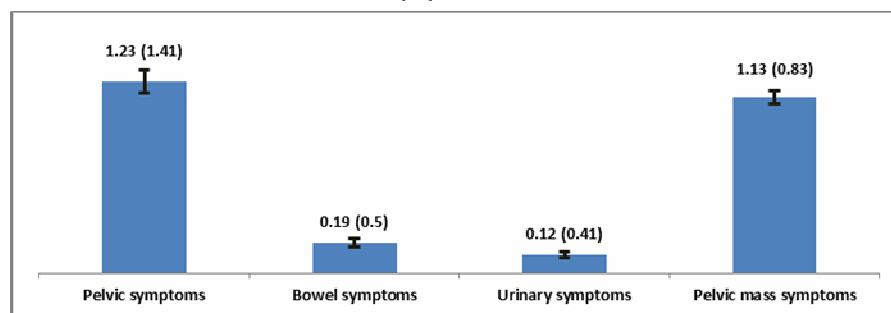
The first four components on principal component analysis displayed eigenvalues greater than 1 (not shown) and were thus retained for rotation. Four items were found to load onto the first component, which was labelled the "pelvic symptoms" factor. Two items also loaded onto the second component, which was labelled the "bowel symptoms" factor. Three items loaded onto the third component, which was labelled the "urinary symptoms" factor and three items loaded onto the fourth component, which was labelled the "pelvic mass" factor (Table 41).

Table 41 - Selected factors and loading variables

Factor 1 ("pelvic symptoms" factor)	Factor 2 ("bowel symptoms" factor)	Factor 3 ("urinary symptoms" factor)	Factor 4 ("pelvic mass" factor)
Pelvic pain	Painful bowel opening	Pain on passing urine	Pelvic mass
Dysmenorrhoea	Bloody bowel opening	Blood in urine	Ovarian cyst
Menorrhagia		Other urinary problems	Not subfertile
Dyspareunia			

As shown in Figure 40, women in the study population presented with an average of 1.2 (SD 1.4) 'pelvic', 0.19 (SD 0.5) 'bowel', 0.12 (SD 0.4) 'urinary' and 1.1 (SD 0.83) 'pelvic mass' symptoms.

Figure 40 - Mean (SD) number of symptoms in symptom groups reported by women in the study population



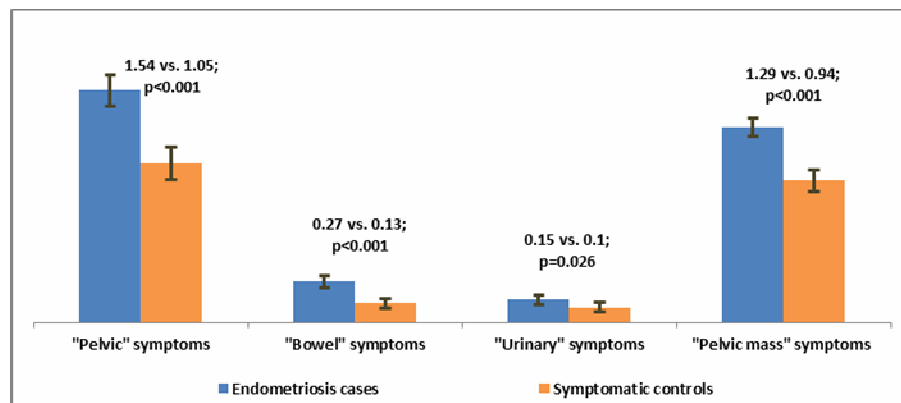
As shown in Table 42, women in Boston (2.4 vs. 1.2 symptoms; $p<0.001$), Oxford (1.7 vs. 1.1 symptoms; $p<0.001$), Sao Paolo (2.5 vs. 1.1 symptoms; $p<0.001$) and Siena (2.2 vs. 1.2 symptoms; $p=0.002$) presented with significantly more 'pelvic' symptoms than the average woman in the remainder of the study population; women in Guangzhou (0.5 vs. 1.4 symptoms; $p<0.001$), Ibadan (0.7 vs. 1.3 symptoms; $p=0.001$) and Shanghai (0.6 vs. 1.3 symptoms; $p<0.001$) presented with significantly fewer 'pelvic' symptoms. Women in Boston (0.4 vs. 0.2 symptoms; $p<0.001$), Dublin (0.4 vs. 0.2 symptoms; $p<0.001$), Leuven (0.3 vs. 0.2 symptoms; $p=0.024$), Rome (0.3 vs. 0.2 symptoms; $p=0.037$) and Sao Paolo (0.4 vs. 0.2 symptoms; $p<0.001$) presented with significantly more 'bowel' symptoms than the average woman in the remainder of the study population; women in Campinas (0.1 vs. 0.2 symptoms; $p=0.033$), Guangzhou (0.1 vs. 0.2 symptoms; $p<0.001$), Ibadan (0.0 vs. 0.2 symptoms; $p=0.001$) and Shanghai (0.1 vs. 0.2 symptoms; $p=0.006$) presented with significantly fewer 'bowel' symptoms. Women in Boston and Sao Paolo (both 0.3 vs. 0.1 symptoms; $p<0.001$) presented with significantly more 'urinary' symptoms than the average woman in the remainder of the study population; women in Guangzhou (0.0 vs. 0.1 symptoms; $p<0.001$), Ibadan (0.0 vs. 0.1 symptoms; $p=0.036$) and Shanghai (0.0 vs. 0.1 symptoms; $p=0.028$) presented with significantly fewer 'urinary' symptoms. Finally, women in Boston (1.4 vs. 1.1 symptoms; $p<0.001$), Rome (1.3 vs. 1.1 symptoms; $p=0.002$), Sao Paolo (1.4 vs. 1.1 symptoms; $p<0.001$), Shanghai (1.6 vs. 1.1 symptoms; $p<0.001$) and Siena (1.6 vs. 1.1 symptoms; $p=0.002$) presented with significantly more 'pelvic mass' symptoms than the average woman in the remainder of the study population; women in Campinas (0.8 vs. 1.1 symptoms; $p<0.001$), Leuven (0.7 vs. 1.2 symptoms; $p<0.001$), Ibadan (0.3 vs. 1.2 symptoms; $p<0.001$) and Oxford (1.0 vs. 1.2 symptoms; $p=0.028$) presented with significantly fewer 'pelvic mass' symptoms.

Table 42 - Centre-wise comparisons of number of individual symptoms in symptom groups presented by women

Centre	Mean (SD) number of Pelvic symptoms			Mean (SD) number of Bowel symptoms			Mean (SD) number of Urinary symptoms			Mean (SD) number of Pelvic mass symptoms		
	Centre	Remainder population	p-value	Centre	Remainder population	p-value	Centre	Remainder population	p-value	Centre	Remainder population	p-value
Barcelona	1.3	1.2	0.85	0.2	0.2	0.76	0.1	0.1	0.41	1.3	1.1	0.065
Boston	2.4	1.2	<0.001	0.4	0.2	<0.001	0.3	0.1	<0.001	1.4	1.1	0.01
Campinas	1.2	1.2	0.84	0.1	0.2	0.033	0.1	0.1	0.82	0.8	1.1	<0.001
Dublin	1.5	1.2	0.18	0.4	0.2	<0.001	0.1	0.1	0.88	0.9	1.1	0.11
Guangzhou	0.5	1.4	<0.001	0.1	0.2	<0.001	0.0	0.1	<0.001	1.1	1.1	0.88
Ibadan	0.7	1.3	0.001	0.0	0.2	<0.001	0.0	0.1	0.036	0.3	1.2	<0.001
Leuven	1.4	1.2	0.16	0.3	0.2	0.024	0.1	0.1	0.95	0.7	1.2	<0.001
Oxford	1.7	1.1	<0.001	0.2	0.2	0.079	0.1	0.1	0.42	1.0	1.2	0.028
Rome	1.2	1.2	0.82	0.3	0.2	0.037	0.2	0.1	0.081	1.3	1.1	0.002
Sao Paolo	2.5	1.1	<0.001	0.4	0.2	<0.001	0.3	0.1	<0.001	1.4	1.1	<0.001
Shanghai	0.6	1.3	<0.001	0.1	0.2	0.006	0.0	0.1	0.028	1.6	1.1	<0.001
Siena	2.1	1.2	0.002	0.4	0.2	0.088	0.1	0.1	0.64	1.6	1.1	0.002
Others	1.4	1.2	0.55	0.3	0.2	0.23	0.0	0.1	0.41	1.2	1.1	0.76

As shown below in Figure 41, compared to symptomatic controls, women who were diagnosed with endometriosis at laparoscopy presented with a significantly greater number of pelvic (1.5 vs. 1.05; $p<0.001$), bowel (0.27 vs. 0.13; $p<0.001$), urinary (0.15 vs. 0.1; $p=0.026$) and pelvic mass (1.29 vs. 0.94; $p<0.001$) symptoms.

Figure 41 - Mean number of symptoms presented by women with endometriosis vs. symptomatic controls



19.3 Symptoms and disease location

There was no correlation between dyschezia and the presence of endometriotic nodules in the recto-uterine pouch (cul-de-sac) (correlation coefficient 0.05, $p=0.058$), bladder (correlation

coefficient 0.020, $p=0.44$) or bowel (correlation coefficient 0.035, $p=0.18$). Dyspareunia correlated significantly with the presence of endometriotic nodules in the cul-de-sac ($r=0.06$, $p=0.025$) and bowel ($r=0.06$, $p=0.023$) but not with bladder nodules ($r=0.05$, $p=0.055$). Finally, there was no correlation between dysuria and presence of endometriotic nodules in the cul-de-sac (correlation coefficient 0.04, $p=0.17$), bladder (correlation coefficient 0.02, $p=0.44$) or bowel (correlation coefficient 0.02, $p=0.43$).

19.4 Ethnic differences in symptoms leading to diagnosis

There were significant differences in presenting symptom profiles by ethnicity. As shown in Table 43, compared to White women, proportionately fewer Asian and Black women underwent laparoscopy on account of dysmenorrhoea, CPP, menorrhagia and dyspareunia. A greater proportion of Black women (62.5%) however significantly underwent surgery for subfertility.

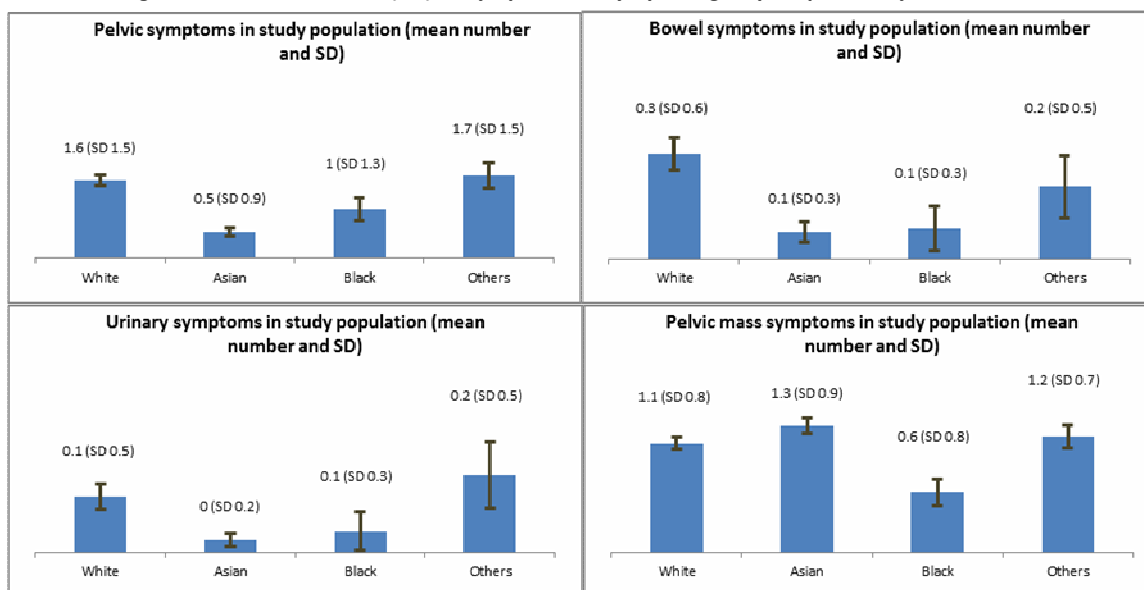
Table 43 – Percentage of women who underwent laparoscopy for symptoms by ethnicity

Symptom	White n=682	Asian n=455	Black n=121	Others n=133	Chi ² p values*
Dysmenorrhoea	51 %	24 %	28.3%	54.9%	<0.001
CPP	51%	26.4 %	41.7%	55.6%	<0.001
Subfertility	34.5%	30.1 %	62.5%	25.6%	<0.001
Menorrhagia	36.4 %	11.9%	20.8 %	41.4%	<0.001
Dyspareunia	27.8 %	7.5%	15%	30.8%	<0.001

*- p values are for chi² test of heterogeneity of proportions

There were also significant racial/ethnic group differences in the mean number of symptoms (pelvic, bowel, urinary and pelvic mass) reported by women across the centres. More specifically, as shown in Figure 42, compared to White women, Asian and Black women reported fewer pelvic (0.5 & 1 for Asian & Black, respectively vs. 1.6 for White), bowel (0.1 & 0.1 for Asian & Black, respectively vs. 0.3 for White) and urinary (0.0 & 0.1 for Asian & Black, respectively vs. 0.1 for White) symptoms. Asian women however reported more pelvic mass symptoms than White women (1.3 vs 1.1) – all ANOVA f-test p values <0.001 (not shown).

Figure 42 - Mean number (SD) of symptoms in symptom groups reported by women



19.5 Endometriosis and Irritable Bowel Syndrome

Three hundred and three (303) out of 1,287 symptomatic women (i.e. 23.5%) also fulfilled the Irritable Bowel Syndrome (IBS) Rome III diagnostic criteria, as did 15.6% (12/77) of asymptomatic women being sterilised (not shown).

As shown in Table 44, 64% of women (208 out of 325) who fulfilled the criteria for IBS were found to have endometriosis. In logistic regression, women who fulfilled the Rome III criteria for IBS were significantly more likely to be diagnosed with endometriosis than those who did not fulfil the criteria but this was not robust to adjustment for CPP (adjusted OR 1.33; $p=0.088$).

Table 44 - Endometriosis and Irritable Bowel Syndrome (IBS)

	Endometriosis	No endometriosis	Total
No IBS	537	556	1,093
IBS	208	117	325
Total	745	673	1,418

20 Discussion

Two in 5 women (40.8%; n=578) in the study population underwent laparoscopy because of pelvic pain (CPP, dysmenorrhoea or dyspareunia) without subfertility; another 20.0% (n=284) because of both pelvic pain and subfertility and 14% (n=198) because of subfertility without pelvic pain. Compared to symptomatic controls, cases were more likely to undergo laparoscopy because of pelvic pain without subfertility (49.1 vs. 30.7%; $p<0.001$) and less likely to do so because of subfertility without pelvic pain (9.0 vs. 22.3%; $p<0.001$). There was no difference in proportions of cases and symptomatic controls who had surgery because of both pelvic pain and subfertility (21.5 vs. 21.1%; $p=0.85$). Compared to women with minimal-mild endometriosis, those with moderate-severe endometriosis were more likely to present with pelvic pain without subfertility (50.6 vs. 40.8 %; $p=0.009$) and less likely to present with pelvic pain and subfertility (15.7 vs. 32.3 %; $p<0.001$) and subfertility without pelvic pain (6.9 vs. 16.3 %; $p<0.001$). The observation that those who had subfertility with or without pelvic pain were more likely to have minimal-mild disease while those with other symptoms than subfertility or pelvic pain were more likely to have moderate-severe disease is interesting. It may be surprising given that pelvic pain and subfertility are common symptoms of endometriosis reported in the study population and their presence might be more easily associated with progressive disease than their absence. However, in this study population, women who were not subfertile were more likely than those who were to have a pelvic (adnexal) mass. The presence of a pelvic mass being synonymous with advanced endometriosis might explain why women without pelvic pain or subfertility in our study population had more moderate-severe disease than those who had those symptoms.

Pelvic pain was more severe in cases than in symptomatic controls (mean 5.0 vs. 4.2; $p<0.001$) but did not differ between cases and sterilisation controls (mean 5.0 vs. 4.6; $p=0.17$). This finding is surprising given that most sterilisation controls were asymptomatic but the small sample size among sterilisation controls could have made any difference in mean pelvic pain severity difficult

to detect. Amongst cases, there was no correlation between endometriosis stage and severity of pelvic pain (correlation coefficient 0.003; $p=0.95$).

The most frequently reported symptoms that led to laparoscopy were chronic pelvic pain (42.8%; $n=605$), dysmenorrhoea (40.8%; $n=581$), ovarian cysts (34.9%; $n=495$) and subfertility (34.5%; $n=489$). Cases were more likely than both symptomatic and sterilisation controls to report CPP (49.3% vs. 34.8% vs. 30.2%), painful periods (52.9% vs. 31.7% vs. 9.3%) and ovarian cysts (45.5% vs. 26.2% vs. 7.0%) but only more likely to be investigated for subfertility compared to sterilisation controls (30.7% vs. 7.0%), a greater proportion of symptomatic controls reporting subfertility (43.6% vs. 30.7%). Compared to women with moderate-severe endometriosis, those with minimal-mild endometriosis were more likely to report CPP (53.1 vs. 43.9%; $p=0.018$) and subfertility (49.0 vs. 22.8%; $p<0.001$) but less likely to be investigated for ovarian cysts (25.2% vs. 57.0; $p<0.001$).

The prevalence of dysmenorrhoea in the study population (40.8%) is generally consistent with reported rates in the literature for women undergoing diagnostic laparoscopy, although both lower and higher rates have been reported previously in geographically limited populations [186,210-213]. The range and median prevalence of dysmenorrhoea across the centres in this multicentre study (from 21.4% in Guangzhou to 73.6% in Sao Paolo; median 43.5%) suggests that the prevalence of 40.8% probably reflects a reliable estimate of the prevalence of dysmenorrhoea in women undergoing laparoscopy. In some reports, CPP is the indication in 40% of women undergoing diagnostic laparoscopy [214,215]. Similar prevalence rates have been reported previously in diverse populations including Asian and North American women [83,216]. The finding in this study that 42.5% of women underwent laparoscopy because of CPP therefore is in line with these previously reported figures.

Compared to endometriosis cases, there was a significantly higher proportion of women in the symptomatic control group who were subfertile but without pelvic pain. This is not surprising given the relatively low proportion of asymptomatic endometriosis in the population. As endometriosis associated with subfertility is typically indicative of asymptomatic disease secondary to other primary causes of subfertility [13], the relatively lower proportion of subfertility associated with endometriosis in the study population may reflect the small proportion of asymptomatic disease in the sample. A much lower occurrence of subfertility in endometriosis was reported by Vessey et al. [70] who found that only 4 women out of 313 with endometriosis were subfertile but it was not clear from their report how many of the cases were asymptomatic.

Dyspareunia was reported as a reason for laparoscopy by 20.6% of all women in the study population. Across centres, the prevalence of dyspareunia as an indication for laparoscopy ranged from 5.4% in Guangzhou to 55.2% in Sao Paolo, with a median rate of 26.0%. A significantly greater proportion of cases reported dyspareunia than did so amongst both control groups. Two previous retrospective assessments of women diagnosed with endometriosis during laparoscopy reported prevalence figures for dyspareunia in affected women ranging from 35.4% to 88% [213,216] but the higher figure reported by Frenna et al. may have been due to the fact that they studied women with severe endometriosis only. Other prospective (pre-diagnostic surgery) assessments of the frequency of dyspareunia in cases suggest that between 33.1% and 53.8% of cases present with dyspareunia [72,186], figures largely consistent with the frequency reported in this study.

On average, dysmenorrhoea was the earliest-onset (20.2 yrs, SD 8.4), and ovarian cyst the latest-onset (28.9 yrs, SD 8.9), symptom reported by women. Women were on average 23.7 yrs old (SD 9.2) when they first noted the symptoms which led to a laparoscopy. Compared to symptomatic

controls, cases presented with a greater number of pelvic (1.5 vs. 1.05; $p<0.001$), bowel (0.27 vs. 0.13; $p<0.001$), urinary (0.15 vs. 0.1; $p=0.026$) and pelvic mass (1.29 vs. 0.94; $p<0.001$) symptoms. There was no correlation between dyschezia and presence of endometriotic nodules in the recto-uterine pouch (cul-de-sac) (correlation coefficient 0.05, $p=0.058$), bladder (correlation coefficient 0.020, $p=0.44$) or bowel (correlation coefficient 0.035, $p=0.18$). Similarly, there was no correlation between dysuria and presence of endometriotic nodules in the cul-de-sac (correlation coefficient 0.04, $p=0.17$), bladder (correlation coefficient 0.02, $p=0.44$) or bowel (correlation coefficient 0.02, $p=0.43$). However, dyspareunia correlated with the presence of endometriotic nodules in the cul-de-sac (correlation coefficient 0.06, $p=0.025$) and bowel (correlation coefficient 0.06, $p=0.023$) but not the bladder (correlation coefficient 0.05, $p=0.055$).

Although women reported that dysmenorrhoea (earliest onset symptom) started at about age 20, the actual onset could be earlier since the signs of endometriosis in the early stages of the disease often appear to be the 'normal' bodily changes that take place with the menstrual cycle [217]. The key difficulty with the validity of this finding, however, relates to the fact that the point at which a 'normal' menstrual characteristic becomes a symptom of endometriosis disease is impossible to tell with any certainty, especially as both the literature and this study confirm the lack of association between endometriosis disease course and the its symptoms. In one case-control study examining the association between early menstrual characteristics and later laparoscopically confirmed moderate-severe endometriosis, a history of dysmenorrhoea was associated with a nearly three-fold risk of disease [202], but the study methods warrant further examination. Although the authors collected menstrual characteristics data in 10-year age bands, they acknowledged that it was difficult to distinguish menstrual characteristics from disease symptoms and therefore excluded from the analyses women who reported both menstrual characteristics and symptom onset in the 10-19 years age band. This approach may not reliably establish a temporal order because a woman may have reported dysmenorrhoea in age band 10-

19 and symptom onset in age band 20-29 because she did not deem her dysmenorrhoea in the former age band to be related to her disease. The clinical usefulness of early onset dysmenorrhoea as a pointer to current or potential endometriosis disease is therefore limited. Perhaps potentially more clinically useful is the interval between menarche and onset of dysmenorrhoea: 7.2 years (SD 8.0) in this study, which is consistent with previous reports [218,219]. Notably, the interval was significantly shorter in women who had minimal-mild compared to moderate-severe endometriosis (5.9 years {SD 7.5} vs 8.5 years {SD 8.3}), corresponding to later onset dysmenorrhoea in moderate-severe compared to minimal-mild endometriosis disease (21.3 years {SD 0.6} vs 18.5 years {SD 0.7}). This is not surprising, as secondary dysmenorrhoea is suggestive of endometriosis [220] and moderate-severe endometriosis may represent genuine disease [35,36]. The clinical implication might be that the index of suspicion for endometriosis should be raised in a woman presenting with new onset dysmenorrhoea 7.5 to 10 years after menarche.

Compared to White women, Asian (24% vs. 51%, OR 0.31; $p < 0.001$) and Black (51% vs. 28.3%, OR 0.39; $p < 0.001$) women had lower odds of undergoing laparoscopy because of dysmenorrhoea. Asian and Black women were also less likely than White women to undergo surgery for CPP, menorrhagia and dyspareunia. Black women were however more likely to have been investigated for subfertility compared to their White counterparts (62.5% vs. 34.5%, OR 3.28; $p < 0.001$). Compared to White women, Asian and Black women reported fewer pelvic (0.5 & 1 for Asian & Black, respectively vs. 1.6 for White), bowel (0.1 & 0.1 for Asian & Black, respectively vs. 0.3 for White) and urinary (0.0 & 0.1 for Asian & Black, respectively vs. 0.1 for White women) symptoms. Asian women however reported more pelvic mass symptoms than White women (1.3 vs 1.1) – all ANOVA f-test p values < 0.001 . Although a possible link between endometriosis and race or ethnicity has been proposed, there are no previous studies that have examined or identified ethnic patterns in the distribution of symptoms leading to the diagnosis of endometriosis as

reported in this study. It is possible that the findings reflect a tendency for the Black women in this study (who were predominantly in a developing country setting) to normalise or delay care for pelvic symptoms associated with menstruation (and with endometriosis) while being driven by cultural attitudes to seek care for subfertility [221]. The potential clinical usefulness of ethnic patterns in symptoms leading to a diagnosis of endometriosis would however appear to be limited.

The results presented in the chapter should be treated with some caution as many comparisons have been made in the analyses and there is a possibility that some positive findings are chance findings. This is however more likely to influence the centre-wise comparisons than the findings relating to the characteristics of presenting symptoms across disease outcome groups. Furthermore, the cross-sectional nature of the study means that longitudinal observations should be treated with great caution. Accordingly however, only cross-sectional analyses have been conducted in keeping with the design of the study and the data it generated.

In summary, there were few key differences in the characteristics and distribution of the symptoms that led to women's diagnostic laparoscopy across participating centres. The lack of correlation between disease stage and symptom severity highlights the importance of examining whether endometriosis impacts on women's lives only via its symptoms or whether there are effects brought about by the disease itself independent of its symptoms. This point is the subject of later chapters.

CHAPTER 6

ENDOMETRIOSIS: ONSET, CARE-SEEKING AND DIAGNOSIS

21 Introduction

In chapter 5, a detailed description of the symptoms for which women underwent laparoscopy was presented. It was observed that over 40% of women in the study population (n=578) presented with pelvic pain (chronic pelvic pain, dysmenorrhoea or dyspareunia) without subfertility, and 14% (n=198) with subfertility without pelvic pain. Affected women presented with a greater number of symptoms in all symptom categories and although they had more severe pelvic pain on average than symptomatic controls, (mean NRS score of average pelvic pain 5.0 vs 4.2; $p<0.001$), there was surprisingly no statistically significant difference in the severity of their pain in comparison with sterilisation controls (5.0 vs. 4.6; $p=0.17$). Dyspareunia correlated with the location of endometriotic nodules in the cul-de-sac ($r=0.06$, $p=0.025$) and bowel ($r=0.06$, $p=0.023$) but endometriosis stage (or severity) did not correlate with the severity of pelvic pain ($r=0.003$; $p=0.95$).

Pelvic pain associated with endometriosis can be experienced by women as a chronic, on-going pain or as an acute episode during menstrual periods. As women tend to expect pain with menstruation, they may find it difficult to distinguish normal from pathological discomfort. Drawing on earlier qualitative research, Manderson *et al.* describe how shared perceptions of the “normality” of menstrual pain amongst women and doctors contribute to diagnostic delays, noting the criticality of major quality of life disruptions and difficulties in conception as triggers of eventual care-seeking [222]. Other factors, such as age at onset of symptoms and type of physician first contacted after symptom onset, have been reported to influence care-seeking and the illness experience [223] but these reports were based on populations of women living with surgically diagnosed endometriosis, risking recall bias.

This chapter examines the care-seeking experience of women, describing in more detail the following: 1) onset of symptoms, 2) contact with primary care physicians on account of

symptoms, 3) frequency of primary care physician consultation before referral to specialists for diagnosis, and 4) nature, duration and determinants of diagnostic delay. The design of the GSWH study allows these questions to be investigated in a cross-sectional sample of prospectively recruited women undergoing a first laparoscopy either on account of symptoms or for sterilisation. It can therefore be expected that any observations reported, e.g. age at onset of symptoms and frequency of primary care physician contact before specialist referral, would be free of the effect of differential recall associated with surveying women living with surgically confirmed disease.

22 Methods

22.1 Comparison groups

As in previous chapters, analyses of care-seeking variables (onset of symptoms, primary care physician contact and diagnostic delay) are conducted according to two main outcome groups: centre of recruitment and disease outcome groups. The variable 'centre' is re-categorised so that the centres at which fewer than 25 women were recruited (Buenos Aires, San Francisco, Palo Alto and Washington DC) are grouped together into an "Other" category. Disease outcome groups include: 1) women with endometriosis; 2) symptomatic controls; and 3) laparoscopic sterilisation controls. The endometriosis group includes all women, regardless of indication for surgery, with endometriosis on laparoscopy; the symptomatic control group includes those without endometriosis who were investigated for symptoms; the laparoscopic sterilisation group includes women without endometriosis, who underwent sterilisation (who may or may not have had symptoms). For women with endometriosis, disease severity is described as "minimal-mild endometriosis" (rASRM stages I+II) or "moderate-severe endometriosis" (rASRM stages III+IV) [33].

22.2 Outcome description

22.2.1 Onset of symptoms

For each symptomatic woman, the age of onset of symptoms is defined as the earliest age at which she reported first noting any of the symptoms for which she underwent laparoscopic surgery. Age at symptom onset is computed for the study population and compared across outcome groups, i.e. centres and disease outcome groups (endometriosis cases and symptomatic controls).

22.2.2 Care-seeking and referral to specialists

Care-seeking for symptoms is described principally in terms of the following: 1) the interval (in years) between onset of symptoms in a symptomatic woman and her first contact with a primary care physician on account of those symptoms; 2) the interval (in years) between a first contact with a primary care physician and eventual surgical diagnosis (or exclusion) of endometriosis; and 3) the average number of times women visited their primary care physicians before referral to a specialist. These are computed for the study population and compared across outcome groups, i.e. centres and disease outcome groups (endometriosis cases and symptomatic controls).

22.2.3 Diagnostic delay

Diagnostic delay (the diagnostic interval) is computed as the interval (in years) between symptom onset and diagnosis (or exclusion) of endometriosis, the age at diagnosis being the current age of women. Diagnostic delay is computed and compared across outcome groups, i.e. centres and disease outcome groups (endometriosis cases and symptomatic controls).

22.3 Statistical methods

For all outcomes of interest, mean values are computed with standard deviations. For each centre, the mean value is compared to that for the remainder of the study population using the Student's t test of equality of means or a non-parametric equivalent if necessary. Similarly, the mean values for outcomes are compared across disease outcome groups (endometriosis vs. symptomatic controls) using the Student's t test of equality of means or a non-parametric equivalent if necessary.

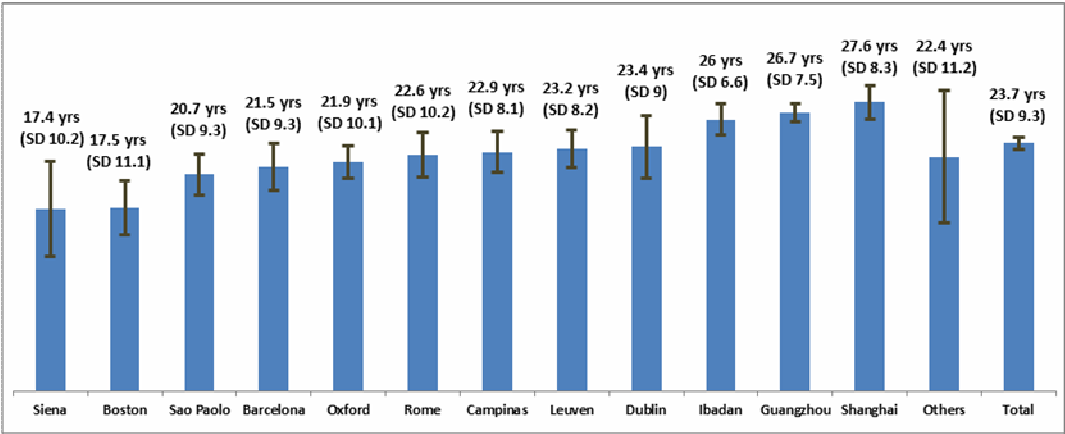
All analyses were done using Stata Release 11 (Stata Corporation, College Station, Texas, USA).

23 Results

23.1 Onset of symptoms and physician contact

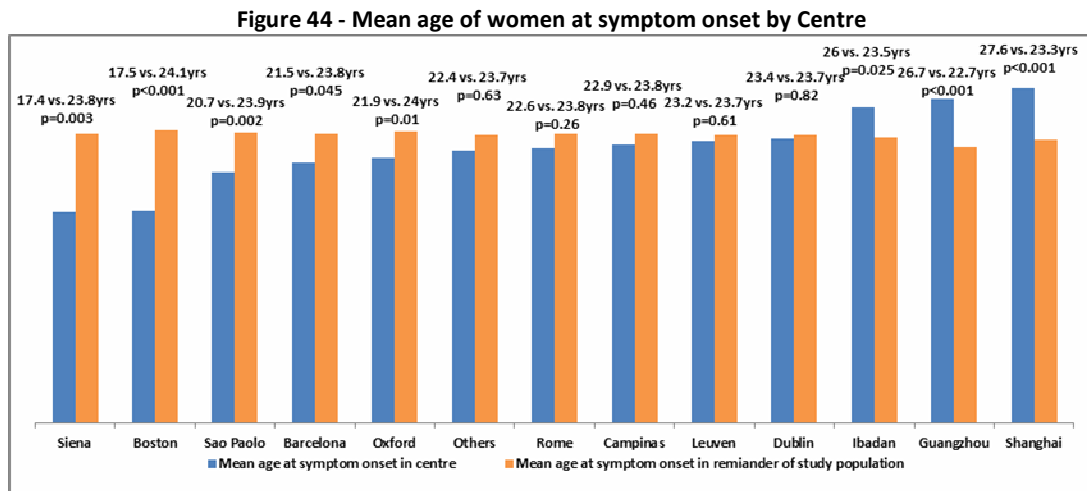
23.1.1 Age at symptom onset & physician contact in study population and centres

Figure 43 - Mean age at reported symptom onset by centre, with 95% confidence intervals



As shown in Figure 43 above, the average age at symptom onset in women in the study was 23.7 years (SD 9.3). This ranged from 17.4 years (SD 10.2) in Siena to 27.6 years (SD 8.3) in Shanghai.

Centre-wise comparisons showed that women at Siena (17.4 vs. 23.8yrs; $p=0.003$), Boston (17.5 vs. 24.1yrs; $p<0.001$), Sao Paolo (20.7 vs. 23.9yrs; $p=0.002$), Barcelona (21.5 vs. 23.8yrs; $p=0.045$) and Oxford (21.9 vs. 24.0yrs; $p=0.010$) were significantly younger at symptom onset than the average woman in the remainder of the study population. Women at Ibadan (26.0 vs. 23.5yrs; $p=0.025$), Guangzhou (26.7 vs. 22.7yrs; $p<0.001$) and Shanghai (27.6 vs. 23.3yrs; $p<0.001$) were significantly older than the average woman in the remainder of the study population at symptom onset (Figure 44).



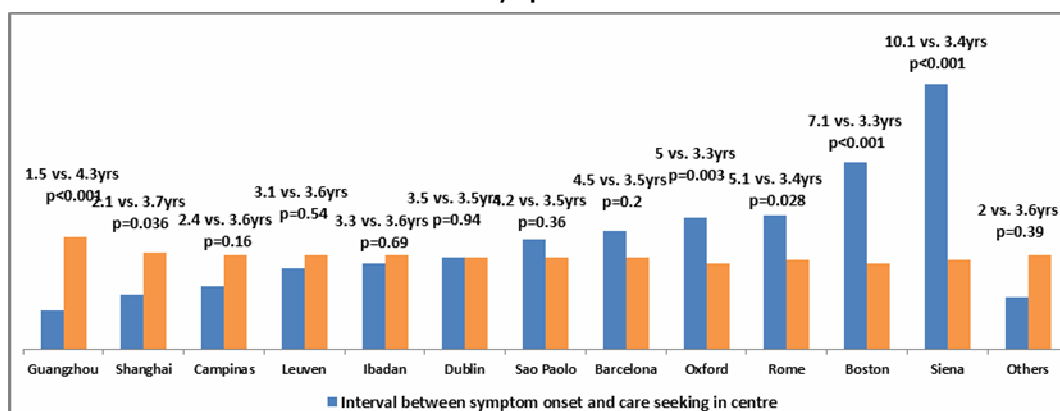
As shown in Table 45, the average age at first contact with a physician on account of symptoms in women in the study population was 27.2 years (SD 7.8). This ranged from 24.4 years (SD 9.7) in the 'Other' centre to 29.7 years (SD 7.1) in Shanghai. Similarly, the average interval between symptom onset and first physician contact on account of symptoms in women in the study population was 3.5 years (SD 6.3). This ranged from 2.0 years (SD 3.7) in the 'Other' centre to 10.1 years (SD 9.8) in Siena.

Table 45 – Mean age at symptom onset, physician contact and interval, by centre

Centre	Mean age in years at symptom onset (SD)	Mean age in years at first contact with physician for symptoms (SD)	Interval in years between symptom onset and first physician contact for symptoms (SD)
Barcelona	21.5 (9.3)	26 (8)	4.5 (6.2)
Boston	17.5 (11.1)	24.6 (9)	7.1 (8.2)
Campinas	22.9 (8.1)	25.3 (7.4)	2.4 (5.9)
Dublin	23.4 (9)	26.8 (7.6)	3.5 (5.2)
Guangzhou	26.7 (7.5)	28.2 (6.7)	1.5 (3.5)
Ibadan	26 (6.6)	29.2 (5.8)	3.3 (4.5)
Leuven	23.2 (8.2)	26.3 (6.7)	3.1 (5.2)
Oxford	21.9 (10.1)	27 (8.7)	5 (8.5)
Rome	22.6 (10.2)	27.7 (7.7)	5.1 (7.5)
Sao Paolo	20.7 (9.3)	24.9 (8.7)	4.2 (6.7)
Shanghai	27.6 (8.3)	29.7 (7.1)	2.1 (4)
Siena	17.4 (10.2)	27.5 (11.7)	10.1 (9.8)
Others	22.4 (11.2)	24.4 (9.7)	2 (3.7)
Total	23.7 (9.3)	27.2 (7.8)	3.5 (6.3)

Centre-wise comparisons showed that the interval between symptom onset and a first physician contact on account of symptoms was significantly shorter in Guangzhou (1.5 vs. 4.3 yrs; $p<0.001$) and Shanghai (2.1 vs. 3.7 yrs; $p=0.036$) compared to the average interval for women in the remainder of the study population. On the other hand, the interval between symptom onset and a first physician contact on account of symptoms was significantly longer in Oxford (5.0 vs. 3.3 yrs; $p=0.003$), Rome (5.1 vs. 3.4 yrs; $p=0.028$), Boston (7.1 vs. 3.3 yrs; $p<0.001$) and Siena (10.1 vs. 3.4 yrs; $p<0.001$) compared to the average interval for women in the remainder of the study population (Figure 45).

Figure 45 - Centre-wise comparisons of interval between symptom onset and first physician contact for symptoms



23.1.2 Age at symptom onset and physician contact in disease outcome groups

Table 46 shows the average age of symptomatic women at the onset of specific symptoms (by endometriosis status). Dysmenorrhoea was the earliest symptom in the study population (mean 20.2 years; SD 8.4) (not shown in table) and in women with endometriosis (mean 19.9 years; SD 8.1). Subfertility was the latest-onset symptom in women with endometriosis (mean 29.1 years; SD 5.5).

Table 46 - Average ages at onset of symptoms for symptomatic women in the study population

Symptom	Mean age at onset (SD)				Missing	N	P value
	Endometriosis	n	Symptomatic controls	n			
Pelvic pain	23.0 (8.8)	289	24.7 (8.8)	147	39	475	0.059
Pelvic mass	28.8 (8.6)	103	29.2 (9.4)	64	9	176	0.77
Painful periods	19.9 (8.1)	374	20.9 (8.9)	158	49	581	0.24
Heavy periods	20.2 (9.0)	229	24.6 (10.5)	128	38	395	<0.001
Subfertility	29.1 (5.5)	207	28.3 (5.9)	231	51	489	0.15
Ovarian cyst	28.7 (7.9)	317	28.1 (8.0)	140	38	494	0.41
Painful intercourse	26.5 (7.4)	194	26.5 (8.2)	72	28	294	0.98
Painful bowel opening	25.7 (7.9)	125	26.2 (10.4)	34	12	170	0.73
Bloody bowel opening	26.8 (8.8)	66	25.3 (10.0)	27	10	103	0.47
Bowel upset	22.6 (9.4)	152	23.2 (10.0)	64	34	250	0.60
Pain passing urine	25.5 (8.4)	54	27.5 (6.0)	22	8	84	0.34
Bloody urination	25.5 (9.6)	14	30.4 (9.7)	9	3	26	0.24
Other urinary	25.9 (8.6)	32	26.1 (8.9)	20	5	57	0.94
Mean age at symptom	22.9 (9.3)	684	24.8 (9.1)	587	0	1271	<0.001

On average, symptom onset was earlier in women with endometriosis (mean 22.9 years, SD 9.3) than in symptomatic controls (mean 24.8 years, SD 9.1) ($p<0.001$) and this difference remained significant even after controlling for age at menarche, which was significantly younger in women with endometriosis. For individual symptoms however, this difference was only significant in respect of heavy bleeding ($p<0.001$).

After accounting for the differences in age of women, endometriosis was significantly associated with both younger age at symptom onset (adjusted OR 0.97; 95% CI 0.96-0.99) and younger age at onset of menorrhagia (adjusted OR 0.96; 95% CI 0.94-0.99) (not shown).

Women with endometriosis, on average, sought care for their symptoms 3.9 years (SD 6.4) after symptom onset, i.e. aged 26.8 years (Table 47). In comparison, symptomatic controls, on average, sought care after 3.1 years (SD 6.1), i.e. aged 27.9 years. After adjusting for age at symptom onset, women with endometriosis did not differ from symptomatic controls in the average interval between symptom onset and first physician contact ($\beta=0.056$; $p=0.17$).

Table 47 - Care-seeking for symptoms

Variables	Endometriosis (n=745)	Symptomatic controls (n=587)	P values
Age at symptom onset (Years)[Mean (SD)]	22.9 (9.3)	24.8 (9.1)	<0.001 ^a
Age at first contact with primary care physician for symptoms (Years) [Mean (SD)]	26.8 (7.9)	27.9 (7.6)	0.003 ^a
Number of visits to primary care physician before referral to specialist [Mean (SD)]	6.5 (10.2)	6.8 (10.6)	0.59
Age at diagnosis (Years) [Mean (SD)]	32.6 (6.2)	33.1 (6.4)	0.071
Diagnostic delay (Years) [Mean (SD)]	9.8 (8.8)	8.3 (8.8)	0.001 ^a

^a - P values are adjusted for age

23.1.3 Further characterisation of symptom onset

Compared to women who reported subfertility without pelvic pain, those who reported pelvic pain without subfertility were, on average, younger at symptom onset (20.0 vs. 27.6 years; $p<0.001$) (data not shown).

Women at the lowest quintile of age at symptom onset (mean age at symptom onset 11.9 years) took a mean 8.7 years (SD 8.6) to report their symptoms to a physician compared to those in the highest quintile (mean age at symptom onset 37.3 years) who took 0.51 years to do so (data not shown). After controlling for the type of symptoms presented (pelvic pain $\pm$ subfertility or subfertility $\pm$ pelvic pain), the interval between symptom onset and medical care-seeking increased as age at symptom onset decreased ($\beta=-2.0$; $p<0.001$).

23.1.3.1 Onset of symptoms and physician contact by stage of endometriosis

Women with moderate-severe endometriosis were older at symptom onset (24.2 years, SD 9.2) than those with mild-moderate disease (22.2 years, SD 8.9) and this difference was stable to adjustment for age (adjusted OR 1.02; 95% CI 1.00-1.04). Similarly, women with moderate-severe endometriosis were older at first contact with a physician on account of symptoms (27.2 years, SD 7.5) than those with mild-moderate disease (25.4 years, SD 8.0) and this difference was stable to adjustment for age (adjusted OR 1.03; 95% CI 1.00-1.05).

23.1.3.2 Early onset of symptoms and endometriosis diagnosis

Women who reported never having had dysmenorrhoea until they were past the age of 25 years were more likely to be diagnosed with endometriosis at laparoscopy compared to those who did report dysmenorrhoea before then ($\beta=-0.19$; $p=0.036$).

23.2 Care-seeking and referral to specialists

23.2.1 Care-seeking and referral to specialists in study population and centres

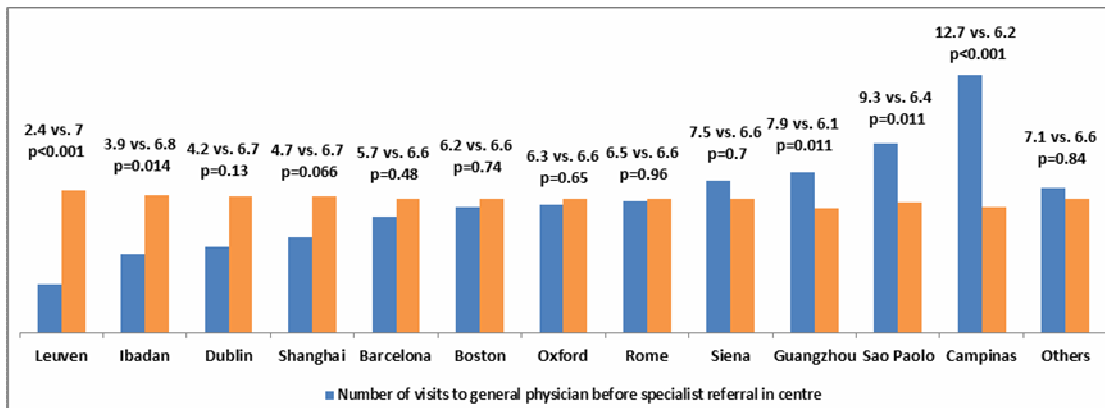
As shown in Table 48, women in the study population reported a mean number of 6.6 (SD 10.4) visits to a primary care physician before referral to a gynaecologist.

Table 48 - Number of primary care physician visits before specialist referral, by Centre

Centre	Mean (SD)	n	Missing
Barcelona	5.7 (13.7)	63	3
Boston	6.5 (12.2)	71	1
Campinas	12.7 (14.1)	68	0
Dublin	4.2 (3.7)	39	5
Guangzhou	7.9 (9.3)	289	0
Ibadan	3.9 (4.8)	80	1
Leuven	2.4 (7.6)	102	2
Others	9.3 (11)	15	2
Oxford	6.3 (9.4)	176	34
Rome	6.5 (17)	72	35
Sao Paolo	9.3 (9.2)	85	1
Shanghai	4.7 (6.3)	97	27
Siena	7.5 (10.8)	19	0
Total	6.6 (10.4)	1,176	111

Centre-wise comparisons showed that women at Leuven (2.4 vs. 7; $p<0.001$) and Ibadan (3.9 vs. 6.8; $p=0.014$) reported significantly fewer visits to a general physician before referral to a specialist. On the other hand, women at Guangzhou (7.9 vs. 6.1; $p=0.011$), Sao Paulo (9.3 vs. 6.4; $p=0.011$) and Campinas (12.7 vs. 6.2; $p<0.001$) reported significantly more visits to a general physician before referral to a specialist (Figure 46).

Figure 46 - Centre-wise comparisons of number of general physician visits before referral to specialist



23.2.2 Care-seeking and referral to specialists in disease outcome groups

As shown in Table 47, women with endometriosis reported an average of 6.5 (SD 10.2) visits to a primary care physician before referral to a gynaecologist but this was not different to the number of visits reported by symptomatic controls (6.8, SD 10.6; $p=0.59$).

Similarly, amongst women with endometriosis, after adjusting for age and site, there was no association between disease stage and number of general physician visits made by women before referral to specialists (adjusted OR 0.99; 95% CI 0.41).

23.2.3 Further characterisation of care-seeking and referral to specialists

Women who were investigated for pelvic pain without subfertility saw their general physicians most frequently (7.7, SD 12.8) before specialist referral; those who were investigated for other

symptoms than pelvic pain and subfertility saw their general physicians the least number of times (3.7, SD 4.6).

Referral to another specialist other than the current gynaecologist was made in 21.6% of women; 58.6% of those referrals were to another gynaecologist in the first instance, although a higher proportion of subsequent referrals involved other specialists, principally gastroenterologists and urologists.

Table 49 - Referral to other specialists

Other specialist referred to	Another Gynaecologist	Gastroenterologist	Urologist	GU clinic	Physiotherapist	Other	n	%*
1st specialist	163	55	14	9	6	20	278	21.6
2nd specialist	10	13	10	1	2	8	44	3.4
3rd specialist	2	2	1	1	1	3	10	0.8
4th specialist	0	0	0	0	0	1	1	0.1

* - based on a denominator of 1,287 women who were symptomatic; Total N for 1st specialist includes 11 missing observations

23.3 Diagnostic delay

As noted earlier, women with endometriosis began to experience symptoms at a significantly younger age than controls. By the time they first sought medical advice for their symptoms, they were on average 26.8 years and controls 27.9 years (age-adjusted $p=0.003$). Considering that the average age at diagnosis was 32.6 years for those with endometriosis, the interval between symptom onset and laparoscopic diagnosis of disease was 9.8 years and this was significantly longer than in symptomatic controls (8.3 years; age-adjusted $p=0.001$). Diagnostic delay was largely accounted for by longer time to laparoscopy after the initial consultation with a primary care physician rather than by the length of the interval between symptom onset and first primary care physician consultation. On average, women with symptoms consulted their primary care physicians 3.5 years (SD 6.3) after symptom onset, this being longer in those with endometriosis (3.9 years, SD 6.4) than in symptomatic controls (3.1 years, SD 6.1; $p=0.043$). Therefore, as shown

in Figure 47, the interval between symptom onset and first primary care physician consultation only accounted for about 38% of the length of the diagnostic delay experienced by women in the study, with primary care physician-related delays accounting for most of the diagnostic delay.

Figure 47 - Relative contributions (in years) of patient- and physician-related delay to overall diagnostic delay (% contributed by patient delays labeled)

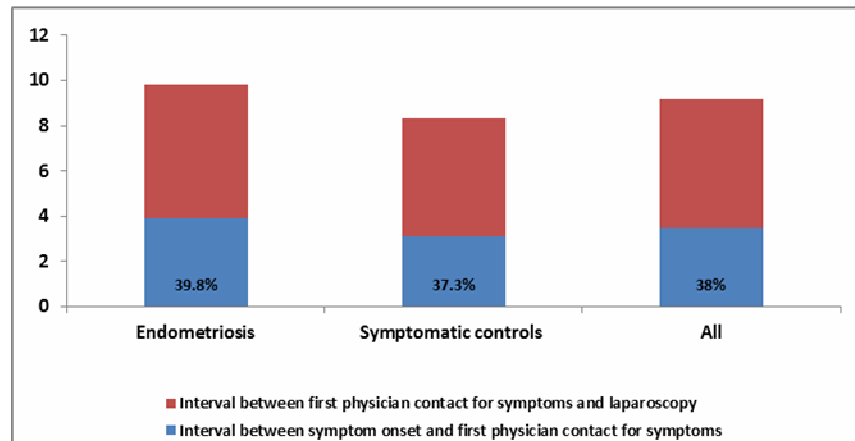


Table 50 - Diagnostic interval for symptomatic women by Centre

Centre	Mean age in years at symptom onset (SD)	Mean age in years at diagnosis (SD)	Diagnostic delay in years (SD)
Barcelona	21.5 (9.3)	35.4 (5.7)	13.9 (8.5)
Boston	17.5 (11.1)	31.4 (6.9)	13.9 (9.3)
Campinas	22.9 (8.1)	33 (5.9)	10.1 (8)
Dublin	23.4 (9)	32.6 (5.8)	9.2 (8.1)
Guangzhou	26.7 (7.5)	30.8 (6.1)	4.1 (5)
Ibadan	26.0 (6.6)	32.5 (5.4)	6.5 (5.5)
Leuven	23.2 (8.2)	31.6 (4.8)	8.4 (7.3)
Oxford	21.9 (10.1)	34.8 (7)	12.9 (10.3)
Rome	22.6 (10.2)	34.3 (5.9)	11.7 (10)
Sao Paulo	20.7 (9.3)	34.7 (6)	14 (9.8)
Shanghai	27.6 (8.3)	32.4 (6.2)	4.8 (6.9)
Siena	17.4 (10.2)	36.4 (5.5)	19 (10.9)
Others	22.4 (11.2)	33.5 (6.4)	11.1 (8.2)
Total	23.7 (9.3)	33 (6.3)	9.2 (8.8)

The mean diagnostic delay was longer in women who underwent investigation for pelvic pain (mean 12.0, 95% CI 11.2 – 12.8 years) than in those who did so for subfertility (mean 4.8, 95% CI 4.1 – 5.4 years) ($p < 0.001$). Women at the lowest quintile of age at symptom onset (mean age at

symptom onset 11.9 years) had a mean diagnostic delay of 19.4 years (SD 7.6) compared to those in the highest quintile (mean age at symptom onset 37.3 years) who had a mean diagnostic delay of 2.4 years (SD 2.4) (data not shown).

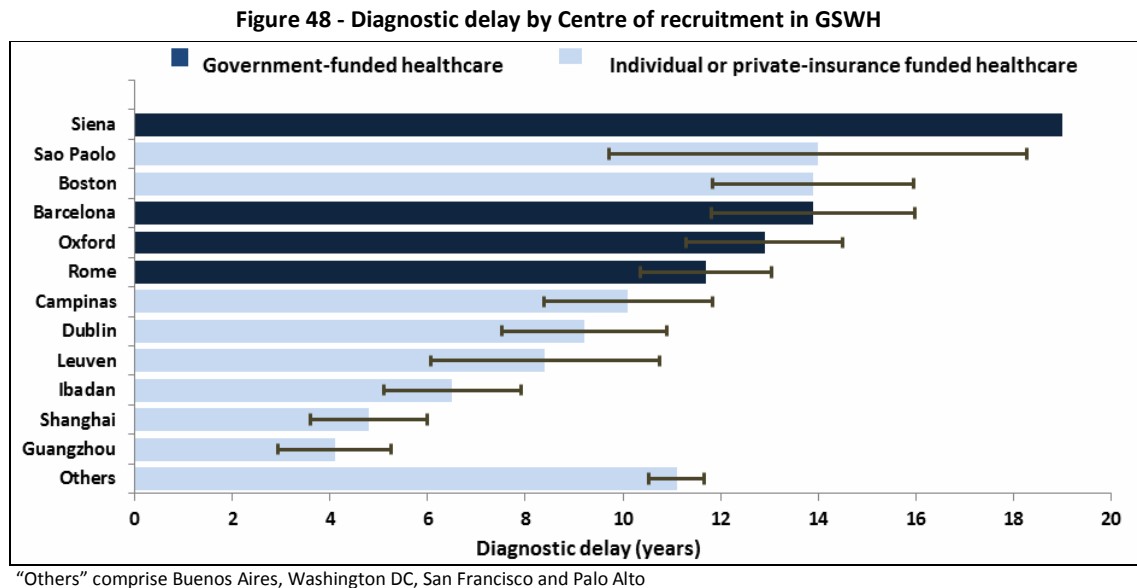


Figure 48 shows the variation in diagnostic delay across centres by nature of health care funding at those centres. Notably, in multivariate regression with diagnostic interval as outcome and nature of health care funding as an independent variable, after adjusting for site, type of symptoms presented (pelvic pain or subfertility), number of pelvic symptoms and pelvic pain severity, average diagnostic delay (12.8 years; 95% CI 11.7-13.9) was significantly longer in centres where patients received predominantly government-funded healthcare (Barcelona, Oxford, Rome, Siena and Washington DC), compared to those where care was self- or private insurance funded (7.6 years; 95% CI 7.1-8.2) (adjusted $p < 0.001$).

In multivariate adjustment for centre, education, ethnicity, co-morbidity and pelvic pain severity, diagnostic delay was longer if women had a higher BMI ($\beta = 0.22$; adjusted $p < 0.001$), reported more pelvic symptoms ($\beta = 2.7$; adjusted $p < 0.001$), reported pelvic pain with subfertility ($\beta = 4.7$;

adjusted $p < 0.001$) and attended care at a centre where healthcare was predominantly state-funded ($\beta = 2.64$; adjusted $p < 0.001$). Amongst women with endometriosis, diagnostic delay did not differ significantly in those with minimal-mild (10.2 years; SD 9.1) and moderate-severe (9.3 years; SD 8.4) endometriosis ($p = 0.24$).

24 Discussion

The early symptoms of endometriosis often involve dysmenorrhoea during the menstrual period, making it sometimes difficult to tell if the symptom represents primary (no underlying disease) or secondary (underlying disorder, in this case endometriosis) dysmenorrhoea [224]. Other symptoms eventually emerge depending on the location of the implanted endometrial tissue. In keeping with this observation, dysmenorrhoea was the earliest-onset symptom for which laparoscopy was performed in all women with endometriosis (19.9 years, SD 8.1) in this study population. In these women, painful intercourse was reported at an average of 26.5 years (SD 7.4) and correlated with the location of endometriotic nodules in the cul-de-sac and bowel.

Generally, women with endometriosis were significantly younger at symptom onset than symptomatic controls (22.9 vs. 24.8 years; $p < 0.001$) and this was independent of their earlier age at menarche. The average age at symptom onset of 23.7 years (SD 9.3) in this study population was similar to the figure of 24.3 years (SD 8.1) reported for a prospectively [224] recruited Australian population of 195 women with pelvic pain, with or without subfertility, and either suspected of having endometriosis or referred to the tertiary centre of study with a known history of surgically confirmed endometriosis. Notably, the mean age of women in that population (34.6 years, SD 7.6) was also similar to that for this study population (33.0 years, SD 6.3).

In keeping with the observation that pelvic pain is usually one of the earliest symptoms of endometriosis, women who reported pelvic pain without subfertility were significantly younger at symptom onset than those who reported subfertility without pelvic pain (20.0 vs. 27.6 years; $p < 0.001$). In light of the tendency for early symptoms of endometriosis to be confused with 'normal' menstrual features, it is perhaps not surprising that, in comparison with women in the oldest quintile of age at symptom onset (mean age 37.3 years), those in the youngest quintile (mean age 11.9 years), irrespective of the nature of their symptoms, took longer to report symptoms to a primary care physician (8.7 vs. 0.51 years; $p < 0.001$). This finding confirms a similar report in a retrospective cohort of 200 Brazilian women with surgically confirmed endometriosis [226].

After accounting for age at symptom onset, women with endometriosis had a similar interval (3.9 years, SD 6.4) between symptom onset and care-seeking compared to symptomatic controls (3.1 years, SD 6.1). Similarly, they visited their primary care physicians an average of 6.5 times before they were referred to a gynaecologist for assessment and surgical diagnosis and this was similar to the number of visits (6.8) made by symptomatic controls ($p = 0.52$). Repeated consultations in primary care before the diagnosis is made are consistently reported in endometriosis. In one retrospective analysis of data collected from primary care records in four English general practices, a third of the women had consulted their primary care physicians 6 or more times before the diagnosis was eventually made [28]. The similarity between affected women and symptomatic controls in the time to initiating care-seeking and frequency of primary care physician visits despite earlier onset of symptoms in the latter group perhaps highlights the importance of symptoms, irrespective of underlying cause, in driving healthcare utilisation in women with symptoms suggestive of endometriosis.

This study found a diagnostic delay of 9.2 years (SD 8.8) in all women; after adjusting for age, there was a significant difference between affected women and symptomatic controls (9.8 vs. 8.3 years; $p=0.001$). After adjusting for the nature of symptom presented, the delay in diagnosis was longer in women who were younger at symptom onset (19.4 vs. 2.4 years in women in the youngest vs. oldest quintile of age at symptom onset, respectively; $p<0.001$). About 62% of the duration of diagnostic delay was due to delays in referral to secondary care after consultation with a primary care physician, while patient-related delays in seeking medical attention for their symptoms accounted for about 38% of the delay duration. After controlling for relevant covariates, diagnostic delay was longer in women with higher BMI ($\beta=0.22$; $p<0.001$) and in those who reported a greater number of pelvic symptoms ($\beta=2.7$; $p<0.001$). Amongst women with endometriosis, diagnostic delay did not differ in women by disease stage ($p=0.24$). Notably too, after controlling for relevant covariates (including site, the type of symptoms women had, the number of pelvic symptoms they reported and the average severity of their pelvic pain), diagnostic delay was significantly longer by 5.2 years (adjusted $p<0.001$) in women at centres where health care was predominantly government-funded.

Reporting onset of dysmenorrhoea only after the age of 25 in this study population was associated with greater likelihood of having endometriosis diagnosed at laparoscopy ($p=0.036$). This finding confirms those of Treloar et al. [202] who reported that dysmenorrhoea, as an early menstrual characteristic, was associated with more than a two-fold increased risk of endometriosis diagnosis in later life. Indeed, it is relatively well reported that secondary dysmenorrhoea due to endometriosis is usually late in onset [227].

The diagnostic delay of 9.8 years in women with endometriosis in this study is not surprising as delays of that duration have been reported previously in the literature. In one of the earliest studies on the subject, Hadfield *et al.* [26] assessed the interval between symptom onset and

eventual diagnosis in 218 UK and USA women with surgically diagnosed endometriosis recruited from self-help groups and found an average delay of 11.7 and 8.0 years in the US and UK women respectively. The sourcing of patients recruited into the study from self-help groups might have meant women were more likely to report longer delays, which was acknowledged by the authors but affected women in this study report a similar length of diagnostic delay. A later study in Norwegian women recruited mainly from the national Endometriosis Association found a similar delay of 6.7 years [228]. In another UK study of general practitioner-registered women with endometriosis read codes, a delay of 9 years was found although the potential for misclassification was significant in this study [28]. A number of reasons for diagnostic delays in endometriosis have been proposed, involving both patient- and physician-related factors. Perhaps the most common reason for delays related to the patient is a lack of awareness of endometriosis and an inability amongst women to distinguish 'normal' from 'abnormal' menstrual features. Indeed, the study by Shah et al. [229] laid the blame with women and their social networks (of both genders) for a lack of awareness resulting in delays in consultations and consequent delayed diagnosis [229]. Seear similarly suggests that women with symptoms of endometriosis may be responsible in large part for the delays, but disputes the importance of lack of awareness or inability to determine what symptoms are 'normal'. Instead, Seear suggests that deliberate avoidance of the subject of menstrual symptoms is the root cause [25]. Drawing from Erving Goffman's treatise on stigma [230], she makes a compelling sociological argument that menstruation and related features, such as menstrual symptoms, are deeply 'discrediting' attributes. The anticipation of social sanctions consequent upon disclosure of such discrediting attributes in the form of discrimination from employers, physicians and social networks, result in a deliberate reluctance to initiate consultation even when women recognise the abnormality of their symptoms. In effect, not wanting to appear weak or unable to cope, and for fear of the risk of stigmatisation, women avoid or delay consultation [25,27]. However, assuming that women's recall of their symptoms was accurate, this study does not establish a significant role for patient

delays since they accounted for only about 38% of the total diagnostic delay. The results thus confirm other findings that indicate delays are predominantly associated with the care-seeking experience within primary care [28,231]. For example, Denny et al. suggest that women's negative experiences in primary care indicate that more sensitive history taking, which avoids trivialising women's symptoms, could reduce diagnostic delays [23,231]. Ballard et al. suggest that specialist guidelines on chronic pain management, which place diagnostic laparoscopy as a second line test after empirical treatment, actually lead to significant diagnostic delays in endometriosis [27]. Indeed, one survey suggested that Brazilian gynaecologists who were better informed suspected and diagnosed endometriosis earlier [232]

Although a positive association between higher BMI and diagnostic delay is recognised in multiple sclerosis, diabetes and breast cancer [233-235], it has never been reported in endometriosis nor are the reasons for the association immediately obvious. The association between BMI and breast cancer is independent of health behaviour, education and social class and is thought to be related to greater difficulty in identifying tumours in bigger breasts assuming breast size correlates with BMI [234]. In the 'Atherosclerosis Risk in Communities' (ARIC) study where baseline obesity strongly predicted delayed diagnosis of type 2 diabetes, the authors noted that the result was unexpected but suggested that higher BMI was associated with fewer symptoms in the study population where symptoms associated with weight loss before diagnosis principally prompted investigation [235]. Marrie et al. [233] offer no explanation for their findings in multiple sclerosis. More general observations that might explain the link between delayed diagnosis in endometriosis and higher BMI include the fact that body fat limits imaging accuracy, resulting potentially in missed pelvic masses that might otherwise have instigated further investigations and a quicker diagnosis. Women with higher BMI also tend to be less avid users of preventive health care services [236]. It is thought that the self-image of obese women influences their attitude to disrobing and manual manipulation of their bodies, especially in pelvic examinations;

similarly, physicians are more likely to be dissuaded from performing physical examinations on obese women, particularly pelvic examination, which they deem to be technically more complicated in such women [237,238]. Finally, it is possible that surgeons may be reluctant to operate on obese women because of increased operative risks, thus contributing to delayed diagnosis. Even with these possible explanations, it still remains unclear whether they could result in diagnostic delay in a population of predominantly symptomatic women whose need is principally for curative rather than preventive health care.

In this study, diagnostic delay was similar in women with minimal-mild and moderate-severe endometriosis. The findings are compatible with those of Hadfield *et al.* [26]; namely that the stage of disease did not affect the length of time between the onset of symptoms and diagnosis. Matsuzaki *et al.*'s finding of a longer diagnostic delay in women with Stage IV (severe), compared to Stage I-III (minimal-moderate) disease, was limited to those with deep infiltrating endometriosis [239]. Our finding of longer diagnostic delays in affected women who were younger at symptom onset replicates similar findings in other studies [226,239].

The association between diagnostic delay in endometriosis and the nature of healthcare funding has not been reported across a broad population to date although longer diagnostic delays in cancer patients with public or no health insurance compared to those privately insured has been observed [240]. In the study by Arruda *et al.* (based in Brazil), the median delay from onset of symptoms to diagnosis at public hospitals (6.3 years) was shorter than that at private clinics (9.1 years). In the present study, the diagnostic delay across the two Brazilian centres, both private institutions, was 8.5 years (95% CI 7.5-9.6 years), which confirms Arruda *et al.*'s findings [226]. The reason for longer diagnostic delays in centres where health care was state- or government funded is not immediately obvious but one could speculate that it may be related to healthcare rationing. This is a necessary approach to optimising value for finite resources. However, the case

has been made that rationing diagnostic procedures delays the treatment of reproductive problems which, if treated early, could prevent future expenditure [241]. The present study cannot establish that rationing was a factor; it is entirely possible that other mechanisms are at play – such as the negative experiences of initial primary care consultations for symptoms, which women have reported [231].

In summary, this study replicates previously reported diagnostic delays in endometriosis and highlights the unacceptable frequency of repeated consultations before women with symptoms suggestive of endometriosis are referred to a specialist. Much more effort is therefore needed to facilitate a raised index of suspicion of endometriosis in primary care and expedite the diagnosis in women with symptoms.

CHAPTER 7

**ENDOMETRIOSIS AND HEALTH-RELATED
QUALITY OF LIFE**

25 Introduction

25.1 Health-related Quality of Life (HRQoL)

The terms *health status*, *functional status*, and *quality of life* (QoL) are often used interchangeably to refer to the same domain of "health", which ranges from negatively valued aspects of life such as death to more positively valued ones such as happiness [242]. Although *quality of life* and *health-related quality of life* (HRQoL) are often used interchangeably, HRQoL is an aspect and probably one of the strongest determinants of QoL [243]. HRQoL, which is a type of patient related outcome measure, is a multi-dimensional dynamic concept that developed from the need to estimate the psychosocial impact of diseases, which includes economic welfare, characteristics of the community and environment, and health status [243]. Although it has increasingly gained prominence in health research and clinical application in the last three decades, the concept of HRQoL takes its origins from the World Health Organisation definition of health over fifty years ago: "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [244]. Three domains are therefore implied in HRQoL – biological functioning, psychological functioning and social functioning. A good HRQoL instrument captures all three domains and summarises them in a single metric. HRQoL is an important means to measure the impact of chronic disease from the perspective of the individual. As the interest in HRQoL measurement over the years has grown, so has the development of a wide variety of assessment instruments. Generally, HRQoL measures can be generic or disease-specific, health profiles or preference-based [245]. They can either be discriminative (differentiating between people who have a better HRQoL and those who have worse HRQoL) or evaluative (measuring how HRQoL has changed over time).

The HRQoL instrument employed in this study to assess the impact of endometriosis on HRQoL is the Short Form 36 version 2 (SF36v2) [162], a generic health profile which has both discriminative

and evaluative properties. In this study however, it is employed specifically as a discriminative, rather than an evaluative, tool since the aim of the research is to distinguish HRQoL in women with and without endometriosis.

25.2 Aim of study

The impact of endometriosis on HRQoL, principally through its symptoms, has been documented but the influence of factors such as disease and symptom severity, the care-seeking experience and treatment interventions on HRQoL remains unclear. Previous studies of HRQoL in endometriosis have not contributed much information because they have focused on highly selected populations, with small sample sizes and poorly selected controls, and used HRQoL surveys that have only been validated in limited populations.

This chapter explores the impact of endometriosis on HRQoL, focusing on five key research questions:

- Is HRQoL affected by endometriosis? What is the nature of the impact?
- Is the impact of endometriosis on HRQoL explained by the symptoms of endometriosis?
- In symptomatic women, what is the relationship between symptom severity and HRQoL impairment?
- What is the relationship between endometriosis severity and HRQoL impairment?
- How does HRQoL in women with CPP differ with underlying endometriosis compared to other underlying conditions, such as IBS?

26 Methods and statistical analysis

Validated language versions of the SF36v2 questionnaire applicable to each of the centres were incorporated into the 67-item study questionnaire to measure HRQoL. The SF36v2 includes 36

questions clustered to measure eight HRQoL domains: physical functioning (10 items), social functioning (2 items), physical role limitation (4 items), emotional role limitation (3 items), mental health (5 items), energy/vitality (4 items), bodily pain (2 items), and general health perception (5 items). An unscaled single item measures health transition. Two summary scores can be calculated for the SF36v2 (see below under “statistical analyses”)

For each dimension of the SF36v2 survey, item scores were coded, summed, and transformed on a scale from 0 (worst possible health state measured by the questionnaire) to 100 (best possible health state); missing data were not substituted. Using normative data from the Third Oxford Health and Lifestyles Survey [168], two standardised summary scores were calculated from the SF36v2: the physical health component summary (PCS) and the mental health component summary (MCS).

Mean dimension scores in cases and sterilisation/symptomatic controls were compared using the t test for differences of means. Relevant covariates were adjusted for in regression analyses of the impact of endometriosis on SF36v2 dimension and component summary scores. To statistically compare component summary scores for the study population with those for the normative population, testing of study population means against a mean of 50 and SD 10 for the normative population using the one sample t test was conducted.

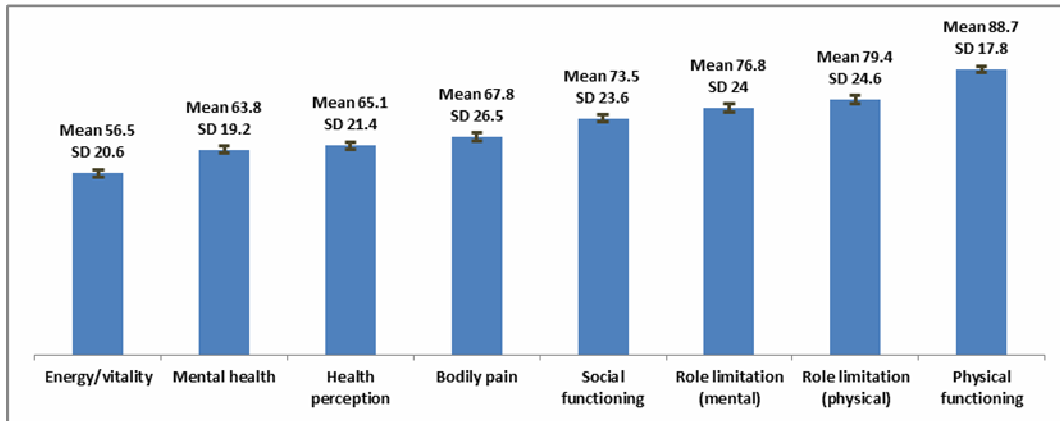
All analyses were done using Stata Release 11 (Stata Corporation, College Station, Texas, USA).

27 Results

27.1 SF36v2 mean dimension scores

27.1.1 Study population dimension scores

Figure 49 - Mean dimension score and SD for SF36v2 dimensions



As shown in Figure 49, SF36v2 dimension scores for women in the study population ranged from 56.5 (SD 20.6) for the energy/vitality dimension to 88.7 (SD 17.8) for the physical functioning dimension. Figures 50-57 show the mean (SD) scores for each SF36v2 dimension for women by centre in addition to the mean study population dimension score.

27.1.2 Centre-wise comparisons on dimension scores

Figure 50 – Mean study population scores (SD) in the SF36v2 dimension of energy/vitality

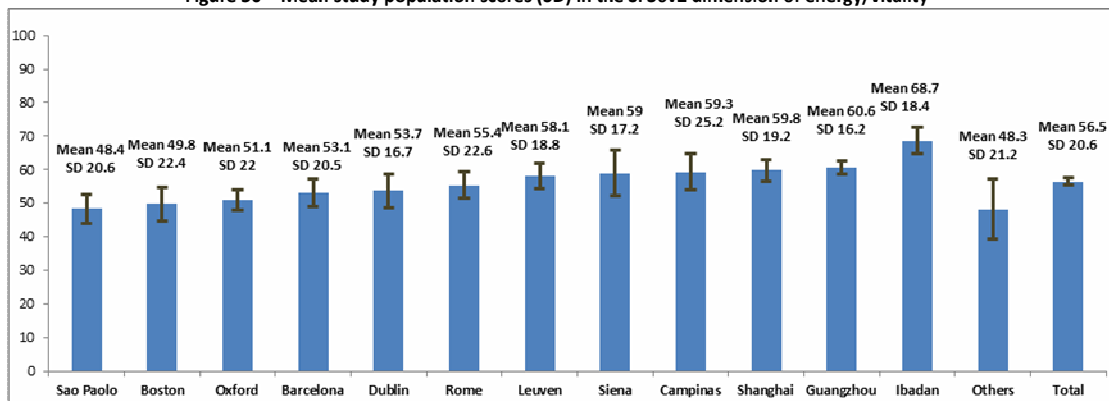


Figure 51 - Mean study population scores (SD) in the SF36v2 dimension of mental health

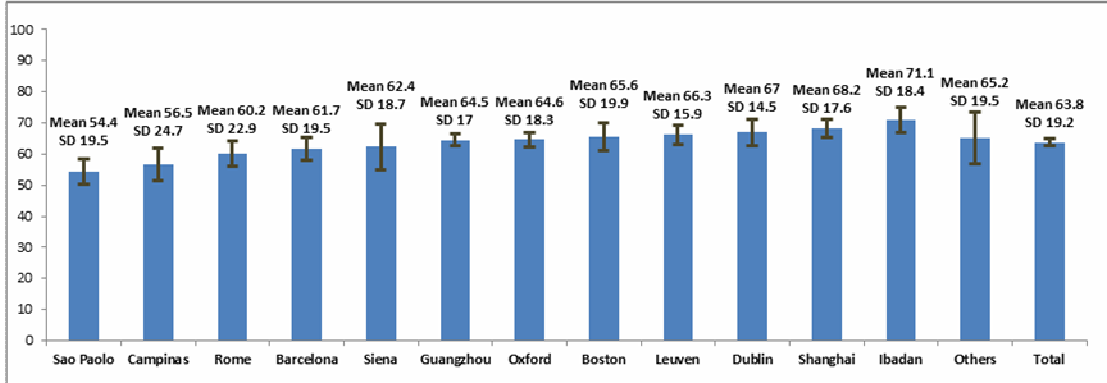


Figure 52 - Mean study population scores (SD) in the SF36v2 dimension of health perception

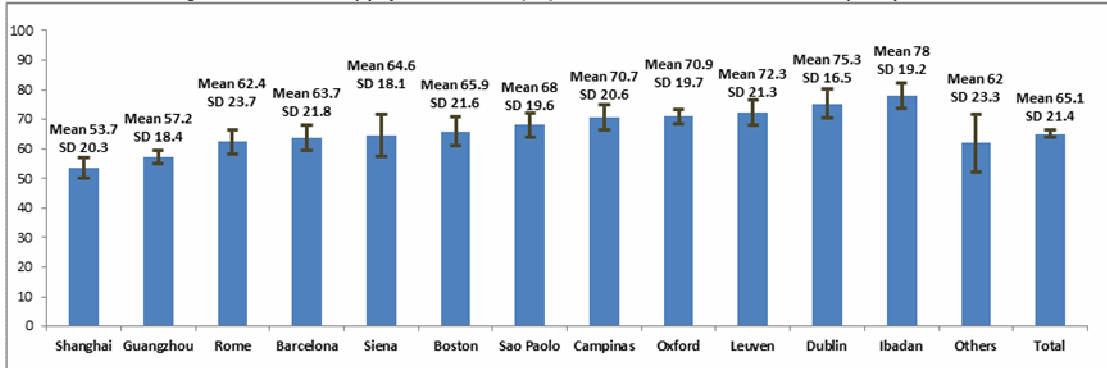


Figure 53 - Mean study population scores (SD) in the SF36v2 dimension of bodily pain

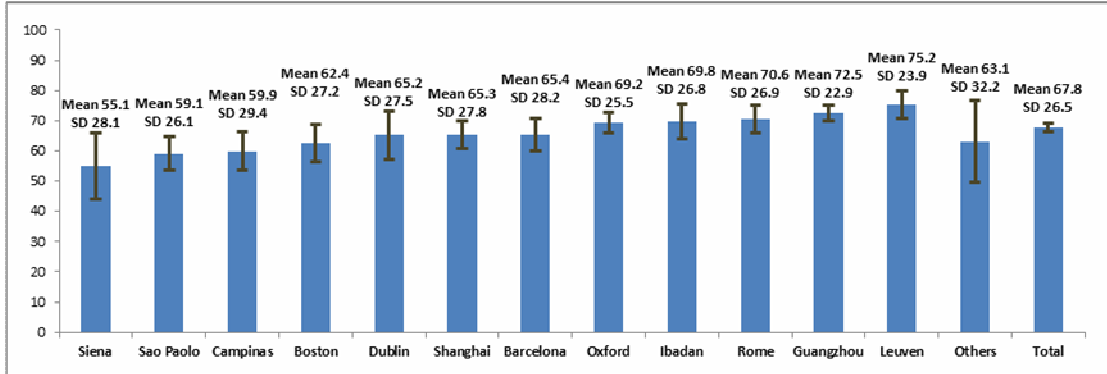


Figure 54 - Mean study population scores (SD) in the SF36v2 dimension of social functioning

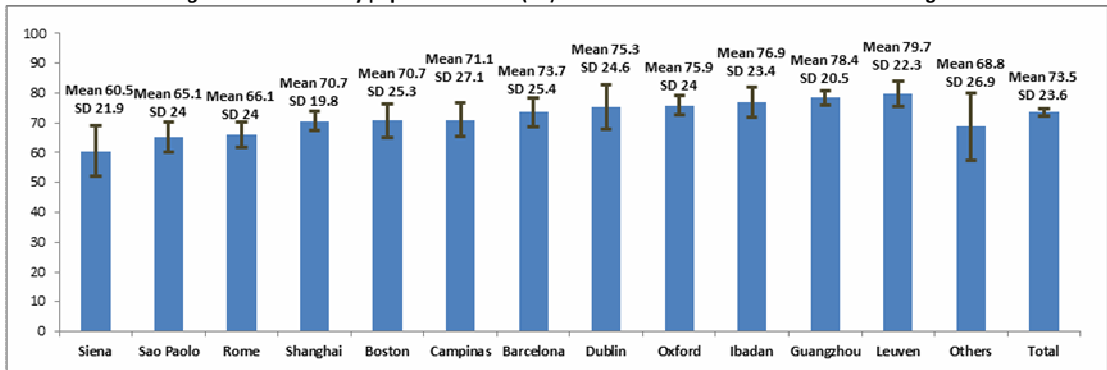


Figure 55 - Mean study population scores (SD) in the SF36v2 dimension of role limitation (mental)

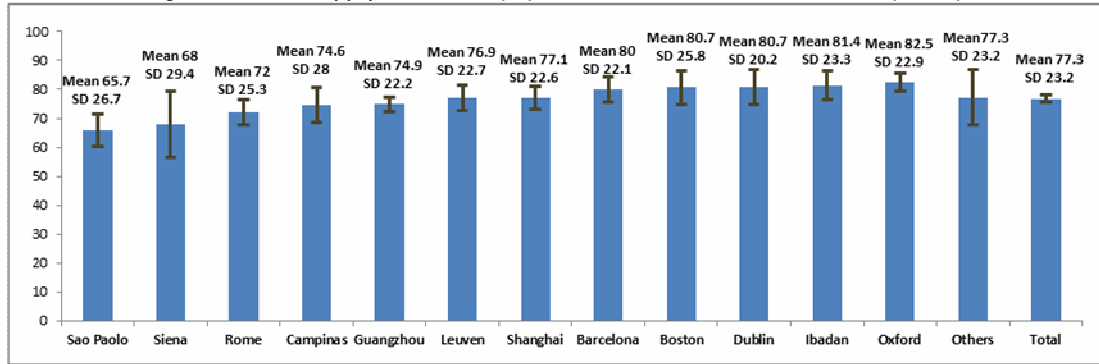


Figure 56 - Mean study population scores (SD) in the SF36v2 dimension of role limitation (physical)

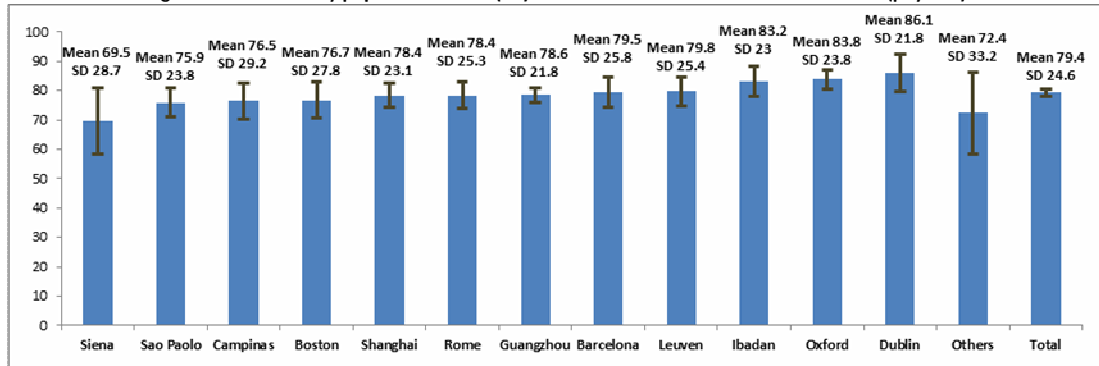
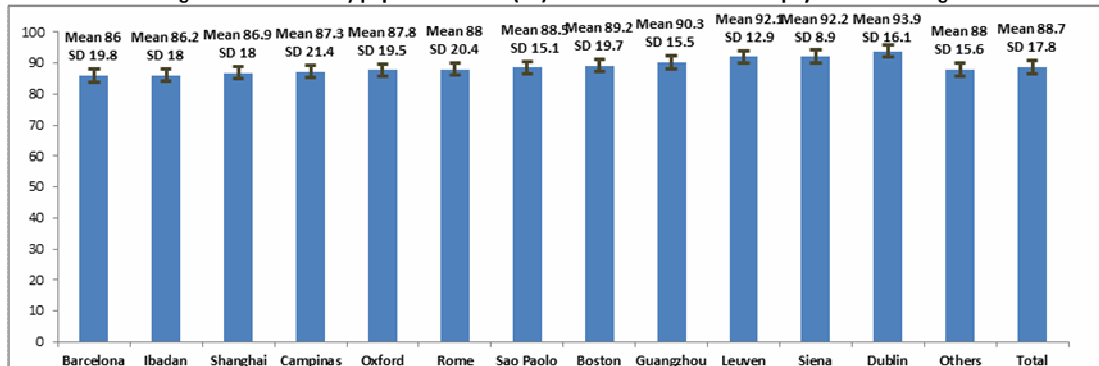


Figure 57 - Mean study population scores (SD) in the SF36v2 dimension of physical functioning



Tables 51-54 display centre-wise comparisons on SF36v2 dimension scores. Women in Guangzhou (60.6 vs. 55.3, $p < 0.001$) and Ibadan (68.7 vs. 55.7, $p < 0.001$) had significantly higher **energy & vitality** dimension scores than the average woman in the remainder of the study population while women in Boston (49.8 vs. 56.8, $p = 0.004$), Oxford (51.1 vs. 57.4, $p < 0.001$) and Sao Paolo (48.4 vs. 57.0, $p < 0.001$) had significantly lower scores than the average woman in the remainder of the study population. Women in Ibadan (71.1 vs. 63.3, $p < 0.001$) and Shanghai (68.2 vs. 63.3, $p = 0.006$)

had significantly higher **mental health** dimension scores than the average woman in the remainder of the study population while women in Campinas (56.5 vs. 64.3, $p<0.001$), Rome (60.2 vs. 64.1, $p=0.033$) and Sao Paolo (54.4 vs. 64.4, $p<0.001$) had significantly lower scores than the average woman in the remainder of the study population. In the **health perception** dimension, women in Campinas (70.7 vs. 64.7, $p=0.012$), Dublin (75.3 vs. 64.7, $p=0.001$), Ibadan (78.0 vs. 64.3, $p<0.001$), Leuven (72.3 vs. 64.5, $p<0.001$) and Oxford (70.9 vs. 64.0, $p<0.001$) had significantly higher scores than the average woman in the remainder of the study population but those in Guangzhou (57.2 vs. 67.2, $p<0.001$) and Shanghai (53.7 vs. 66.2, $p<0.001$) had significantly lower scores than the average woman in the remainder of the study population. In the **bodily pain** dimension, women in Guangzhou (72.5 vs. 66.6, $p<0.001$) and Leuven (75.2 vs. 67.2, $p=0.003$) had significantly higher scores than the average woman in the remainder of the study population but those in Campinas (59.9 vs. 68.3, $p=0.004$), Sao Paolo (59.1 vs. 68.4, $p=0.002$) and Siena (55.1 vs. 68.1, $p=0.015$) had significantly lower scores than the average woman in the remainder of the study population.

Similarly, Tables 55-58 display centre-wise comparisons on SF36v2 dimension scores. Women in Guangzhou (78.4 vs. 72.3, $p<0.001$) and Leuven (79.7 vs. 73.1, $p=0.006$) had significantly higher **social functioning** dimension scores than the average woman in the remainder of the study population while women in Rome (66.1 vs. 74.3, $p<0.001$), Sao Paolo (65.1 vs. 74.1, $p<0.001$) and Siena (60.5 vs. 73.8, $p=0.005$) had significantly lower scores than the average woman in the remainder of the study population. Women in Oxford (82.5 vs. 75.7, $p<0.001$) had a significantly higher **mental role limitation** dimension score than the average woman in the remainder of the study population while women in Rome (72.0 vs. 77.2, $p=0.019$) and Sao Paolo (65.7 vs. 77.5, $p<0.001$) had significantly lower scores than the average woman in the remainder of the study population. In the **physical role limitation** dimension, women in Oxford (83.8 vs. 78.6, $p=0.004$) had a significantly higher score than the average woman in the remainder of the study population

but those in Siena (69.5 vs. 79.6, $p=0.042$) had a significantly lower score than the average woman in the remainder of the study population. Finally, in the **physical functioning** dimension, women in Leuven (92.1 vs. 88.4, $p=0.047$) had a significantly higher mean score than the average woman in the remainder of the study population.

Table 51 – Energy/vitality – Centre-wise comparisons

Centre	Mean dimension score (SD) in Centre	Mean dimension score (SD) in remainder of study population	Student's t test p-value
Barcelona	53.1	56.7	0.089
Boston	49.8	56.8	0.004
Campinas	59.3	56.3	0.19
Dublin	53.7	56.5	0.37
Guangzhou	60.6	55.3	<0.001
Ibadan	68.7	55.7	<0.001
Leuven	58.1	56.3	0.40
Oxford	51.1	57.4	<0.001
Rome	55.4	56.6	0.55
Sao Paolo	48.4	57.0	<0.001
Shanghai	59.8	56.1	0.051
Siena	59.0	56.4	0.53
Others	48.3	56.6	0.061

Table 52 – Mental health – Centre-wise comparisons

Centre	Mean dimension score (SD) in Centre	Mean dimension score (SD) in remainder of study population	Student's t test p-value
Barcelona	61.7	64.0	0.26
Boston	65.6	63.7	0.40
Campinas	56.5	64.3	<0.001
Dublin	67.0	63.7	0.26
Guangzhou	64.5	63.6	0.46
Ibadan	71.1	63.3	<0.001
Leuven	66.3	63.6	0.18
Oxford	64.6	63.6	0.50
Rome	60.2	64.1	0.033
Sao Paolo	54.4	64.4	<0.001
Shanghai	68.2	63.3	0.006
Siena	62.4	63.8	0.72

Table 53 - Health perception – Centre-wise comparisons

Centre	Mean dimension score (SD) in Centre	Mean dimension score (SD) in remainder of study population	Student's t test p-value
Barcelona	63.7	65.2	0.50
Boston	65.9	65.0	0.73
Campinas	70.7	64.7	0.012
Dublin	75.3	64.7	0.001
Guangzhou	57.2	67.2	<0.001
Ibadan	78.0	64.3	<0.001
Leuven	72.3	64.5	<0.001
Oxford	70.9	64.0	<0.001
Rome	62.4	65.3	0.14
Sao Paolo	68.0	64.9	0.18
Shanghai	53.7	66.2	<0.001
Siena	64.6	65.1	0.91
Others	62.0	65.1	0.50

Table 54 – Bodily pain – Centre-wise comparisons

Centre	Mean dimension score (SD) in Centre	Mean dimension score (SD) in remainder of study population	Student's t test p-value
Barcelona	65.4	68.0	0.33
Boston	62.4	68.1	0.068
Campinas	59.9	68.3	0.004
Dublin	65.2	67.9	0.50
Guangzhou	72.5	66.6	<0.001
Ibadan	69.8	67.7	0.48
Leuven	75.2	67.2	0.003
Oxford	69.2	67.6	0.39
Rome	70.6	67.5	0.21
Sao Paolo	59.1	68.4	0.002
Shanghai	65.3	68.1	0.24
Siena	55.1	68.1	0.015
Others	62.1	67.9	0.40

Table 55 – Social functioning – centre-wise comparisons

Centre	Mean dimension score (SD) in Centre	Mean dimension score (SD) in remainder of study population	Student's t test p-value
Barcelona	73.7	73.5	0.94
Boston	70.7	73.7	0.28
Campinas	71.1	73.7	0.32
Dublin	75.3	73.5	0.63
Guangzhou	78.4	72.3	<0.001
Ibadan	76.9	73.3	0.19
Leuven	79.7	73.1	0.006
Oxford	75.9	73.1	0.11
Rome	66.1	74.3	<0.001
Sao Paolo	65.1	74.1	<0.001
Shanghai	70.7	73.8	0.14
Siena	60.5	73.8	0.005
Others	68.8	73.6	0.34

Table 56 – Role-limitation (mental) – Centre-wise comparisons

Centre	Mean dimension score (SD) in Centre	Mean dimension score (SD) in remainder of study population	Student's t test p-value
Barcelona	80.0	76.5	0.16
Boston	80.7	76.5	0.14
Campinas	74.6	76.9	0.39
Dublin	80.7	76.6	0.26
Guangzhou	74.9	77.2	0.15
Ibadan	81.4	76.5	0.075
Leuven	76.9	76.7	0.94
Oxford	82.5	75.7	<0.001
Rome	72.0	77.2	0.019
Sao Paolo	65.7	77.5	<0.001
Shanghai	77.1	76.7	0.88
Siena	68.0	76.9	0.066
Others	77.2	76.9	0.92

Table 57 – Role-limitation (physical) – Centre-wise comparisons

Centre	Mean dimension score (SD) in Centre	Mean dimension score (SD) in remainder of study population	Student's t test p-value
Barcelona	79.5	79.4	0.96
Boston	76.7	79.6	0.33
Campinas	76.5	79.6	0.27
Dublin	86.1	79.2	0.059
Guangzhou	78.6	79.6	0.53
Ibadan	83.2	79.2	0.15
Leuven	79.8	79.4	0.85
Oxford	83.8	78.6	0.004
Rome	78.4	79.5	0.65
Sao Paolo	75.9	79.6	0.17
Shanghai	78.4	79.5	0.62
Siena	69.5	79.6	0.042
Others	72.4	79.5	0.18

Table 58 – Physical functioning – centre-wise comparisons

Centre	Mean dimension score (SD) in Centre	Mean dimension score (SD) in remainder of study population	Student's t test p-value
Barcelona	86.0	88.9	0.10
Boston	89.2	88.7	0.79
Campinas	87.3	88.8	0.46
Dublin	93.9	88.5	0.05
Guangzhou	90.3	88.3	0.09
Ibadan	86.2	88.8	0.19
Leuven	92.1	88.4	0.047
Oxford	87.8	88.9	0.42
Rome	88.0	88.8	0.65
Sao Paolo	88.5	88.7	0.94
Shanghai	86.9	88.9	0.21
Siena	92.2	88.6	0.32
Others	88.0	88.7	0.84

27.1.3 Disease outcome group comparisons on dimension scores

Table 59 – p values for association of variables with endometriosis and SF36v2 dimensions

Variable associated with endometriosis	Energy & vitality	Mental health	Health perception	Bodily pain	Social functioning	Mental role limitation	Physical role limitation	Physical functioning
Gravidity	0.48	0.16	0.24	0.32	0.032	0.059	0.58	0.001
Pelvic pain severity	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Non-endometriotic adhesions	0.96	0.32	0.45	0.55	0.64	0.73	0.68	0.92

As shown in Table 59 above, for each SF36v2 dimension, only gravidity and/or pelvic pain severity were associated with endometriosis on multivariate regression (see chapter 4) as well as independently with individual dimensions of the SF36v2 in the study population.

Table 60 - Comparison of SF36v2 dimension scores across disease outcome groups, with adjusted p values (following adjustment for relevant confounding variables as detailed in Table 59)

SF36v2 dimension	Endometriosis n=745	No endometriosis					
		Symptomatic controls N=587	Unadjusted p value	Adjusted p value	Sterilisation controls N=86	Unadjusted p value	Adjusted p value
<i>Health-related quality of life</i> [Mean (SD)]							
Energy & vitality	54.4 (20.3)	58.0 (20.6)	0.002	0.77	60.5 (20.8)	0.010	0.13
Mental health	62.7 (19.9)	64.8 (18.2)	0.050	0.73	64.1 (20.0)	0.56	0.74
Health perception	62.5 (21.9)	67.5 (20.4)	<0.001	0.052	72.3 (20.2)	<0.001	0.033
Bodily pain	62.6 (26.6)	72.7 (24.7)	<0.001	0.002	77.4 (26.5)	<0.001	<0.001
Social functioning	70.4 (23.6)	77.0 (22.9)	<0.001	0.020	76.6 (24.9)	0.022	0.29
Role limitation (mental)	74.4 (24.8)	78.2 (23.1)	0.005	0.029	83.1 (24.2)	0.002	0.001
Role limitation (physical)	76.4 (25.5)	82.1 (23.0)	<0.001	0.042	83.2 (25.2)	0.021	0.11
Physical functioning	88.0 (18.1)	90.1 (16.3)	0.034	0.059	85.0 (22.9)	0.16	0.69

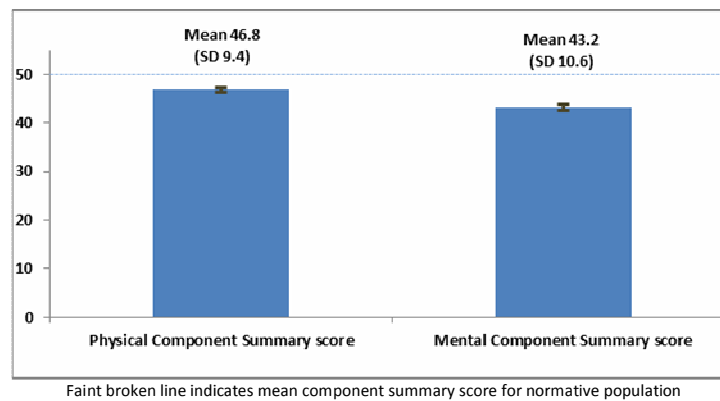
As shown in Table 60, SF36v2 mean dimension scores before adjusting for relevant covariates indicated that compared to symptomatic controls, HRQoL in women with endometriosis was poorer in all dimensions except mental health (62.7 (SD 19.9) vs. 64.8 (SD 18.2); p=0.050). Similarly, compared to sterilisation controls, HRQoL before adjustment for relevant covariates in affected women was poorer in all dimensions except mental health (62.7 (SD 19.9) vs. 64.1 (SD 20.0); p=0.56) and physical functioning (88.0 (SD 18.1) vs. 85.0 (SD 22.9); p=0.16).

After adjusting for relevant potential confounders however (*as per* Table 59), compared to symptomatic controls, women with endometriosis had poorer HRQoL in bodily pain (62.6 vs. 72.7; adjusted $p=0.002$), social functioning (70.4 vs. 77.0; adjusted $p=0.020$) and in physical (76.4 vs. 82.1; adjusted $p=0.042$) and mental (74.4 vs. 78.2; adjusted $p=0.029$) role limitation dimensions. Similarly, after adjusting for relevant covariates, compared to sterilisation controls, women with endometriosis had poorer HRQoL in health perception (62.5 vs. 72.3; adjusted $p=0.033$), bodily pain (62.6 vs. 77.4; adjusted $p<0.001$) and mental role limitation (74.4 vs. 83.1; adjusted $p=0.001$) dimensions.

27.2 SF36v2 component summary scores

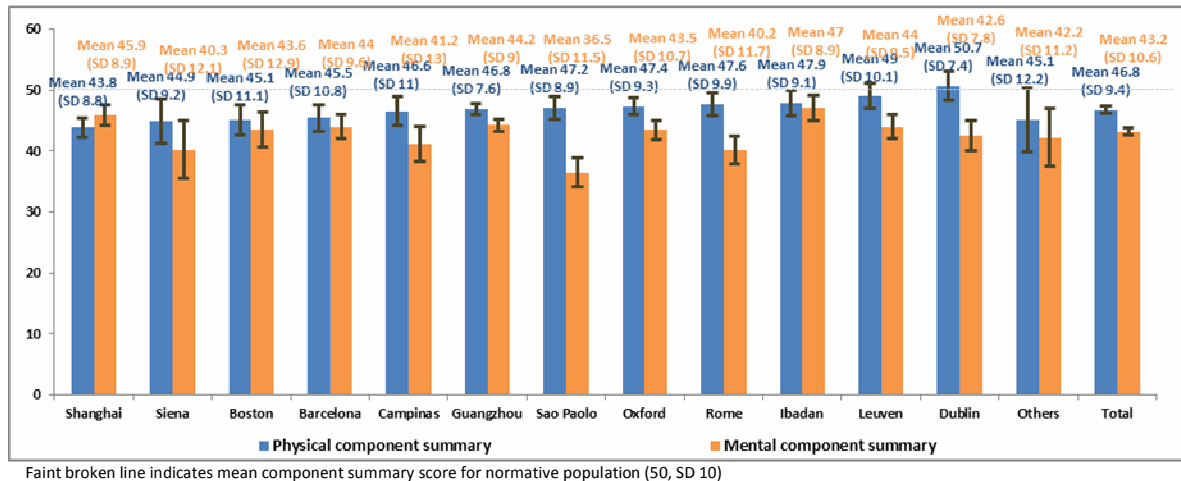
27.2.1 Study population and centre-wise component summary scores

Figure 58 - Mean (SD) SF36v2 component summary scores for the study population, with 95% confidence intervals



As shown in Figures 58 and 59, women in the study population on average had reduced health-related quality of life in both physical and mental health aspects compared to the normative population (Mean 50, SD 10).

Figure 59 - Mean (SD) sf36v2 component summary scores for centres, with 95% confidence intervals



Statistical testing using the one sample t test against a mean of 50 and SD 10 for the normative population showed that women in all centres except Dublin (mean 50.7, SD 7.4; $p=0.57$), Ibadan (mean 47.9, SD 9.1; $p=0.050$), Leuven (mean 49.0, SD 10.1; $p=0.33$) and 'Others' (mean 45.1, SD 12.2; $p=0.083$) had significantly poorer physical HRQoL than the normative population. Women in all the centres however had poorer mental HRQoL than the normative population (Table 61).

Table 61 - Physical and Mental Component Summary scores compared for each centre vs. the normative population (mean 50, SD 10)

Centre	Physical Component Summary		Mental Component Summary	
	Mean score at centre	p- value	Mean score at centre	p- value
Barcelona	45.5 (10.8)	<0.001	44.0 (9.6)	<0.001
Boston	45.1 (11.1)	<0.001	43.6 (12.9)	<0.001
Campinas	46.6 (11.0)	0.007	41.2 (13.0)	<0.001
Dublin	50.7 (7.4)	0.57	42.6 (7.8)	<0.001
Guangzhou	46.8 (7.6)	<0.001	44.2 (9.0)	<0.001
Ibadan	47.9 (9.1)	0.050	47.0 (8.9)	0.005
Leuven	49.0 (10.1)	0.33	44.0 (9.5)	<0.001
Oxford	46.8 (9.4)	<0.001	43.8 (10.9)	<0.001
Rome	47.6 (9.9)	0.015	40.3 (11.6)	<0.001
Sao Paolo	47.2 (8.9)	0.004	36.5 (11.5)	<0.001
Siena	44.9 (9.2)	0.010	40.3 (12.1)	<0.001
Shanghai	43.8 (8.8)	<0.001	45.9 (8.9)	<0.001
Others	45.1 (12.2)	0.083	42.2 (11.2)	0.005

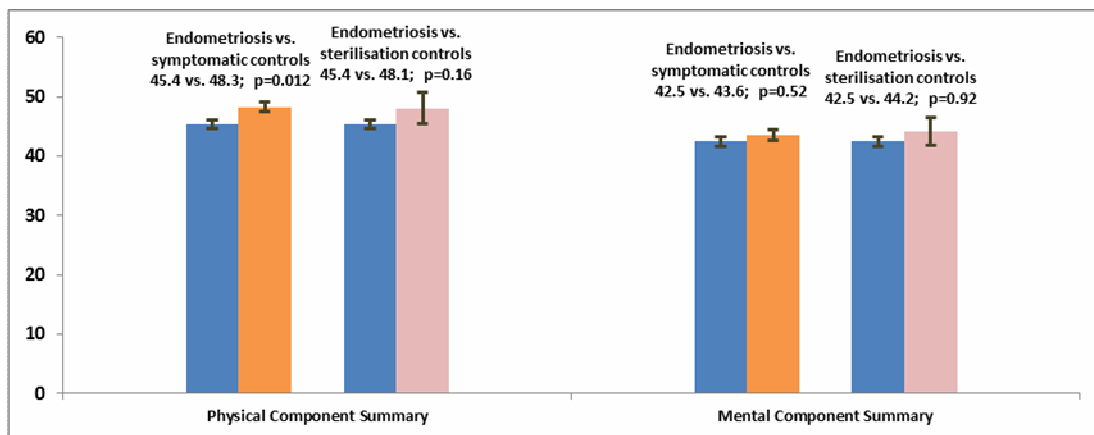
27.2.2 Disease outcome group comparisons on component summary scores

Table 62 - Physical and Mental Component Summary scores compared for each disease outcome group vs. the normative population (mean 50, SD 10)

Centre	Endometriosis		Symptomatic controls		Sterilisation controls	
	Mean score	p- value	Mean score	p- value	Mean score	p- value
Physical Component Summary	45.4 (9.6)	<0.001	48.3 (8.6)	<0.001	48.1 (11.8)	0.17
Mental Component Summary	42.5 (11.1)	<0.001	43.6 (10.1)	<0.001	44.2 (10.6)	<0.001

As shown in Table 62, compared to the normative population, women with endometriosis (mean 45.4, SD 9.6; $p<0.001$) and symptomatic controls (mean 48.3, SD 8.6; $p<0.001$) had significantly poorer physical HRQoL but sterilisation controls (mean 48.1, SD 11.8; $p=0.17$) were not different to the normative population in respect of physical HRQoL. Women in all 3 disease outcome groups however had significantly poorer mental HRQoL compared to the normative population.

Figure 60 – Mean sf36v2 component summary scores by outcome groups, with adjusted p values for comparisons



As shown in Figure 60, compared to symptomatic (mean 48.3, SD 8.6; $p<0.001$) and sterilisation (mean 48.1, SD 11.8; $p=0.02$) controls, women with endometriosis had a lower mean PCS score (mean 45.4; SD 9.6). After adjusting for pelvic pain severity *as per* the multivariate model in chapter 4, physical HRQoL was significantly lower in affected women vs. symptomatic controls

(45.4 vs. 48.3; $p=0.012$) but similar in affected women and sterilisation controls (45.4 vs. 48.1; $p=0.094$).

Women with endometriosis had similar mean MCS score (mean 42.5; SD 11.1) to symptomatic (mean 43.6, SD 10.1; $p=0.095$) and sterilisation (mean 44.2, SD 10.6; $p=0.20$) controls. After adjusting for gravidity and pelvic pain severity *as per* multivariate model in chapter 4, mental HRQoL remained similar in affected women vs. symptomatic controls (42.5 vs. 43.6; $p=0.87$) and affected women vs. sterilisation controls (42.5 vs. 44.2; $p=0.38$).

In multivariate analysis, after adjusting for relevant covariates, physical HRQoL increased with paid or self-employment ($\beta=3.2$; $p<0.001$), and decreased with increasing pelvic pain severity ($\beta=-1.16$; $p<0.001$), presentation with pelvic pain without subfertility ($\beta=-2.2$; $p=0.020$) and presentation with more “pelvic” symptoms (chronic pelvic pain, dysmenorrhoea, dyspareunia and menorrhagia) ($\beta=-0.96$; $p=0.001$). Similarly, mental HRQoL decreased with increasing pelvic pain severity ($\beta=-0.73$; $p<0.001$), presentation with pelvic pain without subfertility ($\beta=-2.5$; $p=0.019$) and presentation with more “pelvic” symptoms ($\beta=-0.95$; $p=0.004$).

In multivariate analysis, including type of healthcare funding, ethnicity, employment status, number of pelvic symptoms, pelvic pain severity and presentation with pelvic pain without subfertility, longer diagnostic delays were associated with reduced physical HRQoL in affected women (regression coefficient -0.12; $p=0.035$).

27.3 HRQoL and self-reported symptoms as reasons for surgery

In Table 63, the HRQoL mean scores for SF36v2 dimensions and summary components are compared across symptom groups: women reporting pelvic pain without subfertility, those reporting subfertility without pelvic pain and those reporting both symptoms, all with or without

additional other symptoms. It shows that compared to women who did not have pelvic pain with subfertility, women who reported pelvic pain without subfertility had significantly poorer HRQoL in all SF36v2 dimensions as well as the mean physical and mental summary component scores (all $p < 0.001$). Conversely, women who had subfertility without pelvic pain had significantly better HRQoL in all SF36v2 dimensions as well as the mean physical and mental summary component scores in comparison to women who did not report subfertility without pelvic pain. Finally, women who reported having both pelvic pain and subfertility did not differ in any of the dimension scores from those who did not report that combination of symptoms. However, while they had a significantly better physical HRQoL (mean 48.0 vs. 46.5, $p = 0.025$), they also had a significantly poorer mental HRQoL (mean 41.6 vs. 43.6, $p = 0.008$).

Table 63 - Comparison of sf36v2 dimension scores across groups of self-reported symptoms for which women underwent surgery, with p values

SF36v2 dimensions	Pelvic pain, no subfertility, with/without other			Subfertility, no pelvic pain, with/without other symptoms			Pelvic pain and subfertility, with/without other symptoms		
	Yes	No	p value	Yes	No	p value	Yes	No	p value
Energy & vitality	50.0	60.9	<0.001	66.5	54.8	<0.001	54.8	56.9	0.15
Mental health	60.7	65.9	<0.001	67.4	63.2	0.004	62.4	64.1	0.19
Health perception	60.1	68.5	<0.001	73.0	63.8	<0.001	67.0	64.6	0.1
Bodily pain	55.1	76.5	<0.001	84.5	65.1	<0.001	66.4	68.2	0.31
Social functioning	66.6	78.3	<0.001	83.0	72.0	<0.001	73.1	73.7	0.71
Role limitation (mental)	72.8	79.5	<0.001	82.3	75.8	<0.001	74.6	77.3	0.09
Role limitation (physical)	71.1	85.1	<0.001	89.1	77.8	<0.001	81.0	79.0	0.21
Physical functioning	85.2	91.1	<0.001	93.9	87.9	<0.001	89.7	88.4	0.31
PCS	42.8	49.5	<0.001	51.9	45.9	<0.001	48.0	46.5	0.025
MCS	41.8	44.1	<0.001	45.4	42.8	0.002	41.6	43.6	0.008

27.4 Pelvic pain severity and HRQoL

As shown in Table 64, after adjusting for relevant covariates (any or a combination of gravidity, pelvic pain severity and non-endometriotic adhesions), increasing pelvic pain severity, as measured on the numerical rating scale, reduced HRQoL in all dimensions of the SF36v2.

Table 64 - Adjusted p values ^a for association of HRQoL and pelvic pain severity

SF36v2 dimension	Average severity of CPP	Average severity of dysmenorrhoea	Severity of pelvic pain during sex	Severity of pelvic pain in 24 hrs after sex	Average severity of all pelvic pain
Bodily pain	-3.37; p<0.001	-4.95; p<0.001	-2.12; p<0.001	-2.38; p<0.001	-4.86; p<0.001
Physical function	-0.88; p=0.008	-1.25; p<0.001	-1.12; p=0.002	-1.00; p=0.002	-1.22; p<0.001
Role limitation (p)	-2.05; p<0.001	-2.50; p<0.001	-1.54; p=0.001	-1.48; p<0.001	-2.53; p<0.001
Role limitation (m)	-1.48; p<0.001	-1.70; p<0.001	-1.47; p=0.001	-0.52; p=0.20	-1.85; p<0.001
Social functioning	-2.53; p<0.001	-2.22; p<0.001	-2.28; p<0.001	-1.51; p<0.001	-2.73; p<0.001
Mental health	-1.74; p<0.001	-1.84; p<0.001	-1.63; p<0.001	-1.04; p=0.001	-2.20; p<0.001
Energy/vitality	-2.24; p<0.001	-2.31; p<0.001	-1.96; p<0.001	-1.41; p<0.001	-2.56; p<0.001
Health perception	-0.85; p=0.023	-0.96; p=0.001	-0.40; p=0.34	-0.59; p=0.12	-1.01; p=0.001
PCS	-0.87; p<0.001	-1.23; p<0.001	-0.56; p=0.003	-0.63; p<0.001	-1.17; p<0.001
MCS	-0.85; p<0.001	-0.82; p<0.001	-0.77; p<0.001	-0.36; p=0.066	-1.03; p<0.001

a - p values adjusted for covariates relevant to each dimension or component summary (see the multivariate model in chapter 4 and Table 59 earlier in this chapter)

More specifically, after adjusting for relevant covariates, increasing CPP severity was associated with poorer HRQoL in all SF36v2 dimensions and the component summary scores. Increasing severity of painful periods was similarly associated with poorer HRQoL in all dimensions of the SF36v2 and the component summary scores. Increasing severity of dyspareunia (during intercourse) was associated with reduced HRQoL in all SF36v2 dimensions and the component summary scores except health perception (regression coefficient -0.40; p=0.34). Notably, although increasing severity of dyspareunia during intercourse was associated with impairment in both physical and mental HRQoL, increasing severity of dyspareunia in the 24 hours after sex only affected physical, not mental, HRQoL.

27.5 Endometriosis severity and HRQoL

Endometriosis severity - as measured by rASRM scores (see methods) – correlated negatively with HRQoL in the SF36v2 dimensions of bodily pain (correlation coefficient -0.085; p=0.023), physical functioning (correlation coefficient -0.085; p=0.024), physical role limitation (correlation coefficient -0.093; p=0.013), social functioning (correlation coefficient -0.13; p<0.001) and health perception (correlation coefficient -0.24; p<0.001). Similarly, endometriosis severity correlated

negatively with physical (correlation coefficient -0.17; $p < 0.001$), but not mental (correlation coefficient -0.008; $p = 0.84$), HRQoL.

Table 65 shows comparisons of mean dimension and component summary scores by stage of endometriosis disease in affected women. After adjustment for relevant covariates (any or a combination of gravidity, pelvic pain severity and presence of non-endometriotic adhesions), women with moderate-severe endometriosis had a poorer HRQoL than those with minimal-mild disease in the SF36v2 dimensions of bodily pain (regression coefficient -4.69; $p = 0.019$), health perception (regression coefficient -9.3; $p < 0.001$) and the physical component summary score (regression coefficient -1.79; $p = 0.035$).

Table 65 – SF36v2 dimension and component summary scores by endometriosis disease stage (with multivariate regression coefficient and p values)

SF36v2 Dimensions	Minimal/mild endometriosis	Moderate/severe endometriosis	Unadjusted p values	Regression coefficient and adjusted p value
Energy/vitality	56.4 (20.2)	53.8 (20.2)	0.094	-
Mental health	63.9 (19.7)	62.2 (20.0)	0.26	-
Health perception	69.2 (20.9)	58.5 (21.6)	<0.001	-9.3; $p < 0.001$
Bodily pain	65.7 (27.1)	61.0 (26.5)	0.023	-4.69; $p = 0.019$
Social functioning	74.2 (23.6)	68.1 (23.4)	<0.001	-3.37; $p = 0.10$
Role limitation (m)	76.6 (24.9)	72.9 (24.7)	0.056	-
Role limitation (p)	79.4 (26.0)	74.6 (24.8)	0.013	-2.48; $p = 0.26$
Physical function	90.0 (18.7)	86.8 (17.6)	0.024	-2.22; $p = 0.21$
PCS	47.5 (9.8)	44.2 (9.1)	<0.001	-2.45; $p = 0.002$
MCS	42.7 (11.1)	42.5 (11.0)	0.84	-

PCS adjusted for subfertility, menstrual duration, co-morbidity, number of pelvic symptoms and type of symptoms presented (pelvic pain without subfertility, pelvic pain with subfertility and subfertility without pelvic pain).

28 Discussion

This study used the SF36v2 survey instrument to assess health-related quality of life (HRQoL) in women scheduled for a first diagnostic laparoscopy on account of symptoms or for sterilisation. The SF36v2 instrument is a generic, rather than disease-specific, instrument for the subjective assessment of health status. It is widely validated in different populations, as have its many language versions, some of which were utilised in this study. The SF36v2, although not specific to

endometriosis, captures disease and treatment effects on quality of life [246] but as the women in the study population had not been diagnosed nor treated specifically for endometriosis, the quality of life effects captured here would be attributed principally to the disease or any specific symptoms associated with the disease. A deliberate decision was made during study design not to employ a disease-specific instrument such as the Endometriosis Health Profile (EHP-30) questionnaire [247] as women recruited into the study were not known to have endometriosis at recruitment and using the EHP-30 would have been inappropriate. Although employed in this study specifically for its discriminative property, the SF36v2 survey instrument has potential for use in longitudinal monitoring of HRQoL. The HRQoL impact described in the study population could therefore serve as a baseline for prospective assessment of treatment effectiveness and modification of treatment strategy in individual patients [158].

In the study population, HRQoL measured in the SF36v2 dimensions ranged from 56.5 (SD 20.6) in the energy & vitality to 88.7 (SD 17.8) in the physical functioning dimensions. The study population, on average, had significantly poorer physical (mean 46.8; SD 9.4) and mental (mean 43.2; SD 10.6) HRQoL than the normative population from the Oxford Healthy Lifestyles Survey. The fact that the extent of impairment in physical HRQoL observed in women in this study population is similar to that reported in women with cancer indicates the significant burden of endometriosis and its symptoms on women [248]. Generally, the average woman in Sao Paolo had significantly poorer HRQoL compared to the average woman in the remainder of the study population in the SF36v2 dimensions of energy/vitality, mental health, bodily pain, social functioning and mental role limitation. On the other hand, the average woman in Leuven had significantly better HRQoL compared to the average woman in the remainder of the study population in the SF36v2 dimensions of health perception, bodily pain, social functioning and physical functioning. Mental HRQoL was comparable amongst affected women, symptomatic and sterilisation controls. After adjusting for pelvic pain severity however, physical HRQoL was

significantly lower in affected women compared to symptomatic controls (45.4 vs. 48.3; $p=0.012$), but similar in affected women and sterilisation controls (45.4 vs. 48.1; $p=0.094$). The latter result is most likely due to the relatively small number of women (87) in the sterilisation control group.

All women in the study population (endometriosis, symptomatic and sterilisation controls) had significantly poorer mental HRQoL than the normative population. Affected women and symptomatic controls both had significantly lower, and sterilisation controls similar, physical component summary scores to the normative population. It is not immediately clear why all women, including sterilisation controls, had poorer mental HRQoL than the normative population but two reasons could potentially explain this. Firstly, all women in the study population who did not have endometriosis on laparoscopy and who underwent sterilisation were classified as sterilisation controls but some of them had symptoms which, though unrelated to their care experience on this occasion, might have affected their quality of life. When this possibility was explored by excluding women who reported any symptoms from the sterilisation group, mental HRQoL in the sterilisation group however remained poorer than the normative population mean (not shown in main results). Secondly, all women (including sterilisation controls) completed the survey before their surgery, at which time they may have experienced anxiety related to their impending surgery. If this was true in this study population, it would be reasonable to expect that women who completed the questionnaire closer to the date of scheduled surgery would have poorer mental HRQoL than those who completed it earlier. However, there was no significant association between mental HRQoL and the interval between questionnaire completion and surgery in all women ($\beta=0.014$; $p=0.35$) (not shown in main results).

Being in paid employment was associated with higher physical HRQoL ($\beta=3.2$; $p<0.001$), which was however lower in women who had more severe pelvic pain ($\beta=-1.16$; $p<0.001$), more pelvic symptoms ($\beta=-0.96$; $p=0.001$), and pelvic pain without subfertility ($\beta=-2.2$; $p=0.020$). It was

interesting to observe that the effect of employment on physical HRQoL was independent of ethnicity, marital status, subfertility, type and number of presenting symptoms, comorbidity and pelvic pain severity. Although the relationship between employment status and HRQoL has never been reported in endometriosis, it has been observed in veterans after major abdominal surgery and in HIV, fibromyalgia and inflammatory bowel disease patients [249-252]. Notably, in the study by Reisine et al. [251], employed women reported better HRQoL than those who were not employed, but only for the physical dimension of HRQoL measured on the SF-12; this study replicates this finding using the SF36v2 instrument. The relationship between employment and HRQoL in endometriosis is complex - the findings of this study suggest that endometriosis can limit a woman's ability to work but being in paid- or self-employment is associated with better HRQoL in affected women. The cross-sectional design of this study does not permit a more thorough understanding of temporality – for example, does employment precipitate better HRQoL or might better HRQoL associated with a more positive individual outlook on life precipitate ability to work? There are a number of possible mechanisms through which being in employment might improve HRQoL irrespective of education, marital status and symptom severity. One such mechanism could be that the financial security of receiving regular income reduces the psychological impact of the disease. Two observations potentially support this position: (i) full-time workers in Horner's study [250] reported higher psychological wellbeing than part-time workers, and (ii) the amount of weekly time paid to work correlated positively with mental (not physical) HRQoL in this study. Therefore, assuming full-time and longer contracted hours of work are associated with higher income, it should perhaps not be surprising that being in employment was associated with better HRQoL. It could also be speculated that employed patients engage their physical and mental capacities at work and might therefore pay less attention to any general health limitations and discomfort they may have [252]. Another possible explanation might be the social interactions afforded by employment. Being in employment does contribute to a sense of social integration and belonging [253] and the access

to professional and social networks afforded by employment may alleviate the HRQoL impact of the disease. This theory is supported by observations in cancer patients and older adults of positive associations between social networks, support, and HRQoL [254,255]. The fact that the association of employment with HRQoL was observed for the physical, rather than the mental, aspect of HRQoL may however cast some doubt on the validity of this theory.

Average severity of pelvic pain (CPP, dysmenorrhoea and dyspareunia) correlated negatively with HRQoL in all dimensions and both component summary scores of the SF36v2 survey after accounting for relevant covariates. More specifically, while dysmenorrhoea and pelvic pain during intercourse were strongly associated with impaired physical ($\beta=-1.23$; $p<0.001$ and $\beta=-0.56$; $p=0.003$, respectively) and mental ($\beta=-0.82$; $p<0.001$ and $\beta=-0.77$; $p<0.001$, respectively) HRQoL, pelvic pain in the 24 hours after intercourse only impaired physical ($\beta=-0.63$; $p<0.001$), but not mental, HRQoL. The association between the severity of endometriosis symptoms and poor HRQoL has been reported previously. In one validation study of a newly developed HRQoL instrument among 137 US women with endometriosis, HRQoL was found to inversely correlate with patient-reported levels of endometriosis pain [256]. In another study of 40 women with four different chronic pain conditions (10 of whom had endometriosis), there was a significant negative correlation between the subjective visual analogue scale (VAS) rating of pain severity and HRQoL [257]. Another prospective study of 104 women diagnosed with pelvic endometriosis assessed its impact on HRQoL measured using the World Health Organization Quality Of Life instrument (WHOQOL-BREF) and reported a positive correlation between the complaints related to physical limitations and the intensity of pain [258]. The correlation between severity of symptoms and HRQoL impairment in endometriosis was however not reported in the study by Marques et al. who assessed HRQoL in women with surgically diagnosed endometriosis and pelvic pain attending an outpatient clinic [157]. It was however unclear from their report how they measured the intensity or severity of pelvic pain in women. The strong association in this study

between pelvic pain severity and HRQoL after controlling for relevant covariates suggests that control of pain is key to mitigating the HRQoL impact of endometriosis.

Notably, after adjusting for relevant covariates (principally pelvic pain severity, comorbidity and number of pelvic symptoms reported), HRQoL in the domains of bodily pain ($\beta=-4.69$; $p=0.019$), health perception ($\beta=-9.3$; $p<0.001$) and the physical component summary ($\beta=-2.45$; $p=0.002$) fell as rASRM endometriosis disease severity increased. The greater impairment in HRQoL (particularly general bodily pain) in moderate-severe vs minimal-mild disease, after accounting for pelvic pain severity and comorbid conditions, is intriguing and could have a number of causes. Despite careful adjustment, there might still be residual differences in symptom severity between affected women and symptomatic controls, or women with endometriosis may have more unreported comorbid conditions. However, we would expect these to affect mental as well as physical dimensions, which was not the case. An intriguing alternative explanation is the role of central sensitisation. This theory, supported by experiments in animals and humans [259-261] suggests that endometriotic tissue, as disease advances, generates persistent pain stimuli in the central nervous system, resulting over time in heightened pain awareness even from regions well removed from the tissue itself. If true, such heightened awareness could explain the persistent impact of worsening endometriosis on HRQoL and work productivity and would highlight the need to reduce the impact of the disease by early symptom control approaches that target central sensitisation.

Although there is a dearth of good quality studies assessing the impact of endometriosis on HRQoL, it is acknowledged that patient groups, mainly in Western countries, have advocated for many years that endometriosis is associated with reduced quality of life. However, the studies that have attempted to elucidate the impact of the disease on HRQoL have lacked methodological rigour and geographical reach. This international, multi-centre study is the first to provide

detailed evidence of the substantial impact of endometriosis and its symptoms on the HRQoL of affected women across continents. More specifically, previous studies have added little to the body of knowledge on this subject because they were mostly limited by small sample sizes [258,262], suboptimal control selection [151] and assessment of geographically limited populations of women with confirmed endometriosis (risking recall bias) [157]. The key strength of this study is that it quantitatively describes the long-suspected personal impact of endometriosis in greater detail than has ever been attempted before, across different countries and ethnicities. Indeed, for many of the countries in the study, such data have not been available to date.

The effect of endometriosis on women's quality of life is multidimensional, affecting more aspects of their lives than the often reported psychosocial parameters [153,263]. Its impact on HRQoL is probably worsened by the fact that until recent times, the understanding of endometriosis has been limited to its pelvic definition and only more recently has supporting evidence emerged of the bigger-picture view of endometriosis as a systemic endocrine, immunological, and gastrointestinal disease [264]. Limited knowledge of endometriosis and consequent lack of information about the disease is similarly thought to result in emotional distress and lack of control and powerlessness among women with the condition [150,153]. The sense of powerlessness and lack of control experienced by women with endometriosis, coupled with the limited ability of pharmacological and surgical treatment regimens to produce lasting relief from the symptoms [265], makes some women resort to complementary and alternative therapies as a means of regaining control [149]. As the impact of a disease on HRQoL is a function of the disease itself and of other factors such as its treatment side effects and duration [258], elucidating the personal and social impact of disease in women who are already living with and receiving care for endometriosis should ideally seek to differentiate between those effects. However, previous studies of the personal impact of endometriosis on HRQoL have mostly been

conducted in women living with and often receiving care for surgically confirmed endometriosis. In addition to introducing a potential for recall bias because women are already aware of their disease status, this makes it difficult to disentangle, in the results of those studies, the genuine effect that endometriosis has on HRQoL of affected women from those effects that are due to its treatment or management. This study addresses this limitation of previous ones by recruiting women scheduled for a first laparoscopy either for symptoms or for sterilisation. Effects on quality of life reported by those women with endometriosis would thus be expected to be valid, being free of recall bias, and to reflect the impact of the disease, rather than of its treatment, on HRQoL. A potential limitation inherent in the design of the study relates to the fact that the data on HRQoL collected in days or weeks leading up to scheduled surgery might be affected both by the impending surgery and symptoms themselves. This effect is perhaps reflected in the reduced SF36v2 mental component summary scores in sterilisation controls compared to the normative population mean. It might be expected that such impact would be greater in women who completed the questionnaire closer to the day of planned surgery. As highlighted earlier however, there was no association between mental HRQoL and this interval in the study population.

The poorer physical HRQoL in affected women and symptomatic (but not sterilisation) controls compared to a normative UK population reflects the key role of symptoms, mainly pain, in driving the HRQoL impact of endometriosis. This recognition of the role of pelvic pain has led some authors to suggest that the HRQoL of women with endometriosis would improve with a greater focus on achieving the long-term relief of pelvic pain [24]. The impact of endometriosis on several dimensions of quality of life has been documented and includes impairment in psychosocial functioning, physical and general health, emotional wellbeing, work-related limitations and daily life activities [19,262,266]. The validity and generalisability of the findings in these studies are, however, significantly limited for reasons highlighted earlier. This study, addressing a number of these limitations, is the first to report that the impact of endometriosis on HRQoL is

predominantly in the physical, rather than the mental, aspect of HRQoL as measured by the SF36v2 survey instrument. Although pain is a major driver of general HRQoL impairment in endometriosis and is highly correlated with the physical aspect of HRQoL measured by the SF36v2 [157], the effect of endometriosis on HRQoL in this study population was not completely explained by pelvic pain.

After adjusting for type of healthcare funding, ethnicity, employment status, number of pelvic symptoms, pelvic pain severity and presentation with pelvic pain without subfertility, poor physical HRQoL in affected women was associated with longer diagnostic delay ($\beta=-0.12$; $p=0.035$). Although this relationship has never been reported explicitly in endometriosis, it has been observed in people with sternocostoclavicular hyperostosis [267]. Possible mechanisms by which diagnostic delay may affect HRQoL include (i) creating a long duration of painful symptoms without an accurate diagnosis, (ii) worsening the prognosis for fertility, and (iii) increasing the risk for repeated operative procedures [239]. Therefore, reducing the length of the diagnostic delay that women with endometriosis experience should be expected to improve their HRQoL.

In summary, this study highlights the significant impact of endometriosis, principally via its symptoms, on health-related quality of life. Although this study was designed to avoid many of the methodological limitations of previous studies, it has important potential limitations itself which need to be borne in mind in interpreting the findings presented in this chapter. Key amongst these potential limitations is the cross-sectional design of the study. As a related point, the impairment of HRQoL associated with not being in employment could simply reflect women's inability to work because of severe symptoms and reduced quality of life; a cross sectional study, being a snapshot in time, is unlikely to clarify this. Another potential limitation is that although the hospitals that participated in this study were experienced in diagnosing endometriosis, disease stage might have been inadequately classified. However, combining minimal with mild

and moderate with severe stages in analyses minimises such potential bias. Endometriosis was diagnosed visually without histological confirmation, following ESHRE guidelines [1], based on the premise that negative histology does not exclude the presence of disease. The key strength of this study is that, to limit information bias, it was restricted to women undergoing a laparoscopy for symptoms suggestive of endometriosis or sterilisation for the first time and collected relevant data prior to diagnosis. The results are therefore generalisable to this patient group, but may underestimate HRQoL among women who have suffered from the condition for longer.

CHAPTER 8

**ENDOMETRIOSIS AND WORK PRODUCTIVITY
IMPAIRMENT**

29 Introduction

In chapter 7, the impact of endometriosis on the personal lives of women, mediated principally through its symptoms, was highlighted. In addition to its impact on health-related quality of life, endometriosis, by afflicting women in their reproductive and economically active years, results in economic losses for society and the women themselves. This should clearly be a matter of concern for public health policy makers and employers alike.

The exact nature and scope of the economic impact of endometriosis has never been clearly described however. Previous analyses have principally focused on estimating the direct costs of endometriosis [268], leaving much remaining to be known of the indirect costs, i.e. those associated with, *inter alia*, loss of work productivity. For example, in a 2006 comprehensive review and evaluation of the cost of endometriosis, Gao and colleagues reviewed 13 studies (11 of which addressed direct costs only) and estimated direct in-patient cost of endometriosis at \$1.1 billion/year in the USA alone [269]. When previous studies have quantified endometriosis-associated indirect costs in addition to direct costs, they have mainly reported costs associated with absence from work. One such study is a 1996 telephone survey of >5,000 women in the USA aged 18-50 years old, 15% of who reported chronic pelvic pain (CPP) [21]. The study estimated the direct cost of CPP (mainly attributable to outpatient hospital visits) at \$881.5 million/year in the US population and reported that women with endometriosis-related CPP missed 1.6 hours of paid work per month, compared to 0.05 hours monthly in those with menstrual cycle-related diagnosis. As work absenteeism due to illness only narrowly describes the spectrum of disease-related work productivity loss, quantifying presenteeism (reduced productivity while at work), as well as absenteeism (time lost from work) [270], is key to generating valid estimates of health-related work productivity loss. Furthermore, most previous reports of the economic cost of endometriosis-associated work productivity impairment often relate to geographically limited

populations and are limited by small sample sizes and potential recall bias associated with surveying women who knew their disease status when answering questions about work impairment [266,269]. The findings of studies based on geographically-limited (mainly Western) populations are restricted in terms of generalisability. Furthermore, inadequately powered studies might fail to detect existing effects of endometriosis on work productivity and studies that involve women living with known endometriosis could generate biased estimates of the work-related impact of the disease.

To address these limitations, this study recruited, in 16 clinical centres across 10 countries, 1,418 women without a previous surgical diagnosis of endometriosis undergoing a first laparoscopy for symptoms or for sterilisation. Using a standardised and validated survey instrument (the Work Productivity and Activity Impairment questionnaire) [163], the impact of symptoms of endometriosis on work productivity in employed women is evaluated. This chapter details the methods and results of the evaluation of the impact of endometriosis on work productivity, focusing on three key research questions:

- Is work productivity affected by endometriosis? What is the nature and size of the impact?
- What are the key drivers of any impact of endometriosis on work productivity?
- What is the relationship between endometriosis severity and work productivity impairment?

30 Methods

30.1 Description of comparison groups

As in previous chapters, analysis of work productivity and activity impairment in the study population is conducted according to two main outcome groups: centre of recruitment and disease outcome groups. The variable 'centre' is re-categorised so that the centres at which fewer

than 25 women were recruited (Buenos Aires, San Francisco, Palo Alto and Washington DC) are grouped together into an “Other” category. Disease outcome groups include: 1) women with endometriosis; and 2) symptomatic controls. Laparoscopic sterilisation controls are excluded from the work productivity impairment since the focus of this chapter is the assessment of impact of symptoms. The endometriosis group includes all women with endometriosis on laparoscopy, regardless of indication for surgery; the symptomatic control group includes those without endometriosis who were investigated for symptoms. For women with endometriosis, disease severity is described as “minimal-mild endometriosis” (rASRM stages I+II) or “moderate-severe endometriosis” (rASRM stages III+IV) [33].

30.2 Assessment of work productivity impairment

A general health version of the Work Productivity and Activity Impairment (WPAI:GH) questionnaire [163] is incorporated into the 67-item study questionnaire (see Appendix 3) to: a) assess the impact of symptoms on absence from work (*absenteeism*) and reduced effectiveness while working (*presenteeism*) in symptomatic employed women, and b) establish the impact of symptoms on activities such as house work and childcare in all symptomatic women, over the past 4 weeks. This time period, is adapted from the original WPAI tool (7 days) as done in other studies [271] because 1) endometriosis-related symptoms fluctuate with the menstrual cycle; and 2) work and daily activities in the week leading up to surgery may be unrepresentative of general patterns. Work productivity is measured on a 0 (“symptoms had no effect on work”) to 10 (“symptoms completely prevented working”) scale; a similar rating scale is used for other daily activities.

30.3 Adjusting for potential confounding variables

As shown in Table 34 (in chapter 4), pelvic pain severity was the only variable associated with endometriosis in multivariate analysis as well as with overall work productivity impairment

independently. It is similarly associated independently with *absenteeism* and *presenteeism* parameters of work productivity. Consequently, it is treated as the potential confounder of the association between endometriosis and work productivity impairment parameters and included accordingly in the analyses detailed in this chapter.

30.4 Missing values

Missing values are dealt with by listwise deletion in Stata 11, i.e. any observation missing a value for a specific variable is dropped completely in the analysis of that variable. More specifically for the WPAI, the computation of absenteeism required data to be available for “*hours missed due to symptoms*” and “*hours actually worked*”. The computation of overall work productivity impairment similarly required data to be available for “*hours missed due to symptoms*”, “*reduced productivity while working*” and “*hours actually worked*”. Observations missing any required variable were dropped in the computation of the relevant work productivity parameter.

30.5 Statistical Methods

30.5.1 Work and work productivity impairment parameters

The proportions of employed women in the study population and the reasons for not being in paid work at the time of the study are described. The study population is also described in terms of the number of weekly hours women were contracted to work and number of weekly hours they actually worked.

Analysis of the WPAI:GH followed standard methods for calculation of the dimensions [162], and was conducted by centre of recruitment and disease outcome status. Absenteeism was calculated as [*hours missed due to symptoms*/(*hours missed due to symptoms* + *hours actually worked*)] expressed as a percentage. Presenteeism was calculated as [*reduced productivity while working*]

expressed as a percentage. Overall productivity loss was calculated as
$$\frac{((\text{hours missed due to symptoms} + (\text{percent reduced productivity while working} \times \text{hours actually worked})))}{(\text{hours missed due to symptoms} + \text{hours actually worked})} \times 100$$
. Mean percentage values and equivalents in hours per week for these dimensions were compared for working women (employed/self-employed) across centres and between endometriosis cases and symptomatic controls.

30.5.2 Centre-wise comparisons

To further describe the above work and work productivity parameters, the mean parameter value at each centre is compared with the mean value for the remainder of the study population, with the p value for the t test of differences in means presented.

30.5.3 Comparisons across disease outcome groups

Disease outcome groups (endometriosis cases vs. symptomatic controls) are compared for differences in the mean values of work and work productivity parameters using the t test of differences in means.

30.5.4 Work productivity loss in monetary terms

Endometriosis-associated work productivity loss was transformed into monetary values by multiplying the number of hours of lost productivity per woman by the year 2008 hourly labour cost for all countries using data on labour costs from the Federal Statistics Office of Germany [272] – a single source for comprehensive and comparable international data on labour costs. Based on approximate endometriosis prevalence of 10% in women of reproductive age and an assumption that women of reproductive age comprise about 20% of country populations, the annual indirect cost of endometriosis associated with overall work productivity loss was expressed as a percentage of 2008 national gross domestic product (GDP) for relevant countries (data on GDP similarly available from the Federal Statistics Office of Germany).

30.5.5 Missing values

For each of the four variables required for the computation of work productivity & activity impairment (hours missed due to symptoms, hours actually worked, reduced productivity while working and activity impairment), women with missing data are compared to those not missing data on key characteristics, stratified by disease outcome, i.e. endometriosis and symptomatic controls. These characteristics include age, pelvic pain severity, number of pelvic symptoms and comorbidity. For continuous variables, mean values are compared in 'women with missing data' vs. 'women without missing data' for both endometriosis cases and symptomatic controls using the Student's t test equality of means. For categorical variables, similar comparisons are done by use of the Pearson's χ^2 test of differences in proportions.

All analyses are done using Stata Release 11 (Stata Corporation, College Station, Texas, USA).

31 Results

31.1 Missing values

Between 24.4 - 33.7% of values required for the computation of work productivity parameters were missing (not shown). As shown in Table 66, women with missing data in the symptomatic control group were significantly less likely than those without missing data to report co-morbidity in their medical history (61.1 vs. 70%; $p=0.038$). In addition, women with missing data in the symptomatic control group were older (mean 36.2 vs. 32.9 years; $p<0.001$) and had more severe pelvic pain (5.1 vs. 4.1 on the numerical rating scale; $p=0.007$) and more pelvic mass symptoms (mean 1.2 vs. 0.9; $p=0.037$).

Table 66 – Comparison of women with missing and those without missing observations for specific variables in relation to work and work productivity parameters, stratified by disease outcome (endometriosis and symptomatic controls)

		Endometriosis			Symptomatic controls		
		Missing	Non-missing	p value	Missing	Non-missing	p value
Hours of work missed due to symptoms	Age	32.4 (SD 7.1)	32.6 (SD 5.9)	0.75	33.5 (SD 7.0)	33.0 (SD 6.0)	0.31
	Pelvic pain severity	5.1 (SD 2.3)	5.0 (SD 2.1)	0.33	4.4 (SD 2.4)	4.0 (SD 2.0)	0.1
	Number of pelvic mass symptoms	1.4 (SD 0.81)	1.3 (SD 0.85)	0.072	1.0 (SD 0.79)	0.9 (SD 0.88)	0.23
	Number of pelvic symptoms	1.5 (SD 1.4)	1.6 (SD 1.5)	0.52	1.1 (SD 1.4)	1 (SD 1.3)	0.56
	Comorbidity	83.3 (160)	82.1 (453)	0.69	62.6 (119)	69.6 (261)	0.095
Hours actually worked	Age	32.2 (SD 7.0)	32.6 (SD 5.9)	0.37	33.6 (SD 7.0)	33.0 (SD 6.0)	0.29
	Pelvic pain severity	5.2 (SD 2.2)	4.9 (SD 2.1)	0.16	4.4 (SD 2.4)	4.0 (SD 2.0)	0.092
	Number of pelvic mass symptoms	1.4 (SD 0.79)	1.3 (SD 0.85)	0.18	1.0 (SD 0.78)	0.9 (SD 0.88)	0.34
	Number of pelvic symptoms	1.5 (SD 1.5)	1.5 (SD 1.5)	0.92	1.1 (SD 1.3)	1 (SD 1.3)	0.84
	Comorbidity	82.0 (159)	82.5 (454)	0.85	63.4 (116)	69.1 (264)	0.18
Loss of productivity at work due to symptoms	Age	32.0 (SD 7.1)	32.7 (SD 5.9)	0.22	33.3 (SD 7.1)	33.1 (SD 6.1)	0.67
	Pelvic pain severity	5.2 (SD 2.3)	4.9 (SD 2.1)	0.25	4.3 (SD 2.4)	4.1 (SD 2)	0.28
	Number of pelvic mass symptoms	1.4 (SD 0.8)	1.3 (SD 0.8)	0.054	1 (SD 0.8)	0.9 (SD 0.9)	0.55
	Number of pelvic symptoms	1.5 (SD 1.4)	1.6 (SD 1.5)	0.46	1 (SD 1.3)	1.1 (SD 1.3)	0.42
	Comorbidity	83.5 (152)	82 (461)	0.65	61.1 (107)	70 (273)	0.038
Activity impairment	Age	32.4 (SD 6.1)	32.5 (SD 6.2)	0.89	36.2 (SD 6.4)	32.9 (SD 6.3)	<0.001
	Pelvic pain severity	5.4 (SD 2.4)	5 (SD 2.1)	0.25	5.1 (SD 2.9)	4.1 (SD 2)	0.007
	Number of pelvic mass symptoms	1.3 (SD 0.8)	1.3 (SD 0.8)	0.79	1.2 (SD 0.8)	0.9 (SD 0.9)	0.037
	Number of pelvic symptoms	1.4 (SD 1.5)	1.5 (SD 1.5)	0.53	1.3 (SD 1.5)	1 (SD 1.3)	0.21
	Comorbidity	83 (44)	82.3 (569)	0.9	61.5 (32)	67.8 (348)	0.36

31.2 Employment status

Most women in the study population were in paid- or self-employment (75.7%; n=1,073) and those who did not work were mostly housewives or carers (55.3%; n=178). Of the symptomatic women who were not in employment, approximately one in eight (13.0%; n=42) reported that they did not work because of the symptoms for which they underwent surgery.

31.3 Description of work productivity impairment in study population and centres

31.3.1 Time paid to work and time actually worked

Women in the study population reported they were contracted to work an average of 38.9 hours/week (SD 13.3), ranging from 31.9 hours/week (SD 12.1) in Siena to 45.6 hours/week (SD 11.0) in Ibadan (Figure 61). However, women in the study population reported actually working

an average of 26.4 hours/week (SD 20.5), ranging from 20.5 hours/week (SD 12.7) in Leuven to 36.8 hours/week (SD 27.5) in Ibadan (Figure 62).

Figure 61 - Mean weekly hours (SD) employed women were contracted to work by centre

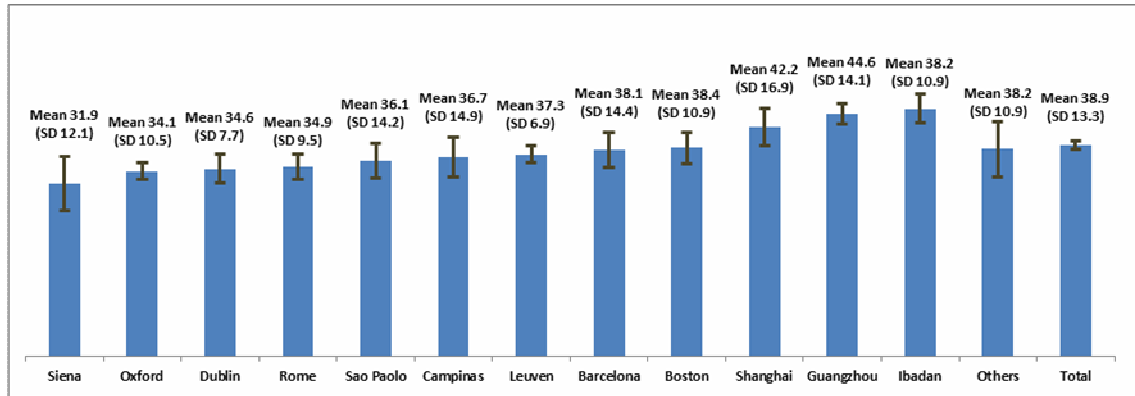
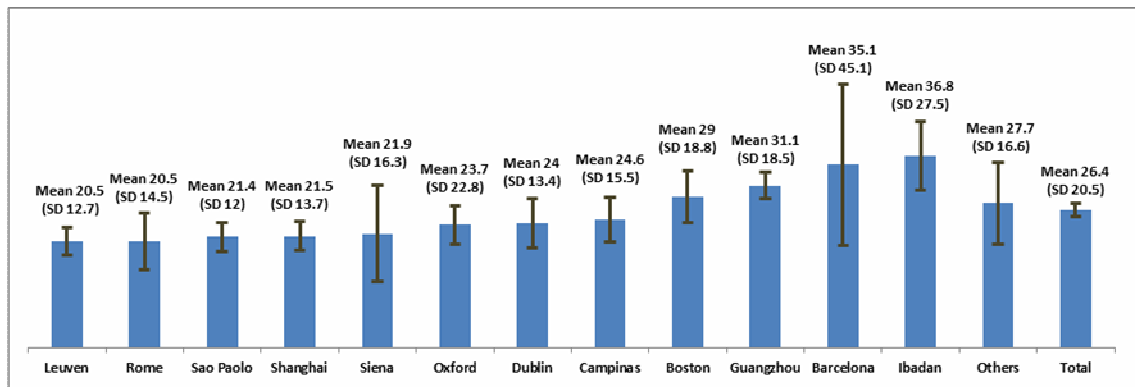


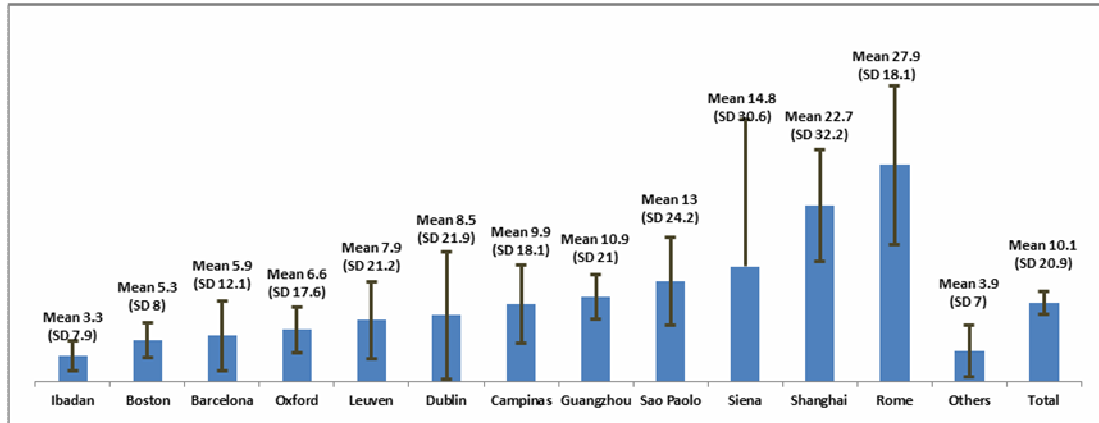
Figure 62 - Mean weekly hours (SD) employed women were contracted to work by centre



31.3.2 Absenteeism

As shown in Figure 63, women in the study population reported absence from work as a result of symptoms a mean 10.1% (SD 20.9) of contracted work time, ranging from 3.3% (SD 7.9) in Ibadan to 27.9% (SD 18.1) in Rome. Translated into actual number of hours of contracted work time that women were absent from work due to their symptoms, mean absenteeism in the study population was 3.9 hours/week per woman (SD 8.2), ranging from 1.5 hours/week in Ibadan (SD 2.9) and 'Other' centres (SD 2.8) to 9.7 hours/week (SD 6.6) in Rome (not shown).

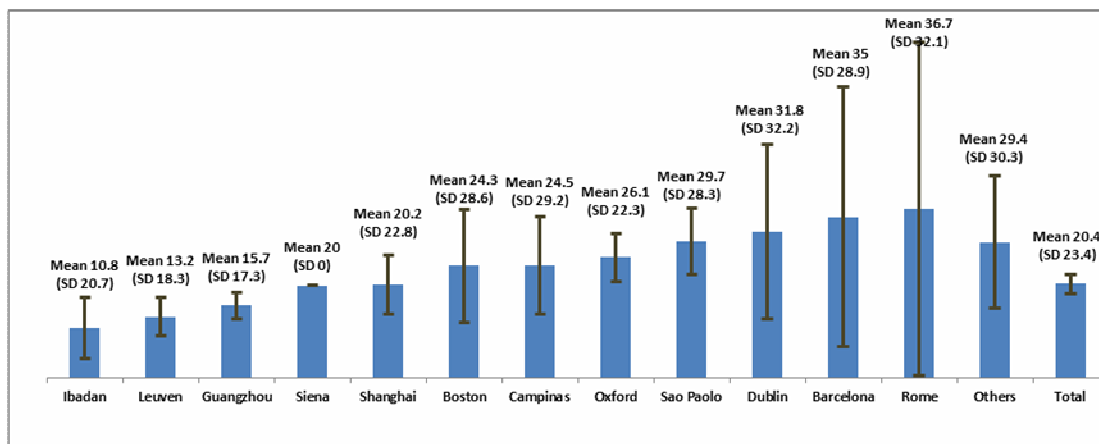
Figure 63 – Mean absenteeism (SD) by Centre



31.3.3 Presenteeism

As shown in Figure 64, women in the study population reported a mean 20.4% (SD 23.4) reduction in effectiveness at work due to symptoms (presenteeism), ranging from 10.8% (SD 20.7) in Ibadan to 36.7% (SD 32.1) in Rome. The presenteeism data for Siena, although contributing only a single observation, is not outlying; its elimination does not alter the presenteeism average and standard deviation for the study population. Translated into actual number of hours of productivity on the job lost due to symptoms, mean presenteeism in the study population was 5.4 hours/week per woman (SD 7.2), ranging from 2.7 hours/week in Leuven (SD 4.8) to 12.3 hours/week (SD 3.7) in Barcelona (not shown).

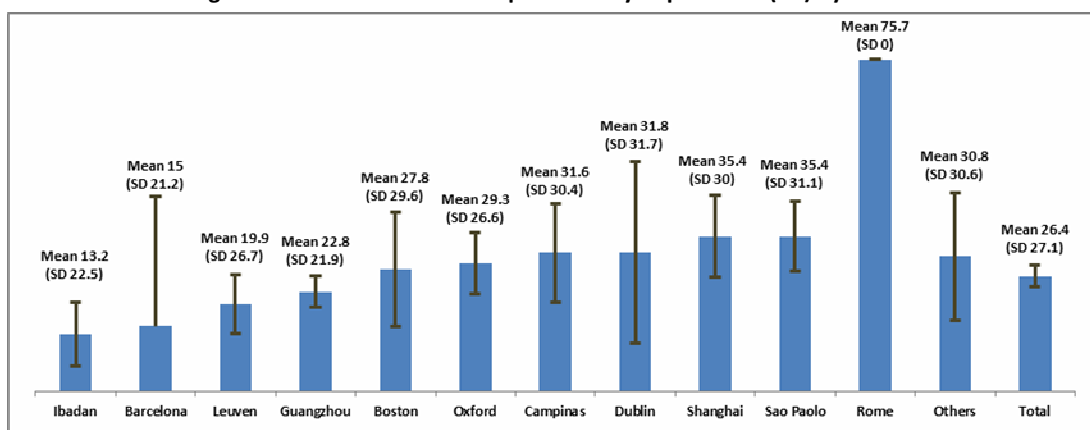
Figure 64 - Mean presenteeism (SD) by Centre



31.3.4 Overall work productivity loss

As shown in Figure 65, women in the study population reported a mean overall work productivity loss of 26.4% (SD 27.1), ranging from 13.2% (SD 22.5) in Ibadan to 35.4% (SD 31.1) in Sao Paolo. The overall work productivity data for Rome is outlying and contributed one observation; its elimination only changes the overall work productivity loss from 26.4% (SD 27.1) to 26.3% (SD 27.1). Overall work productivity loss was not computable for Siena as all observations in that centre had one or more requisite missing values. Translated into actual number of hours, mean overall work productivity loss in the study population was 9.3 hours/week per woman (SD 10.1), ranging from 5.5 hours/week in Ibadan (SD 4.8) to 14.6 hours/week (SD 4.5) in Barcelona (not shown).

Figure 65 - Mean overall work productivity impairment (SD) by Centre



31.3.5 Centre-wise comparisons

As shown in Table 67, women in Ibadan (mean 3.3 vs. 10.7%; $p=0.006$) and Oxford (mean 6.6 vs. 10.8%; $p=0.035$) reported significantly less absence from work as a result of their symptoms compared to the remainder of the study population but women in Rome (mean 27.9 vs. 9.8%; $p=0.003$) and Shanghai (mean 22.7 vs. 8.8%; $p<0.001$) reported significantly greater work absence due to symptoms. In respect of presenteeism, women in Guangzhou (mean 15.7 vs. 22.1%; $p=0.005$), Ibadan (mean 10.8 vs. 21.1%; $p=0.001$) and Leuven (mean 13.2 vs. 21.6%; $p=0.004$)

reported significantly less productivity loss at work due to symptoms compared to the remainder of the study population; those in Oxford (mean 26.1 vs. 19.5%; $p=0.026$) and Sao Paolo (mean 29.7 vs. 19.1%; $p<0.001$) reported significantly greater loss of productivity while at work due to symptoms. In respect of overall work productivity loss, women in Ibadan (mean 13.2 vs. 27.5%; $p=0.002$) and Leuven (mean 19.9 vs. 27.3%; $p=0.047$) had significantly less overall work productivity impairment due to their symptoms compared to the remainder of the study population; those in Sao Paolo (mean 35.4 vs. 25.1%; $p=0.007$) and Shanghai (mean 35.4 vs. 25.5%; $p=0.029$) reported significantly greater overall work productivity impairment.

Table 67 - Centre wise comparisons of work productivity impairment indices

Centres	Absenteeism (Mean)			Presenteeism			Overall work productivity loss		
	Centre	Remainder of study population	P value for t test	Centre	Remainder of study population	P value for t test	Centre	Remainder of study population	P value for t test
Barcelona	5.9	10.2	0.28	35.0	20.3	0.21	15.0	26.4	0.55
Boston	5.3	10.4	0.094	24.3	20.2	0.43	27.8	26.3	0.8
Campinas	9.9	10.1	0.96	24.5	20.1	0.33	31.6	26.0	0.29
Dublin	8.5	10.1	0.69	31.8	20.1	0.1	31.8	26.3	0.54
Guangzhou	10.9	9.8	0.53	15.7	22.1	0.005	22.8	27.9	0.065
Ibadan	3.3	10.7	0.006	10.8	21.1	0.01	13.2	27.5	0.002
Leuven	7.9	10.3	0.36	13.2	21.6	0.004	19.9	27.3	0.047
Oxford	6.6	10.8	0.035	26.1	19.5	0.026	29.3	26.0	0.39
Rome	27.9	9.8	0.003	36.7	20.3	0.23	75.7	26.3	-
Sao Paolo	13.0	9.8	0.23	29.7	19.1	<0.001	35.4	25.1	0.007
Shanghai	22.7	8.8	<0.001	20.2	20.4	0.96	35.4	25.5	0.029
Siena	14.8	10.0	0.48	20.0	20.4	-	-	-	-
Others	3.9	10.2	0.22	29.4	20.1	0.1	30.8	26.2	0.49

31.4 Description of work productivity impairment in disease outcome groups

As shown in Table 68, there was no difference between women with endometriosis and symptomatic controls in the number of hours they were paid to work (39.3 vs. 38.5 hrs/week; $p=0.097$). Similarly, after adjusting for pelvic pain severity, there was no significant difference between women with endometriosis and symptomatic controls in the number of hours they actually worked (24.9 vs. 28.6 hrs/week; $p=0.18$).

31.4.1 Endometriosis and work productivity loss

As shown in Table 68, although women with endometriosis reported greater absence from work due to symptoms (4.4 hours weekly per woman), this was not significantly different to the reported absence from work in symptomatic controls after account was taken of severity of pelvic pain. Similarly, although women with endometriosis reported greater reduced effectiveness while working due to symptoms (equivalent of 5.6 hours weekly per woman), this was not significantly different to the reported reduced effectiveness while working due to symptoms in symptomatic controls after account had been taken of severity of pelvic pain. Hence, after adjustment for severity of pelvic pain, the overall work productivity loss was 10.0 hours weekly per woman (SD 10.6) in women with endometriosis and 8.0 hours weekly per woman (SD 9.2) in symptomatic controls ($p=0.10$). In multivariate analysis, the strongest predictors of overall work productivity loss were pelvic pain severity, comorbidity and number of pelvic mass symptoms women reported ($R^2=21.3\%$) (Not shown).

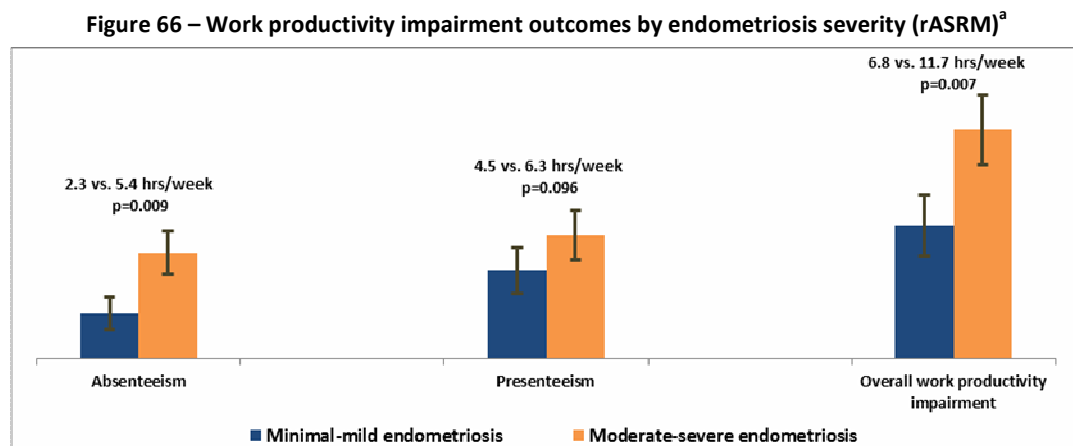
Table 68 - Work productivity in symptomatic women with and without endometriosis

Work and productivity loss variables	Endometriosis n=745	Symptomatic controls (n=587)	Unadjusted P value	Adjusted P value
<i>General</i>				
Weekly hours paid to work [Mean (SD)]	39.3 (14.0)	38.5 (12.2)	0.39	0.097
Weekly hours actually worked [Mean (SD)]	24.9 (16.1)	28.6 (25.3)	0.009	0.16
<i>Work Productivity & Activity Impairment dimensions</i>				
Absenteeism ^a	11.3 (21.6)	8.7 (20.1)	0.084	0.45
% [Mean (SD)]	4.4 (8.0)	3.3 (8.4)	0.28	0.67
Hours /week [Mean (SD)]				
Presenteeism ^b	23.5 (24.7)	16.3 (20.8)	0.001	0.41
% [Mean (SD)]	5.6 (7.8)	4.7 (6.6)	0.011	0.44
Hours /week [Mean (SD)]				
Overall work productivity loss ^c	30.5 (28.4)	21.2 (24.4)	<0.001	0.12
% [Mean (SD)]	10.0 (10.6)	8.0 (9.2)	0.002	0.10
Hours /week [Mean (SD)]				
Activity impairment ^d	28.5 (26.9)	19.9 (23.6)	<0.001	0.070
% [Mean (SD)]				

a – time absent from work due to symptoms; b – reduced effectiveness while on the job due to symptoms; c – combination of absenteeism and presenteeism; d – reduced effectiveness while doing non-work related activities e.g. child caring, exercise, housekeeping etc.

31.5 Endometriosis severity and work productivity loss

After adjusting for number of pelvic mass symptoms, severity of pelvic pain and comorbidity, absence from work due to symptoms increased with increasing disease severity (2.3 vs. 5.4 hrs/week/woman in stage I-II vs. III-IV disease; $p=0.009$), as did overall work productivity loss (6.8 vs. 11.7 hrs/week/woman in stage I-II vs. III-IV disease $p=0.007$) (Figure 66).



^a - Adjusted p-values for the association between each work productivity dimension and rASRM disease stage (trend test) are given. Variables adjusted for included number of pelvic mass symptoms, severity of pelvic pain and comorbidity.

After adjusting for diagnostic delay, number of pelvic mass symptoms, severity of pelvic pain and comorbidity, the mean overall work productivity loss per woman in centres where patients received predominantly government-funded healthcare was similar to that for women at centres where healthcare was predominantly funded through out-of-pocket payments or private insurance (8.4 hrs/week/woman vs. 8.7 hrs/week/woman; $p=0.33$).

31.6 Endometriosis and activity impairment

As shown in Table 68, compared to symptomatic controls, women with endometriosis had greater activity impairment [28.5% (SD 26.9) vs 19.9% (SD 23.6)] but after adjustment for severity of pelvic pain, the statistical significance of the difference was lost ($p=0.07$).

31.7 Monetary value of work productivity losses

The monetary impact of endometriosis-related work absenteeism and presenteeism was substantial (Figure 67). Absenteeism-related costs per employed woman ranged from US\$1.69/week in Ibadan (Nigeria) to US\$436.47/week in Rome (Italy). Presenteeism was associated with higher monetary losses, ranging from US\$6.21/week in Ibadan (Nigeria) to US\$403.46/week in Dublin (Ireland).

Figure 67 – Weekly monetary loss from endometriosis-associated work absenteeism and presenteeism

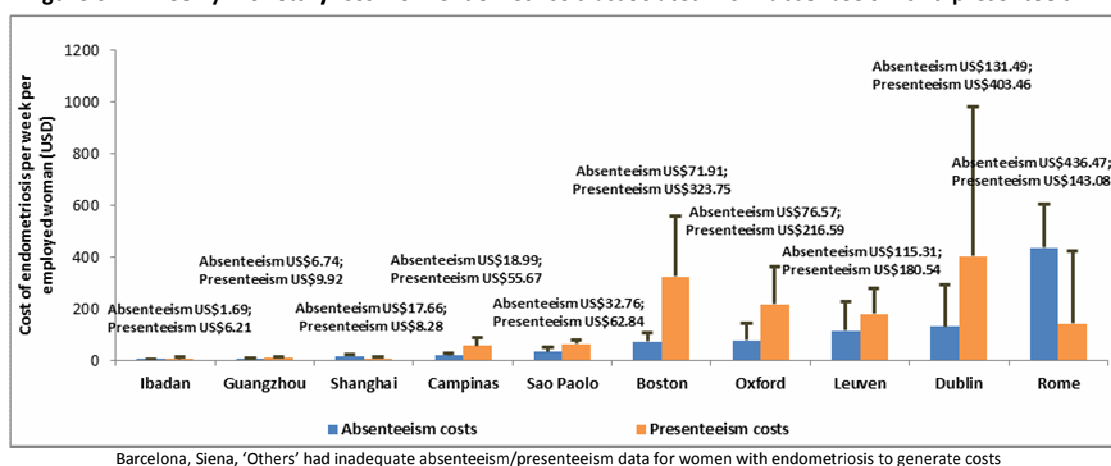


Table 69 – Annual indirect cost of endometriosis associated with work productivity loss and expressed as a percentage of Gross Domestic Product for countries

Centre	Overall work productivity loss in hrs/wk among women with endometriosis			2008 hourly labour cost (USD) in country	Annual indirect cost of endometriosis per woman in USD (based on 50-week year)			2008 GDP	Indirect cost of endometriosis as percentage of GDP
	Mean	95% LCL	95% UCL		Mean	95% LCL	95% UCL		
Boston	11.5	3.3	19.7	32.26	18586	5403	31769	46,436.40	4.00
Campinas	9.0	4.6	13.3	8.28	3724	1925	5523	8,114.12	4.59
Dublin	3.0	0.5	5.4	44.8	6612	1132	12092	51,049.39	1.30
Guangzhou	9.5	7.2	11.8	1.82	864	655	1073	3,743.81	2.31
Ibadan	8.0	2.0	13.9	1.00	399	102	695	1,092.19	3.65
Leuven	7.4	3.8	10.9	47.14	17368	9046	25691	43,429.66	4.00
Oxford	8.3	3.1	13.6	35.81	14917	5561	24273	35,164.86	4.24
Sao Paolo	11.0	7.9	14.1	8.28	4568	3289	5846	8,114.12	5.63
Shanghai	13.8	9.7	17.8	1.82	1251	885	1617	3,743.81	3.34

Barcelona, Siena, 'Others' and Rome had inadequate overall work productivity data for women with endometriosis to generate costs

As shown in Table 69, the annual indirect cost of endometriosis associated with work productivity loss ranged from US\$399 per woman in Ibadan (Nigeria) to US\$18,586 per woman in Boston (USA). Overall, total per-patient indirect cost of endometriosis ranged from an equivalent of 1.30% of gross domestic product in Dublin (Ireland) to 5.63% of gross domestic product in Sao Paolo (Brazil).

Therefore, assuming an endometriosis prevalence rate of 5% in 18-45 year old women in the USA, a total population of women in that age group of 33 million and an employment rate of 70% in that population, the annual indirect cost of endometriosis associated with absenteeism in the USA (based on Boston work productivity parameters) would be around US\$4.2 billion. The annual indirect cost associated with reduced effectiveness while at work due to symptoms in endometriosis would be a further US\$18.7 billion.

32 Discussion

The significant impact of endometriosis-associated symptoms on work productivity is highlighted in this study. One in eight (13.0%) symptomatic women who were not in paid or self-employment at the time of the survey reported that this was because of the symptoms for which they underwent laparoscopy. After adjusting for the severity of pelvic pain, there was no difference between affected women and symptomatic controls in the number of weekly hours of actual work that they reported (24.9 vs. 28.6 hrs/woman/ week; adjusted $p=0.16$). There was no difference between affected women and symptomatic controls in mean number of hours of work missed due to symptoms (absenteeism) before and after adjustment for pelvic pain (4.4 vs. 3.3 hrs/woman/week; adjusted $p=0.67$). The severity of pelvic pain was a major driver of work absence but the lack of significant difference in absenteeism between affected women and symptomatic controls despite differences in symptom severity suggests that affected women may be going to work in spite of their symptoms. Affected women reported greater reduced

effectiveness while working due to symptoms (presenteeism) compared to symptomatic controls (equivalent of 5.6 vs. 4.7 hrs/woman/week; $p=0.011$) but this was not robust to adjustment for pelvic pain severity ($p=0.44$). This study is the first to report that presenteeism (lost effectiveness because of symptoms, while at work) accounts for about 60% of the total work productivity loss in women with endometriosis, a finding that supports the position that women work through their pains and a focus on reducing understanding the mechanisms of pain in endometriosis and treatment to mitigate symptom severity would benefit individual women with endometriosis specifically and society in general. Overall work productivity loss after adjusting for severity of pelvic pain was similar in affected women and symptomatic controls (10.0 hours/week vs. 8.0 hours/week; adjusted $p=0.10$). These findings highlight the centrality of pelvic pain severity as a driver of the work productivity impact of endometriosis in employed women. Since women with missing data in the symptomatic control group were significantly less likely than those without missing data to report co-morbidity in their medical history (61.1 vs. 70%; $p=0.038$), it is possible that the impact of endometriosis on work productivity loss has been underestimated in this analysis.

After adjusting for number of pelvic mass symptoms, severity of pelvic pain and comorbidity, absence from work due to symptoms increased with increasing disease severity (2.3 vs. 5.4 hrs/week/woman in stage I-II vs. III-IV disease; $p=0.009$), as did overall work productivity loss (6.8 vs. 11.7 hrs/week/woman in stage I-II vs. III-IV disease $p=0.007$).

In monetary terms, absenteeism-related costs per employed woman ranged from US\$1.69/week in Nigeria to US\$436.47/week in Italy. Presenteeism was associated with higher monetary losses, ranging from US\$6.21/week in Nigeria to US\$403.46/week in the Ireland. The annual indirect cost of endometriosis associated with work productivity loss ranged from US\$399 per woman in Ibadan (Nigeria) to US\$18,586 per woman in Boston (USA). Overall, total per-patient indirect

costs of endometriosis ranged from an equivalent of 1.3% of gross domestic product in Dublin (Ireland) to 5.63% in Sao Paolo (Brazil). Studies of the impact of endometriosis on work productivity and activity are very few and often have significant limitations in respect of study design and methods. Most of the earlier studies on the subject either focused on describing the work productivity impact of chronic pelvic pain (CPP) and dysmenorrhoea [273,274] or drew cautious attention to the adverse association between the recurrent pain of endometriosis and work productivity [24]. In 1995 however, the Gallup Organization embarked on a telephone interview-based study of over 5,000 18-50 year old women [21]. About 15% of them had CPP and 9% of those with CPP had endometriosis as an underlying cause. They were surveyed on their symptoms, work absence, reduced productivity at work and healthcare utilisation. Amongst the employed participants with CPP, the mean number of hours of work missed due to symptoms was 2.2 ± 11.2 per month; those who reported underlying endometriosis missed 1.6 hours of paid work per month (cf 17.6 hours absenteeism in this study). On a scale of 0-10, 45% of employed women with CPP rated their work productivity with pelvic pain at 7 or lower. The authors put the total annual indirect cost associated with missed time from work in the US population due to CPP at \$555.3 million (cf \$4 billion in this study); direct costs (comprising physician costs and out-of-pocket expenses) were estimated at \$2.8 billion. The impact of endometriosis on work in the Gallup study may be significantly under-estimated and there are a number of possible reasons for this. First, over half of the women in the Gallup study had no known cause for their CPP and the potential for underestimation of the role of endometriosis is thus significant. Secondly, the Gallup study only assessed work productivity loss in women who had CPP but CPP is only one of a number of pain-related symptoms of endometriosis and the potential for underestimation as a result is significant. Thirdly, the sample in this study comprised women seeking care while the Gallup study sampled women outside of a care context. It is possible that differences in work absence due to symptoms reflect that an overwhelming proportion of the women who were not seeking care in the Gallup sample possibly had less severe disease. Fourthly, the Gallup study did

not use the standardised survey instruments which since became available to investigate work productivity losses associated with disease and its findings should thus be interpreted with caution.

Gao et al. in a 2006 systematic review set out to quantify the direct economic cost of endometriosis [269]. They noted the scarcity of studies that examined the indirect costs of the disease (principally those associated with loss in work productivity, loss in earned income and social withdrawal) and made reference to the Gallup study as a source of data on the indirect costs of endometriosis. In 2007 however, another systematic review of studies quantifying the costs of endometriosis concluded that estimates of the number of hours missed from work due to endometriosis ranged from 19.2 - 86.4 hours per patient per year [268], again quoting the Gallup study and another earlier US study quantifying the cost of endometriosis treatment in a California Medicaid population [275]. The authors of the review suggested that the upper limit of the productivity loss of 86.4 hours translated into annual indirect costs of \$1,023 per patient. This figure, though closer, is still much lower than the absenteeism costs of \$3,595 per patient which we found in the current study for US women. It is however worth noting that most previous studies have largely focused on quantifying the productivity loss associated with absenteeism from work. Work absenteeism due to illness however only narrowly describes the spectrum of work productivity loss associated with disease conditions. To generate more valid estimates of disease-related work productivity loss, reduced productivity while at work (presenteeism), as well as absenteeism, needs to be considered [270], as has been done in this study.

More recent studies of the impact of endometriosis on work productivity do not seem to have added very much in terms of methodological rigour. In 2009, investigators in Germany published the pilot of a qualitative study involving 65 female employees (aged 18–60) working at a city supermarket [276]. The impact of endometriosis on work-based and/or professional performance

was assessed by means a purposefully designed questionnaire during in-depth interviews. Only 3% of the women had received treatment for endometriosis but 92.3% of them (95% CI 85.8-98.8%) had CPP, dyspareunia or dysmenorrhoea. The authors also reported that 10 of 10 (100%) women with only dysmenorrhoeal symptoms reported impaired abilities to participate in gardening, house-work, sports and leisure activities, suggesting that pain was as a major cause of professional or work-related impairment among women with endometriosis. Important limitations with the study should however be noted. Firstly, the sample size of 65 almost certainly would not have afforded enough power to detect associations with any certainty. Secondly, although designed as a qualitative study, the impact of endometriosis on work and activity might have been better measured using validated instruments and quantified more accurately rather than being expressed as the proportion of women reporting an unquantified impact. Thirdly, although almost all women were symptomatic, the impact on work productivity that the authors describe could not with certainty be attributed to endometriosis since only 3% of women in the sample had confirmed endometriosis.

A more recent survey of 107 women with self-reported surgically diagnosed endometriosis in Puerto Rico assessed the impact of symptoms of the disease on work performance in four dimensions: [1] quality of work, [2] physical disability, [3] absenteeism, and [4] professional growth [266]. The majority of patients in the study (85%) perceived that there was a noticeable decrease in the quality of their work and almost 20% reported being unable to work because of pain. As was the case in the study by Oehmke et al. [262], the authors expressed the impact of endometriosis in terms of the proportion of women reporting unquantified absence from work due to symptoms and reduced effectiveness while working. They however quantified absenteeism in women with endometriosis as a mean 19.3 days (SD 19.3) of work missed yearly due to treatments, surgeries and recovery.

In light of the limitations of studies in the existing literature, the findings of the current study add significant value by reason of the robust design and study methods. The findings highlight the significant impact of endometriosis on both dimensions of work productivity as well as the role of symptoms of endometriosis in producing this adverse effect. The finding that 3.3% of symptomatic women did not work because of their symptoms compares with findings in an earlier study that 18.8% (95% CI 11.2-26.4%) of women did not work because of their symptoms but it was unclear in the latter study whether they were reporting on employed women who were sometimes unable to work because of symptoms. As the 3.3% of symptomatic women unable to work because of their symptoms did not contribute work productivity data in this study, the estimates of work productivity loss reported in this study should be considered conservative. This potential for a conservative estimation of work productivity loss is however balanced by a potential for over-estimation arising from: 1) imminent surgery and possible associated anxiety; 2) the alteration to 4 weeks made to the standard 7-day recall period of the WPAI in this study for reasons given earlier. A study which similarly extended the recall period to 4 weeks found that the construct validity of the modified questionnaire for was similar to that of the original questionnaire although estimates of work productivity impairment were higher.

The association of endometriosis disease rASRM stage (severity) with work productivity loss after adjusting for pelvic pain severity, comorbidity and other covariates is intriguing and could be due to a number of reasons. Firstly, despite careful adjustment, there remains the possibility of residual differences in symptom severity between women with endometriosis and symptomatic controls. Secondly, women with endometriosis may have a greater frequency of comorbid conditions that may not have been reported and thus accounted for in the analysis, confounding the association with work productivity. Lastly, as discussed in relation to HRQoL results in the previous chapter, an intriguing possible explanation is the potential role of central sensitisation. This theory, supported by experimental evidence from animals and humans [259,261] suggests

that endometriotic tissue, as disease advances, generates persistent pain stimuli in the central nervous system, resulting over time in a heightened awareness of pain even from areas of the body well removed from the site of the ectopic endometrial tissue. If true, this heightened generalised pain awareness could account for the persistent impact of worsening endometriosis on work productivity, and may present an opportunity to reduce both the personal and societal impact of the disease by early symptom control approaches that target central sensitisation.

CHAPTER 9

SUMMARY AND CONCLUSIONS

1 Summary of the key findings of study

1.1 Characteristics of population and diagnostic incidence of endometriosis

Over an 18-month period from June 2008 to January 2010, this study recruited 1,418 premenopausal women undergoing a first laparoscopy either for diagnosis or for sterilisation across 16 clinical centres in 10 countries across 5 continents. The average recruitment rate for the study was 89.0% and ranged from 60.9% in Ibadan to 97.7% in Guangzhou. Women who took part in the study, on average, completed the survey questionnaire 4.9 days (SD 19.9) before the day of their scheduled laparoscopic surgery although this interval was 12.3 days (SD 14.8) in women in Leuven. The average age of women in the study population was 33.0 years (SD 6.3), ranging from a mean of 30.8 years (SD 6.1) in Guangzhou to 36.4 years (SD 5.5) in Siena.

Seven hundred and forty-five women in the study population were diagnosed with endometriosis at laparoscopy, yielding a diagnostic incidence of endometriosis of 52.5% (95% CI 49.0-56.1%) in all women and 14.3% (11/77; 95% CI 6.5-22.1%) in asymptomatic women who underwent sterilisation. This study confirmed the well reported finding that endometriosis disease stage (or severity) does not correlate with the severity of symptoms (specifically dysmenorrhoea, chronic pelvic pain and dyspareunia). The range of endometriosis prevalence from 34.8% in Oxford to 100% in Siena is interesting. Although recruitment to this study was based on a uniform set of criteria, participating centres had different routine protocols for investigating women with pelvic symptoms. For example, at centres such as Siena, Shanghai and Sao Paolo, which had relatively high incidence of endometriosis, all women had pre-surgical ultrasound scans, with surgery possibly prioritised in those with evidence of ovarian (endometriotic) cysts. Consequently, detection bias could have played a role in some of the findings reported here since a high probability of endometriosis indicated by a scan might affect the detail of laparoscopic examination. Indeed, women who underwent a pre-surgical ultrasound scan were more than 1.5

times as likely as controls to be diagnosed with endometriosis after controlling for presence of ovarian cysts and number of pelvic mass symptoms reported (OR 1.65; 95% CI 1.20-2.26).

Amongst women who had endometriosis, 60.5% (n=451; 95% CI 57.0-64.0%) had moderate-severe endometriosis. Interestingly, amongst women who underwent sterilisation but who also had endometriosis diagnosed at laparoscopy, 58.1% (25/43; 95% CI 43.4-72.9%) had moderate-severe disease, although this incidence was 36.3% (4/11; 95% CI 7.9-64.8%) when restricted to asymptomatic women who underwent sterilisation. The relatively high proportion of moderate-severe endometriosis even in asymptomatic women undergoing sterilisation is interesting and may raise questions about the accuracy of staging or indeed about the extent to which women were indeed symptomatic. The participating hospitals and clinicians were however experienced in diagnosing endometriosis and the likelihood of staging errors is limited. Furthermore, combining minimal with mild and moderate with severe stages in analyses would have minimised the possibility of staging errors further. The possibility of diagnostic and staging errors was however explored more formally in a post-GSWH validation study in which 29 surgeons from 12 of the 16 participating centres viewed 9 standardised videos to identify/eliminate and stage endometriosis. Preliminary analysis of inter-rater agreement suggested substantial agreement in disease identification and staging (both Fleiss $\kappa > 0.60$).

In multivariate analysis adjusting for key sociodemographic (including age, education, ethnicity, marital status) and clinical (e.g. age at menarche, use of contraception, subfertility, gravidity and parity) variables, endometriosis odds were higher with lower gravidity (adjusted OR 0.36; 95% CI 0.16-0.81) and more severe pelvic pain (adjusted OR 1.19; 95% CI 1.01-1.41). The findings support the observation that when proper account is taken of potential confounding variables, endometriosis probably has few known or previously assessed modifiable risk factors [277]. Indeed, the findings suggest the possibility that some of the reported associations of

endometriosis with specific risk factors probably reflect the design limitations of those studies and inadequate consideration of potential confounding factors. Although the current study is itself not without important limitations (discussed in a later paragraph), particularly those inherent in its cross-sectional design, it perhaps highlight the potentially limited scope for substantial risk modification in endometriosis, although this study only considered a limited set of risk factors. Awareness of these associations could however support investigative decision-making when other symptoms point to endometriosis.

1.2 Presenting symptoms

Women who had endometriosis had on average more symptoms in each symptom category (pelvic, urinary, bowel and pelvic mass symptoms). The importance of pelvic pain (CPP, dysmenorrhoea or dyspareunia) as a feature of endometriosis is perhaps reflected in the fact that pelvic pain without subfertility was the reason for surgery in over 40% of women in the study population and was most strongly associated with endometriosis (adjusted OR 2.3; 95% CI 1.8-3.1). A related observation was that the commonest individual symptoms that led to laparoscopy were chronic pelvic pain (42.8%; n=605), dysmenorrhoea (40.8%; n=581), ovarian cysts (34.9%; n=495) and subfertility (34.5%; n=489). The triad of dysmenorrhoea (adjusted OR 2.7; 95% CI 2.0-3.7), dyspareunia (adjusted OR 1.4; 95% CI 1.0-2.0) and dyschezia (adjusted OR 2.0; 95% CI 1.2-3.2) was most strongly associated with increased odds of endometriosis diagnosis. This triad, also termed the “3D-syndrome”, is well recognized in the literature [278]. Establishing its association with endometriosis in a geographically and ethnically diverse study population as in this study should aid clinical decision-making in early consideration of the possibility of endometriosis in symptomatic women. Dyspareunia correlated positively with presence of endometriotic nodules in the cul-de-sac ($r=0.06$, $p=0.025$) and bowel ($r=0.06$, $p=0.023$) but not with bladder nodules ($r=0.05$, $p=0.055$); dyschezia and dysuria did not correlate with lesion location. Compared to White women, Asian and Black women were less likely to undergo laparoscopy because of

dysmenorrhoea, CPP, menorrhagia and dyspareunia. Black women were however more likely to undergo laparoscopy because of subfertility than White and Asian women.

1.3 Disease onset and care-seeking in endometriosis

The mean age of women at symptom onset, defined as age at the earliest onset of any of the symptoms for which they underwent laparoscopy, was 23.7 years (SD 9.3) and those with endometriosis were, on average, significantly younger than symptomatic controls at symptom onset (22.9 vs. 24.8 years; $p<0.001$). In addition, after controlling for the effect of age, women with endometriosis made contact with their physicians on account of their symptoms earlier than did symptomatic controls (26.8 vs. 27.9 years; $p=0.003$). Women who reported pelvic pain without subfertility were significantly younger at symptom onset than those who reported subfertility without pelvic pain (20.7 vs. 27.7 years; $p<0.001$), this perhaps reflecting the emergence of subfertility in later life when women marry and attempt conception. Affected women visited their primary care physicians an average of 6.5 times before being referred to a gynaecologist but despite their greater severity of pelvic pain, this was not significantly different to the number of times symptomatic controls visited their general physicians (an average of 6.8 times). Diagnostic delay reached 9.2 years (SD 8.8) in all women; after accounting for age, this was significantly longer in affected women compared to symptomatic controls (9.8 vs. 8.3 years $p=0.001$). In keeping with findings of previous studies [226], diagnostic delay was longer in women who were investigated for pelvic pain and was due principally to delay in referral to a specialist after consultation with a primary care physician. More specifically, the finding in this study that 38% of the average length of diagnostic delay was attributable to patient-related delays in seeking care for their symptoms compares with the proportion of 15% reported by Arruda and colleagues in a retrospective cohort study of 200 Brazilian women with surgically confirmed endometriosis [226]. The observations related to care-seeking and diagnosis of endometriosis in this study compare with those reported in analysis of data collected in a survey

of >4,000 members of the North American Endometriosis Association in 1998. That survey revealed that 47% of women had seen a health care provider ≥ 5 times before being diagnosed or referred and that the length of diagnostic delay averaged 9.28 years, with the average woman taking 4.67 years to report her symptoms to a physician, and the average physician taking another 4.61 years to diagnose the disease [264].

As similarly observed by Arruda et al [226], women who were younger at symptom onset in this study population not only took a significantly longer time to report their symptoms to a physician (8.7 vs. 0.5 years; $p < 0.001$) but also experienced longer diagnostic delays (19.4 vs. 2.4 years; $p < 0.001$). It is possible that unfamiliarity with the symptoms of endometriosis during the first years after menarche, and the normalisation of painful menstrual experiences, explain why women who were younger at symptom onset took significantly longer to report their symptoms to a physician. Finally, diagnostic delay was longer in women with higher BMI and who reported more pelvic symptoms. Diagnostic delay was significantly longer, by 5.2 years, in women at centres where health care was predominantly government-funded and this difference was stable to adjustment for site. This rather worrying observation might indicate that women who could not afford to privately fund their care were waiting much longer to be diagnosed. As higher BMI, which correlates with poorer socioeconomic status [279], was also associated with diagnostic delay, efforts to reduce the time to diagnosis should target ability to pay for care in women with higher BMI.

1.4 Endometriosis and HRQoL

This study elucidates in more detail the HRQoL impact of endometriosis. With mean SF36v2 dimension scores ranging from a possible 0 (representing worst quality of life) to 100 (representing best quality of life), women in the study population had mean dimension scores ranging from 56.5 (SD 20.6) in the energy/vitality dimension to 88.7 (SD 17.8) in the physical

functioning dimension. Generally, the average woman in Sao Paolo had significantly poorer HRQoL compared to the average woman in the remainder of the study population in the SF36v2 dimensions of energy/vitality, mental health, bodily pain, social functioning and mental role limitation. On the other hand, the average woman in Leuven had significantly better HRQoL compared to the average woman in the remainder of the study population in the SF36v2 dimensions of health perception, bodily pain, social functioning and physical functioning. The poorer HRQoL in women at Sao Paolo is unlikely to have been due entirely to their having more severe pelvic pain, on average, in comparison with the remainder of the study population (5.3 vs. 4.6; $p=0.004$), as women in Barcelona, Boston, Campinas and Siena had worse pelvic pain. Another possible reason could be the long period of diagnostic delay experienced by women in Sao Paolo (14 years on average), as long diagnostic delay in this study population was associated with reduced HRQoL, particularly in the physical dimension. After adjusting for the severity of pelvic pain and/or gravidity, compared to symptomatic controls, affected women had poorer HRQoL in the SF36v2 dimensions of bodily pain, social functioning and mental and physical role limitation. Similarly, they had poorer HRQoL in the dimensions of health perception, bodily pain and mental role limitation compared to sterilisation controls, after adjusting for severity of pelvic pain and/or gravidity.

Affected women (mean 42.5, SD 11.1) and both symptomatic (mean 43.6, SD 10.1) and sterilisation (mean 44.2, SD 10.6) controls had poorer mental HRQoL than the normative population (all $p<0.001$) but sterilisation controls did not differ from the normative population in the measure of physical HRQoL (mean 48.1; $p=0.17$). The key impact of endometriosis was seen on the physical aspect of HRQoL, where after adjusting for pelvic pain severity, affected women had a significantly poorer summary score than symptomatic controls (45.4 vs. 48.3; $p=0.012$). The poorer mental HRQoL in sterilisation controls compared to the normative population was perhaps surprising. The inclusion of some symptomatic women in the sterilisation group was explored as a

possible explanation but excluding them from the sterilisation group did not change that result. Secondly, anxiety related to upcoming surgery might have similarly affected all women and resulted in poorer mental HRQoL compared to the normative population. However, mental HRQoL did not correlate with the interval between questionnaire completion and surgery ($\beta=0.014$; $p=0.35$).

Physical HRQoL was higher in women in paid or self-employment but lower in those with more severe pelvic pain and more “pelvic” symptoms. Diagnostic delay reduced physical HRQoL in women with endometriosis. After adjustment for relevant covariates (pelvic pain severity and co-morbidity), women with moderate-severe endometriosis had a poorer HRQoL than those with minimal-mild disease in the SF36v2 dimensions of bodily pain ($\beta=-4.69$; $p=0.019$), health perception ($\beta=-9.3$; $p<0.001$) and the physical component summary score ($\beta=-1.79$; $p=0.035$). The association of moderate-severe endometriosis and HRQoL in the bodily pain dimension after adjusting for pelvic pain severity and co-morbidity is interesting. Although it could be due to residual confounding despite careful adjustment for potential confounders, it could also be explained by heightened pain awareness from regions well removed from pelvic endometriotic tissue as disease advances, the now well-reported “central sensitisation” phenomenon.

In summary, although presence and severity of symptoms are a major driver of the HRQoL impact of endometriosis, endometriosis has residual effects on physical HRQoL over and above that attributable solely to its symptoms. Further studies are clearly needed to elucidate the mechanisms of these effects but more effective symptom control and quicker access to diagnostic investigation are key to reducing the HRQoL impact of the condition.

1.5 Endometriosis and work productivity

One in eight symptomatic women did not work because of their symptoms. Mean absenteeism in the study population was 3.9 hours/week per woman (SD 8.2), ranging from 1.5 hours/week in Ibadan (SD 2.9) and 'Other' centres (SD 2.8) to 9.7 hours/week (SD 6.6) in Rome. Similarly, mean presenteeism in the study population was 5.4 hours/week per woman (SD 7.2), ranging from 2.7 hours/week in Leuven (SD 4.8) to 12.3 hours/week (SD 3.7) in Barcelona. Mean overall work productivity loss in the study population was therefore 9.3 hours/week per woman (SD 10.1), ranging from 5.5 hours/week in Ibadan (SD 4.8) to 14.6 hours/week (SD 4.5) in Barcelona. Centre-wise comparisons suggest that women in Ibadan (mean 13.2 vs. 27.5%; $p=0.002$) and Leuven (mean 19.9 vs. 27.3%; $p=0.047$) were least likely to suffer work productivity impairment, while those in Sao Paolo (mean 35.4 vs. 25.1%; $p=0.007$) and Shanghai (mean 35.4 vs. 25.5%; $p=0.029$) suffered the most impairment in comparison with the average woman in the remainder of the study population. These centre-specific work productivity impairment figures are novel and highlight the geographical variations in the impact of endometriosis symptoms on work productivity. The relatively low impairment in work productivity in women in Ibadan and Leuven accords with the relatively low mean severity of pelvic pain reported by the average woman in those centres. The greater impact in women in Sao Paolo and Shanghai would however seem to suggest that other factors (such as endometriosis severity) may be driving work productivity impairment in addition to severity of pelvic pain.

Compared to symptomatic controls (3.3 hours/woman/week), there was no difference for affected women (4.4 hours/woman/week) in the mean number of hours of work missed due to symptoms (absenteeism). There was similarly no difference between affected women (5.6 hours/woman/week) and symptomatic controls (4.7 hours/woman/week) in reduced effectiveness while working due to symptoms (presenteeism) after account was taken of pelvic pain severity. In addition, overall work productivity loss after adjusting for pelvic pain severity was

similar in affected women (10.0 hours/woman/week) and symptomatic controls (8.0 hours/woman/week). Presenteeism accounted for more overall work productivity loss (57.8%) than did absenteeism (42.2%). The similarity in work productivity impairment in affected women and symptomatic controls reflects the significant role of pelvic pain severity as a driver of work productivity loss.

In monetary terms, the annual indirect cost of endometriosis associated with work productivity loss ranged from US\$399 per woman in Ibadan (Nigeria) to US\$18,586 per woman in Boston (USA). Extended to the US population for illustration, these per-woman annual indirect costs of endometriosis would translate to US\$4.2 billion related to absenteeism and US\$18.7 related to presenteeism. Overall, total per-patient indirect costs of endometriosis in the current study ranged from an equivalent of 1.30% of gross domestic product in Dublin (Ireland) to 5.63% in Sao Paulo (Brazil). Although a number of studies have examined the direct costs of endometriosis, this is the first study to quantify in monetary terms the indirect costs of the condition accruing from a comprehensive estimation of work productivity loss in endometriosis. One previous study which attempted to quantify absenteeism-related costs of endometriosis-associated chronic pelvic pain (CPP) in the US population may represent a significant under-estimate as productivity loss was only estimated in women who had CPP, many of whom had no known cause for their CPP [21].

While endometriosis might redound to the individual patient's poor HRQoL, it additionally carries significant cost to society in terms of work productivity losses. It could be speculated that employers' attitudes to endometriosis-related work absences [280] compels affected women to go to work in spite of their symptoms, who then experience greatly reduced productivity at work due to those symptoms. As with HRQoL, symptoms are a major driver of work productivity loss and good symptom control is clearly key to mitigating the impact of endometriosis on women in particular and on society in general.

2 Strengths and limitations of the study

The GSWH study represents a substantial improvement on the limitations of many previous attempts at elucidating the risk factors for and impact of endometriosis but its strengths and limitations are worth examining in more detail. One potential limitation relates to the possibility of selection bias. A good case control study that samples cases from a population (rather than recruiting all cases in the population) should ensure that every case in the source population has an equal chance to other cases of being a member of the sample. Similarly, controls should represent the exposure distribution in the source population for cases. It was not an explicit goal of the GSWH to sample all cases in the general population and potential under-ascertainment is a possibility if potential cases in the population were systematically excluded from recruitment. Indeed, there are a number of reasons why the women attending the participating clinics may not necessarily be representative of all women with endometriosis in the reference populations. For example, the clinics were a mix of facilities where patient care was either state- or privately funded. Therefore it is conceivable that the average profile of the patients attending for care at those centres might have differed significantly 1) from one another, and 2) from the general population of women with endometriosis in a manner that would have introduced some selection bias. Furthermore, the pathway leading up to a scheduled laparoscopy, at which point patients were recruited, might have varied significantly across centres, with women getting quicker referrals from primary care in some centres than at others and access to pre-laparoscopy work-ups varying across centres. Indeed the range of the mean number of visits to a primary care physician before specialist referral across the centres in this study (2-13 visits per woman) supports this. In addition, recruiting and then excluding from the analysis women whose laparoscopy appointments were cancelled or who missed such appointments (especially if they had milder or more recent-onset symptoms) may exaggerate outcomes like diagnostic delay but this is likely to involve small numbers. It could be a matter of concern that some centres in the

study participated with a small number of women, reducing the likelihood of consecutive recruitment and increasing the chance that some form of selection might have occurred. There are three problems potentially related to this: 1) selection bias if women were excluded from laparoscopy because ultrasound scans were negative; 2) detection bias if women with positive ultrasound scans were assessed intra-operatively with greater detail than were women with negative ultrasound scan results, and 3) bias related to differences in routine treatment routes between different centres (e.g. medical intervention first, followed by laparoscopy).

Careful attention was given in the design of this study to collecting adequate information to enable robust adjustment for potential confounders but residual confounding was still possible.

Another key limitation was around the study instruments and regards the deployment of the WPAI over a 4-week, rather than a 7-day, recall period. The decision was based on the need to collect information over a reasonable period of time to allow the effect of symptoms to be captured. Where this has been done previously, over-estimates of work productivity loss has been found. In addition, assessing quality of life and work productivity loss over a month when women would have been awaiting surgery, and thus may have been anxious, may over-estimate the impact of endometriosis disease on these parameters. However, although this might have affected absolute values of HRQoL and work productivity measures, there is no reason to believe that it would differentially affect affected women and symptomatic controls. Consequently, the comparison of HRQoL between affected women and symptomatic controls should have produced unbiased results.

This study also has some important areas of strength. Standardised and comprehensive epidemiological information on endometriosis and its associated symptoms was collected on an unprecedented global scale. The design of the study attempted to address methodological

limitations of previous epidemiological studies, particularly in relation to the application of consistent case definitions, appropriate selection of controls sampled from the same source population as cases, and collection of comprehensive information on risk-factor exposure to allow control of confounding factors. The design allowed for cross sectional and case-control analyses that provide novel insights into the effects of endometriosis on women's lives and tested the association of the disease with a number of sociodemographic, reproductive, contraceptive, lifestyle and personal characteristics.

In the study, incident (i.e. newly diagnosed) rather than prevalent endometriosis cases were recruited to allow for the collection of unbiased exposure information pre-dating disease onset [14]. The interval between risk-factor exposure and onset of disease is however unknown and recruiting incident cases may not completely isolate the influence of disease duration on exposure and its reporting, particularly if symptoms are long-standing. Another area of strength of the study is that it recruited women across diverse health systems, thus enabling comparisons across these settings.

The use of web-based questionnaires assumed that participating patients had access to the internet and were relatively competent in using a personal computer. Indeed, substantial selection bias was likely to occur if participants would require access to a personal computer to participate in the studies. In the design of the GSWH, therefore, women were equally encouraged to complete a paper copy or an online version of the questionnaire, which should reduce the potential of this bias occurring.

The GSWH represents a response to a call by the international endometriosis research community for better designed, adequately powered multi-centre epidemiological studies conducted in collaboration across global research groups, using standardised protocols for

information collection. The study results provide major improvements in the insight into the impact of endometriosis in different countries worldwide. It is potentially an ideal framework for longitudinal follow-up studies, and in particular the establishment of a collaborative Endometriosis Biobank implementing standardised collection of DNA and tissue samples. Such an initiative would allow much-needed integrated investigations of environmental and biological hypotheses and the discovery of biomarkers for endometriosis.

References

1. Kennedy S, Bergqvist A, Chapron C, D'Hooghe T, Dunselman G, Greb R, et al. ESHRE guideline for the diagnosis and treatment of endometriosis. *Hum Reprod* 2005;20(10):2698-2704.
2. Eskenazi B, Warner ML. Epidemiology of endometriosis. *Obstet Gynecol Clin North Am* 1997;24(2):235-258.
3. Rogers PAW, D'Hooghe TM, Fazleabas A, Gargett CE, Giudice LC, Montgomery GW, et al. Priorities for Endometriosis Research: Recommendations From an International Consensus Workshop. *Reprod Sci* 2009;
4. Cramer DW, Missmer SA. The epidemiology of endometriosis. *Ann N Y Acad Sci* 2002;955:11-22; discussion 34.
5. Montgomery GW, Nyholt DR, Zhao ZZ, Treloar SA, Painter JN, Missmer SA, et al. The search for genes contributing to endometriosis risk. *Hum Reprod Update* 2008;14(5):447-457.
6. 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.
7. D'Hooghe TM, Kyama CM, Chai D, Fassbender A, Vodolazkaia A, Bokor A, et al. Nonhuman primate models for translational research in endometriosis. *Reprod Sci* 2009;16(2):152-161.
8. Missmer SA, Hankinson SE, Spiegelman D, Barbieri RL, Malspeis S, Willett WC, et al. Reproductive history and endometriosis among premenopausal women. *Obstet Gynecol* 2004;104(5 Pt 1):965-974.
9. Rock JA, Zacur HA, Dlugi AM, Jones HW, TeLinde RW. Pregnancy success following surgical correction of imperforate hymen and complete transverse vaginal septum. *Obstet Gynecol* 1982;59(4):448-451.
10. 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.
11. Bulun SE. Endometriosis. *N Engl J Med* 2009;360(3):268-279.
12. Missmer SA, Hankinson SE, Spiegelman D, Barbieri RL, Marshall LM, Hunter DJ, et al. Incidence of laparoscopically confirmed endometriosis by demographic, anthropometric, and lifestyle factors. *Am J Epidemiol* 2004;160(8):784-796.
13. Missmer SA, Hankinson SE, Spiegelman D, Barbieri RL, Michels KB, Hunter DJ, et al. In utero exposures and the incidence of endometriosis. *Fertil Steril* 2004;82(6):1501-1508.
14. 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.
15. Missmer SA, Cramer DW. The epidemiology of endometriosis. *Obstet Gynecol Clin North Am* 2003;30(1):1-19, vii.

16. Revicki DA. Health-related quality of life in the evaluation of medical therapy for chronic illness. *J Fam Pract* 1989;29(4):377-380.
17. Goldberg DP, Blackwell B. Psychiatric illness in general practice. A detailed study using a new method of case identification. *Br Med J* 1970;1(5707):439-443.
18. Cooper P, Osborn M, Gath D, Feggetter G. Evaluation of a modified self-report measure of social adjustment. *Br J Psychiatry* 1982;141:68-75.
19. Gao X, Yeh YC, Outley J, Simon J, Botteman M, Spalding J, et al. Health-related quality of life burden of women with endometriosis: a literature review. *Curr Med Res Opin* 2006;22(9):1787-1797.
20. Low WY, Edelmann RJ, Sutton C. A psychological profile of endometriosis patients in comparison to patients with pelvic pain of other origins. *J Psychosom Res* 1993;37(2):111-116.
21. 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.
22. Peveler R, Edwards J, Daddow J, Thomas E. Psychosocial factors and chronic pelvic pain: a comparison of women with endometriosis and with unexplained pain. *J Psychosom Res* 1996;40(3):305-315.
23. Denny E. Women's experience of endometriosis. *J Adv Nurs* 2004;46(6):641-648.
24. Damario MA, Rock JA. Pain recurrence: a quality of life issue in endometriosis. *Int J Gynaecol Obstet* 1995;50 Suppl 1:S27-S42.
25. Seear K. The etiquette of endometriosis: stigmatisation, menstrual concealment and the diagnostic delay. *Soc Sci Med* 2009;69(8):1220-1227.
26. Hadfield R, Mardon H, Barlow D, Kennedy S. Delay in the diagnosis of endometriosis: a survey of women from the USA and the UK. *Hum Reprod* 1996;11(4):878-880.
27. 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.
28. Pugsley Z, Ballard K. Management of endometriosis in general practice: the pathway to diagnosis. *Br J Gen Pract* 2007;57(539):470-476.
29. Somigliana E, Vercellini P, Vigano' P, Benaglia L, Crosignani PG, Fedele L, et al. Non-invasive diagnosis of endometriosis: the goal or own goal? *Hum Reprod* 2010;25(8):1863-1868.
30. Audebert A, Bäckström T, Barlow DH, Benagiano G, Brosens I, Bühler K, et al. Endometriosis 1991: a discussion document. *Hum Reprod* 1992;7(3):432-435.
31. Pinkert TC, Catlow CE, Straus R. Endometriosis of the urinary bladder in a man with prostatic carcinoma. *Cancer* 1979;43(4):1562-1567.

32. Donnez J, Nisolle M, Smoes P, Gillet N, Beguin S, Casanas-Roux F, et al. Peritoneal endometriosis and "endometriotic" nodules of the rectovaginal septum are two different entities. *Fertil Steril* 1996;66(3):362-368.
33. rASRM. Revised American Society for Reproductive Medicine classification of endometriosis: 1996. *Fertil Steril* 1997;67(5):817-821.
34. Roberts CP, Rock JA. The current staging system for endometriosis: does it help? *Obstet Gynecol Clin North Am* 2003;30(1):115-132.
35. 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;734:333-341.
36. Vercellini P, Bocciolone L, Crosignani PG. Is mild endometriosis always a disease? *Hum Reprod* 1992;7(5):627-629.
37. Donnez J, Van Langendonck A, Casanas-Roux F, Van Gossum JP, Pirard C, Jadoul P, et al. Current thinking on the pathogenesis of endometriosis. *Gynecol Obstet Invest* 2002;54 Suppl 1:52-8; discussion 59.
38. Guo SW, Wang Y. Sources of heterogeneities in estimating the prevalence of endometriosis in infertile and previously fertile women. *Fertil Steril* 2006;86(6):1584-1595.
39. Hediger ML, Hartnett HJ, Louis GMB. Association of endometriosis with body size and figure. *Fertil Steril* 2005;84(5):1366-1374.
40. Hemmings R, Rivard M, Olive DL, Poliquin-Fleury J, Gagné D, Hugo P, et al. Evaluation of risk factors associated with endometriosis. *Fertil Steril* 2004;81(6):1513-1521.
41. Meyer-Weitz A, Reddy P, Van Den Borne HW, Kok G, Pietersen J. The determinants of health care seeking behaviour of adolescents attending STD clinics in South Africa. *J Adolesc* 2000;23(6):741-752.
42. Houston DE, Noller KL, Melton LJ, Selwyn BJ, Hardy RJ. Incidence of pelvic endometriosis in Rochester, Minnesota, 1970-1979. *Am J Epidemiol* 1987;125(6):959-969.
43. Moen MH, Schei B. Epidemiology of endometriosis in a Norwegian county. *Acta Obstet Gynecol Scand* 1997;76(6):559-562.
44. Ferguson BR, Bennington JL, Haber SL. Histochemistry of mucosubstances and histology of mixed müllerian pelvic lymph node glandular inclusions. Evidence for histogenesis by müllerian metaplasia of coelomic epithelium. *Obstet Gynecol* 1969;33(5):617-625.
45. Fox H. The pathology of endometriosis. *Ir J Med Sci* 1983;152 Suppl 2:9-13.
46. Matsuura K, Ohtake H, Katabuchi H, Okamura H. Coelomic metaplasia theory of endometriosis: evidence from in vivo studies and an in vitro experimental model. *Gynecol Obstet Invest* 1999;47 Suppl 1:18-20; discussion 20.

47. Koninckx PR, Ide P, Vandenbroucke W, Brosens IA. New aspects of the pathophysiology of endometriosis and associated infertility. *J Reprod Med* 1980;24(6):257-260.
48. Barbieri RL, Callery M, Perez SE. Directionality of menstrual flow: cervical os diameter as a determinant of retrograde menstruation. *Fertil Steril* 1992;57(4):727-730.
49. Lucidi RS, Witz CA, Chrisco M, Binkley PA, Shain SA, Schenken RS, et al. 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.
50. Koninckx PR, Barlow D, Kennedy S. Implantation versus infiltration: the Sampson versus the endometriotic disease theory. *Gynecol Obstet Invest* 1999;47 Suppl 1:3-9; discussion 9.
51. Jabbour HN, Sales KJ, Smith OPM, Battersby S, Boddy SC. Prostaglandin receptors are mediators of vascular function in endometrial pathologies. *Mol Cell Endocrinol* 2006;252(1-2):191-200.
52. Zondervan KT, Treloar SA, Lin J, Weeks DE, Nyholt DR, Mangion J, et al. Significant evidence of one or more susceptibility loci for endometriosis with near-Mendelian inheritance on chromosome 7p13-15. *Hum Reprod* 2007;22(3):717-728.
53. Zondervan K, Cardon L, Desrosiers R, Hyde D, Kemnitz J, Mansfield K, et al. The genetic epidemiology of spontaneous endometriosis in the rhesus monkey. *Ann N Y Acad Sci* 2002;955:233-8; discussion 293.
54. Moore J, Copley S, Morris J, Lindsell D, Golding S, Kennedy S, et al. A systematic review of the accuracy of ultrasound in the diagnosis of endometriosis. *Ultrasound Obstet Gynecol* 2002;20(6):630-634.
55. Mol BW, Bayram N, Lijmer JG, Wiegerinck MA, Bongers MY, van der Veen F, et al. The performance of CA-125 measurement in the detection of endometriosis: a meta-analysis. *Fertil Steril* 1998;70(6):1101-1108.
56. Koninckx PR, Meuleman C, Oosterlynck D, Cornillie FJ. Diagnosis of deep endometriosis by clinical examination during menstruation and plasma CA-125 concentration. *Fertil Steril* 1996;65(2):280-287.
57. Koninckx PR, Riittinen L, Seppala M, Cornillie FJ. CA-125 and placental protein 14 concentrations in plasma and peritoneal fluid of women with deeply infiltrating pelvic endometriosis. *Fertil Steril* 1992;57(3):523-530.
58. Kinkel K, Frei KA, Balleyguier C, Chapron C. Diagnosis of endometriosis with imaging: a review. *Eur Radiol* 2006;16(2):285-298.
59. Stratton P, Winkel C, Premkumar A, Chow C, Wilson J, Hearn-Stokes R, et al. Diagnostic accuracy of laparoscopy, magnetic resonance imaging, and histopathologic examination for the detection of endometriosis. *Fertil Steril* 2003;79(5):1078-1085.
60. Adamson G, Kennedy S, Hummelshoj L. Creating solutions in endometriosis: global collaboration through the World Endometriosis Research Foundation. *J of Endometriosis* 2010;2(1):3-6.

61. Hornstein MD, Gleason RE, Orav J, Haas ST, Friedman AJ, Rein MS, et al. The reproducibility of the revised American Fertility Society classification of endometriosis. *Fertil Steril* 1993;59(5):1015-1021.
62. Nisolle M, Paindaveine B, Bourdon A, Berlière M, Casanas-Roux F, Donnez J, et al. Histologic study of peritoneal endometriosis in infertile women. *Fertil Steril* 1990;53(6):984-988.
63. Duleba AJ. Diagnosis of endometriosis. *Obstet Gynecol Clin North Am* 1997;24(2):331-346.
64. Eskenazi B, Warner M, Bonsignore L, Olive D, Samuels S, Vercellini P, et al. Validation study of nonsurgical diagnosis of endometriosis. *Fertil Steril* 2001;76(5):929-935.
65. Nnoaham K, Sivananthan S, Hummelshoj L, Jenkinson C, Webster P, Kennedy S, et al. Multi-center studies of the global impact of endometriosis and the predictive value of associated symptoms. *J of Endometriosis* 2009;1(1):36-45.
66. 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):267-741.
67. Greenland S. Modeling and variable selection in epidemiologic analysis. *Am J Public Health* 1989;79(3):340-349.
68. Bérubé S, Marcoux S, Maheux R. Characteristics related to the prevalence of minimal or mild endometriosis in infertile women. Canadian Collaborative Group on Endometriosis. *Epidemiology* 1998;9(5):504-510.
69. Sangi-Haghpeykar H, Poindexter AN. Epidemiology of endometriosis among parous women. *Obstet Gynecol* 1995;85(6):983-992.
70. Vessey MP, Villard-Mackintosh L, Painter R. Epidemiology of endometriosis in women attending family planning clinics. *BMJ* 1993;306(6871):182-184.
71. Houston DE. Evidence for the risk of pelvic endometriosis by age, race and socioeconomic status. *Epidemiol Rev* 1984;6:167-191.
72. Matalliotakis IM, Cakmak H, Fragouli YG, Goumenou AG, Mahutte NG, Arici A, et al. Epidemiological characteristics in women with and without endometriosis in the Yale series. *Arch Gynecol Obstet* 2008;277(5):389-393.
73. Parazzini F, Cipriani S, Bianchi S, Gotsch F, Zanconato G, Fedele L, et al. Risk factors for deep endometriosis: a comparison with pelvic and ovarian endometriosis. *Fertil Steril* 2008;90(1):174-179.
74. Parazzini F, La Vecchia C, Franceschi S, Negri E, Cecchetti G. Risk factors for endometrioid, mucinous and serous benign ovarian cysts. *Int J Epidemiol* 1989;18(1):108-112.
75. Waller K, Shaw R. Risk Factors for Endometriosis: Menstrual and Life-Style Characteristics. *Med Principles Pract* 1998;7:127-133.

76. Makhoulf Obermeyer C, Armenian H, Azoury R. Endometriosis in Lebanon: A case-control study. *Am J Epidemiol* 1986;124:762-767.
77. Louis GMB, Weiner JM, Whitcomb BW, Sperrazza R, Schisterman EF, Lobbelt DT, et al. Environmental PCB exposure and risk of endometriosis. *Hum Reprod* 2005;20(1):279-285.
78. Arumugam K, Lim JM. Menstrual characteristics associated with endometriosis. *Br J Obstet Gynaecol* 1997;104(8):948-950.
79. Cramer DW, Wilson E, Stillman RJ, Berger MJ, Belisle S, Schiff I, et al. The relation of endometriosis to menstrual characteristics, smoking, and exercise. *JAMA* 1986;255(14):1904-1908.
80. Darrow SL, Vena JE, Batt RE, Zielesny MA, Michalek AM, Selman S, et al. Menstrual cycle characteristics and the risk of endometriosis. *Epidemiology* 1993;4(2):135-142.
81. Heilier JF, Donnez J, Nackers F, Rousseau R, Verougstraete V, Rosenkranz K, et al. Environmental and host-associated risk factors in endometriosis and deep endometriotic nodules: a matched case-control study. *Environ Res* 2007;103(1):121-129.
82. Buck Louis GM, Hediger ML, Peña JB. Intrauterine exposures and risk of endometriosis. *Hum Reprod* 2007;22(12):3232-3236.
83. Lebel G, Dodin S, Ayotte P, Marcoux S, Ferron LA, Dewailly E, et al. Organochlorine exposure and the risk of endometriosis. *Fertil Steril* 1998;69(2):221-228.
84. Parazzini F, Ferraroni M, Fedele L, Bocciolone L, Rubessa S, Riccardi A, et al. Pelvic endometriosis: reproductive and menstrual risk factors at different stages in Lombardy, northern Italy. *J Epidemiol Community Health* 1995;49(1):61-64.
85. Klip H, Burger CW, Kenemans P, van Leeuwen FE. Cancer risk associated with subfertility and ovulation induction: a review. *Cancer Causes Control* 2000;11(4):319-344.
86. Barnhart KT, Izquierdo A, Pretorius ES, Shera DM, Shabbout M, Shaunik A, et al. Baseline dimensions of the human vagina. *Hum Reprod* 2006;21(6):1618-1622.
87. Liang CC, Liou B, Tsai CC, Chen TC, Soong YK. Scar endometriosis. *Int Surg* 1998;83(1):69-71.
88. Wicherek L, Klimek M, Skret-Magierlo J, Czekierdowski A, Banas T, Popiela TJ, et al. The obstetrical history in patients with Pfannenstiel scar endometriomas--an analysis of 81 patients. *Gynecol Obstet Invest* 2007;63(2):107-113.
89. Douglas C, Rotimi O. Extragenital endometriosis--a clinicopathological review of a Glasgow hospital experience with case illustrations. *J Obstet Gynaecol* 2004;24(7):804-808.
90. Scott R, Telinde R. Clinical external endometriosis: probable viability of menstrually shed fragments of endometrium. *Obstet Gynecol* 1954;4(5):502-510.
91. Wicherek L, Dutsch-Wicherek M, Galazka K, Banas T, Popiela T, Lazar A, et al. Comparison of RCAS1 and metallothionein expression and the presence and activity of immune cells in human ovarian and abdominal wall endometriomas. *Reprod Biol Endocrinol* 2006;4:41.

92. Lamb K, Berg N. Tampon use in women with endometriosis. *J Community Health* 1985;10(4):215-225.
93. Olive DL, Henderson DY. Endometriosis and mullerian anomalies. *Obstet Gynecol* 1987;69(3 Pt 1):412-415.
94. Meaddough EL, Olive DL, Gallup P, Perlin M, Kliman HJ. Sexual activity, orgasm and tampon use are associated with a decreased risk for endometriosis. *Gynecol Obstet Invest* 2002;53(3):163-169.
95. Archer JC, Mabry-Smith R, Shojaee S, Threet J, Eckert JJ, Litman VE, et al. Dioxin and furan levels found in tampons. *J Womens Health (Larchmt)* 2005;14(4):311-315.
96. Irwin CE, Millstein SG. Emerging patterns of tampon use in the adolescent female: the impact of toxic shock syndrome. *Am J Public Health* 1982;72(5):464-467.
97. Ranney B. Etiology, prevention, and inhibition of endometriosis. *Clin Obstet Gynecol* 1980;23(3):875-882.
98. Buttram VC. Cyclic use of combination oral contraceptives and the severity of endometriosis. *Fertil Steril* 1979;31(3):347-348.
99. 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.
100. Parazzini F, Ferraroni M, Bocciolone L, Tozzi L, Rubessa S, La Vecchia C, et al. Contraceptive methods and risk of pelvic endometriosis. *Contraception* 1994;49(1):47-55.
101. Darrow SL, Selman S, Batt RE, Zielezny MA, Vena JE. Sexual activity, contraception, and reproductive factors in predicting endometriosis. *Am J Epidemiol* 1994;140(6):500-509.
102. MacMahon B, Trichopoulos D, Cole P, Brown J. Cigarette smoking and urinary estrogens. *N Engl J Med* 1982;307(17):1062-1065.
103. Barbieri RL, McShane PM, Ryan KJ. Constituents of cigarette smoke inhibit human granulosa cell aromatase. *Fertil Steril* 1986;46(2):232-236.
104. Barbieri RL, Gochberg J, Ryan KJ. Nicotine, cotinine, and anabasine inhibit aromatase in human trophoblast in vitro. *J Clin Invest* 1986;77(6):1727-1733.
105. Mendelson JH, Lukas SE, Mello NK, Amass L, Ellingboe J, Skupny A, et al. Acute alcohol effects on plasma estradiol levels in women. *Psychopharmacology (Berl)* 1988;94(4):464-467.
106. Grodstein F, Goldman MB, Cramer DW. Infertility in women and moderate alcohol use. *Am J Public Health* 1994;84(9):1429-1432.
107. Parazzini F, Chiaffarino F, Surace M, Chatenoud L, Cipriani S, Chiantera V, et al. Selected food intake and risk of endometriosis. *Hum Reprod* 2004;19(8):1755-1759.

108. Warren MP, Perlroth NE. The effects of intense exercise on the female reproductive system. *J Endocrinol* 2001;170(1):3-11.
109. Dhillon PK, Holt VL. Recreational physical activity and endometrioma risk. *Am J Epidemiol* 2003;158(2):156-164.
110. Graham DM. Caffeine--its identity, dietary sources, intake and biological effects. *Nutr Rev* 1978;36(4):97-102.
111. Petridou E, Katsouyanni K, Spanos E, Skalkidis Y, Panagiotopoulou K, Trichopoulos D, et al. Pregnancy estrogens in relation to coffee and alcohol intake. *Ann Epidemiol* 1992;2(3):241-247.
112. Ferrini RL, Barrett-Connor E. Caffeine intake and endogenous sex steroid levels in postmenopausal women. The Rancho Bernardo Study. *Am J Epidemiol* 1996;144(7):642-644.
113. Lucero J, Harlow BL, Barbieri RL, Sluss P, Cramer DW. Early follicular phase hormone levels in relation to patterns of alcohol, tobacco, and coffee use. *Fertil Steril* 2001;76(4):723-729.
114. Barker DJ. The fetal origins of adult hypertension. *J Hypertens Suppl* 1992;10(7):S39-S44.
115. Barker DJ, Martyn CN. The maternal and fetal origins of cardiovascular disease. *J Epidemiol Community Health* 1992;46(1):8-11.
116. Barker DJ. Fetal growth and adult disease. *Br J Obstet Gynaecol* 1992;99(4):275-276.
117. Barker DJ. The effect of nutrition of the fetus and neonate on cardiovascular disease in adult life. *Proc Nutr Soc* 1992;51(2):135-144.
118. Barker DJ. The fetal origins of diseases of old age. *Eur J Clin Nutr* 1992;46 Suppl 3:S3-S9.
119. Hales CN, Barker DJ. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia* 1992;35(7):595-601.
120. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer* 2004;4(8):579-591.
121. Ferrero S, Anserini P, Remorgida V, Ragni N. Body mass index in endometriosis. *Eur J Obstet Gynecol Reprod Biol* 2005;121(1):94-98.
122. McCann SE, Freudenheim JL, Darrow SL, Batt RE, Zielezny MA. Endometriosis and body fat distribution. *Obstet Gynecol* 1993;82(4 Pt 1):545-549.
123. Missmer SA, Spiegelman D, Hankinson SE, Malspeis S, Barbieri RL, Hunter DJ, et al. Natural hair color and the incidence of endometriosis. *Fertil Steril* 2006;85(4):866-870.
124. McKusick V. Mendelian inheritance in man. Baltimore: Johns Hopkins Press; 1988.
125. Liem E, Hollensead S, Lenhardt R, Sessler D. Decreased platelet function in people with red hair. *Anesthesiology* 2003;99:A-146.

126. Woodworth SH, Singh M, Yussman MA, Sanfilippo JS, Cook CL, Lincoln SR, et al. A prospective study on the association between red hair color and endometriosis in infertile patients. *Fertil Steril* 1995;64(3):651-652.
127. 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.
128. Brinton LA, Gridley G, Persson I, Baron J, Bergqvist A. Cancer risk after a hospital discharge diagnosis of endometriosis. *Am J Obstet Gynecol* 1997;176(3):572-579.
129. Olson JE, Cerhan JR, Janney CA, Anderson KE, Vachon CM, Sellers TA, et al. Postmenopausal cancer risk after self-reported endometriosis diagnosis in the Iowa Women's Health Study. *Cancer* 2002;94(5):1612-1618.
130. Frisch RE, Wyshak G, Albert LS, Sober AJ. Dysplastic nevi, cutaneous melanoma, and gynecologic disorders. *Int J Dermatol* 1992;31(5):331-335.
131. Brinton LA, Westhoff CL, Scoccia B, Lamb EJ, Althuis MD, Mabie JE, et al. Causes of infertility as predictors of subsequent cancer risk. *Epidemiology* 2005;16(4):500-507.
132. Wyshak G, Frisch RE, Albright NL, Albright TE, Schiff I. Reproductive factors and melanoma of the skin among women. *Int J Dermatol* 1989;28(8):527-530.
133. Bukantz S, Lockey R. IgE immediate hypersensitivity. In: Weiss, E; Stein, M., editor. *Bronchial Asthma. Mechanisms and Therapeutics*. Boston, USA: Little Brown; 1993. p. 68-79.
134. Morgan MA, Gincherman Y, Mikuta JJ. Endometriosis and tamoxifen therapy. *Int J Gynaecol Obstet* 1994;45(1):55-57.
135. Bertelsen L, Mellekjaer L, Frederiksen K, Kjaer SK, Brinton LA, Sakoda LC, et al. Risk for breast cancer among women with endometriosis. *Int J Cancer* 2007;120(6):1372-1375.
136. Ness RB, Modugno F. Endometriosis as a model for inflammation-hormone interactions in ovarian and breast cancers. *Eur J Cancer* 2006;42(6):691-703.
137. Weed JC, Arquembourg PC. Endometriosis: can it produce an autoimmune response resulting in infertility? *Clin Obstet Gynecol* 1980;23(3):885-893.
138. 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.
139. Matarese G, De Placido G, Nikas Y, Alviggi C. Pathogenesis of endometriosis: natural immunity dysfunction or autoimmune disease? *Trends Mol Med* 2003;9(5):223-228.
140. Matorras R, Ocerin I, Unamuno M, Nieto A, Peiró E, Burgos J, et al. Prevalence of endometriosis in women with systemic lupus erythematosus and Sjogren's syndrome. *Lupus* 2007;16(9):736-740.

141. Tietjen GE, Bushnell CD, Herial NA, Utley C, White L, Hafeez F, et al. Endometriosis is associated with prevalence of comorbid conditions in migraine. *Headache* 2007;47(7):1069-1078.
142. Ferrero S, Pretta S, Bertoldi S, Anserini P, Remorgida V, Del Sette M, et al. Increased frequency of migraine among women with endometriosis. *Hum Reprod* 2004;19(12):2927-2932.
143. Tietjen GE, Conway A, Utley C, Gunning WT, Herial NA. Migraine is associated with menorrhagia and endometriosis. *Headache* 2006;46(3):422-428.
144. Carlson KJ, Miller BA, Fowler FJ. The Maine Women's Health Study: I. Outcomes of hysterectomy. *Obstet Gynecol* 1994;83(4):556-565.
145. Carlson KJ, Miller BA, Fowler FJ. The Maine Women's Health Study: II. Outcomes of nonsurgical management of leiomyomas, abnormal bleeding, and chronic pelvic pain. *Obstet Gynecol* 1994;83(4):566-572.
146. Boling RO, Abbasi R, Ackerman G, Schipul AH, Chaney SA. Disability from endometriosis in the United States Army. *J Reprod Med* 1988;33(1):49-52.
147. Barnack JL, Chrisler JC. The experience of chronic illness in women: a comparison between women with endometriosis and women with chronic migraine headaches. *Women Health* 2007;46(1):115-133.
148. Jones GL, Kennedy SH, Jenkinson C. Health-related quality of life measurement in women with common benign gynecologic conditions: a systematic review. *Am J Obstet Gynecol* 2002;187(2):501-511.
149. Cox H, Henderson L, Wood R, Cagliarini G. Learning to take charge: women's experiences of living with endometriosis. *Complement Ther Nurs Midwifery* 2003;9(2):62-68.
150. Lemaire GS. More than just menstrual cramps: symptoms and uncertainty among women with endometriosis. *J Obstet Gynecol Neonatal Nurs* 2004;33(1):71-79.
151. Petrelluzzi KFS, Garcia MC, Petta CA, Grassi-Kassisse DM, Spadari-Bratfisch RC. Salivary cortisol concentrations, stress and quality of life in women with endometriosis and chronic pelvic pain. *Stress* 2008;11(5):390-397.
152. Siedentopf F, Tariverdian N, Rucke M, Kentenich H, Arck PC. Immune status, psychosocial distress and reduced quality of life in infertile patients with endometriosis. *Am J Reprod Immunol* 2008;60(5):449-461.
153. Jones G, Jenkinson C, Kennedy S. The impact of endometriosis upon quality of life: a qualitative analysis. *J Psychosom Obstet Gynaecol* 2004;25(2):123-133.
154. 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.
155. Dubernard G, Piketty M, Rouzier R, Houry S, Bazot M, Darai E, et al. Quality of life after laparoscopic colorectal resection for endometriosis. *Hum Reprod* 2006;21(5):1243-1247.

156. Denny E, Mann CH. Endometriosis-associated dyspareunia: the impact on women's lives. *J Fam Plann Reprod Health Care* 2007;33(3):189-193.
157. Marques A, Bahamondes L, Aldrighi JM, Petta CA. Quality of life in Brazilian women with endometriosis assessed through a medical outcome questionnaire. *J Reprod Med* 2004;49(2):115-120.
158. Daraï E, Coutant C, Bazot M, Dubernard G, Rouzier R, Ballester M, et al. [Relevance of quality of life questionnaires in women with endometriosis]. *Gynecol Obstet Fertil* 2009;37(3):240-245.
159. Broadhead WE, Blazer DG, George LK, Tse CK. Depression, disability days, and days lost from work in a prospective epidemiologic survey. *JAMA* 1990;264(19):2524-2528.
160. Zhang J, Yu KF. "What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes." *JAMA* 1998; 280:1690–1691.
161. Walters SJ. Sample size and power estimation for studies with health related quality of life outcomes: a comparison of four methods using the SF-36. *Health Qual Life Outcomes* 2004;2:26.
162. 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.
163. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993;4(5):353-365.
164. Gwee KA. Irritable bowel syndrome and the Rome III criteria: for better or for worse? *Eur J Gastroenterol Hepatol* 2007;19(6):437-439.
165. Zondervan KT, Yudkin PL, Vessey MP, Jenkinson CP, Dawes MG, Barlow DH, et al. The community prevalence of chronic pelvic pain in women and associated illness behaviour. *Br J Gen Pract* 2001;51(468):541-547.
166. Zondervan KT, Yudkin PL, Vessey MP, Jenkinson CP, Dawes MG, Barlow DH, et al. Chronic pelvic pain in the community--symptoms, investigations, and diagnoses. *Am J Obstet Gynecol* 2001;184(6):1149-1155.
167. Garratt A, Schmidt L, Mackintosh A, Fitzpatrick R. Quality of life measurement: bibliographic study of patient assessed health outcome measures. *BMJ* 2002;324(7351):1417.
168. 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..
169. Reilly MC, Lavin PT, Kahler KH, Pariser DM. Validation of the Dermatology Life Quality Index and the Work Productivity and Activity Impairment-Chronic Hand Dermatitis questionnaire in chronic hand dermatitis. *J Am Acad Dermatol* 2003;48(1):128-130.
170. Wahlqvist P. Symptoms of gastroesophageal reflux disease, perceived productivity, and health-related quality of life. *Am J Gastroenterol* 2001;96(8 Suppl):S57-S61.
171. Drossman DA. The functional gastrointestinal disorders and the Rome III process. *Gastroenterology* 2006;130(5):1377-1390.

172. Drossman DA. Rome III: the new criteria. *Chin J Dig Dis* 2006;7(4):181-185.
173. Drossman DA, Dumitrascu DL. Rome III: New standard for functional gastrointestinal disorders. *J Gastrointest Liver Dis* 2006;15(3):237-241.
174. Edworthy SM. World wide web: opportunities, challenges, and threats. *Lupus* 1999;8(8):596-605.
175. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: recommendations for good practice. *J Eval Clin Pract* 2004;10(2):307-312.
176. Centers for Disease Control and Prevention (CDC). Cigarette smoking-attributable morbidity--United States, 2000. *MMWR Morb Mortal Wkly Rep* 2003;52(35):842-844.
177. World Health Organisation. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. *World Health Organ Tech Rep Ser* 1995;854:1-452.
178. Jolliffe I. *Principal Component Analysis*. New York: Springer-Verlag; 1986.
179. Ajossa S, Mais V, Guerriero S, Paoletti AM, Caffiero A, Murgia C, et al. The prevalence of endometriosis in premenopausal women undergoing gynecological surgery. *Clin Exp Obstet Gynecol* 1994;21(3):195-197.
180. Waller KG, Lindsay P, Curtis P, Shaw RW. The prevalence of endometriosis in women with infertile partners. *Eur J Obstet Gynecol Reprod Biol* 1993;48(2):135-139.
181. Johnson N, Farquhar C. Endometriosis. *Clin Evid* 2007;2007
182. Vercellini P, Trespidi L, De Giorgi O, Cortesi I, Parazzini F, Crosignani PG, et al. Endometriosis and pelvic pain: relation to disease stage and localization. *Fertil Steril* 1996;65(2):299-304.
183. Modugno F, Ness RB, Allen GO, Schildkraut JM, Davis FG, Goodman MT, et al. Oral contraceptive use, reproductive history, and risk of epithelial ovarian cancer in women with and without endometriosis. *Am J Obstet Gynecol* 2004;191(3):733-740.
184. Holt VL, Weiss NS. Recommendations for the design of epidemiologic studies of endometriosis. *Epidemiology* 2000;11(6):654-659.
185. Vercellini P, Fedele L, Aimi G, Pietropaolo G, Consonni D, Crosignani PG, et al. 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.
186. Porpora MG, Koninckx PR, Piazze J, Natili M, Colagrande S, Cosmi EV, et al. Correlation between endometriosis and pelvic pain. *J Am Assoc Gynecol Laparosc* 1999;6(4):429-434.
187. Koike H, Egawa H, Ohtsuka T, Yamaguchi M, Ikenoue T, Mori N, et al. Correlation between dysmenorrheic severity and prostaglandin production in women with endometriosis. *Prostaglandins Leukot Essent Fatty Acids* 1992;46(2):133-137.

188. Moen MH. Is a long period without childbirth a risk factor for developing endometriosis? *Hum Reprod* 1991;6(10):1404-1407.
189. Arumugam K, Templeton AA. Endometriosis and race. *Aust N Z J Obstet Gynaecol* 1992;32(2):164-165.
190. Miyazawa K. Incidence of endometriosis among Japanese women. *Obstet Gynecol* 1976;48(4):407-409.
191. Obermeyer CM, Armenian HK, Azoury R. ENDOMETRIOSIS IN LEBANON :research-article. *Am J Epidemiol* 1986;124(5):762-767.
192. Pauwels A, Schepens PJ, D'Hooghe T, Delbeke L, Dhont M, Brouwer A, et al. The risk of endometriosis and exposure to dioxins and polychlorinated biphenyls: a case-control study of infertile women. *Hum Reprod* 2001;16(10):2050-2055.
193. Heilier JF, Nackers F, Verougstraete V, Tonglet R, Lison D, Donnez J, et al. Increased dioxin-like compounds in the serum of women with peritoneal endometriosis and deep endometriotic (adenomyotic) nodules. *Fertil Steril* 2005;84(2):305-312.
194. Tsukino H, Hanaoka T, Sasaki H, Motoyama H, Hiroshima M, Tanaka T, et al. Associations between serum levels of selected organochlorine compounds and endometriosis in infertile Japanese women. *Environ Res* 2005;99(1):118-125.
195. Taskinen HK, Kyrrönen P, Sallmén M, Virtanen SV, Liukkonen TA, Huida O, et al. Reduced fertility among female wood workers exposed to formaldehyde. *Am J Ind Med* 1999;36(1):206-212.
196. Marino JL, Holt VL, Chen C, Davis S. Shift work, hCLOCK T3111C polymorphism, and endometriosis risk. *Epidemiology* 2008;19(3):477-484.
197. Fuortes L, Clark MK, Kirchner HL, Smith EM. Association between female infertility and agricultural work history. *Am J Ind Med* 1997;31(4):445-451.
198. Smith EM, Hammonds-Ehlers M, Clark MK, Kirchner HL, Fuortes L. Occupational exposures and risk of female infertility. *J Occup Environ Med* 1997;39(2):138-147.
199. Vercellini P, Somigliana E, Viganò P, De Matteis S, Barbara G, Fedele L, et al. Post-operative endometriosis recurrence: a plea for prevention based on pathogenetic, epidemiological and clinical evidence. *Reprod Biomed Online* 2010;21(2):259-265.
200. Vercellini P, Parazzini F, Oldani S, Panazza S, Bramante T, Crosignani PG, et al. Adenomyosis at hysterectomy: a study on frequency distribution and patient characteristics. *Hum Reprod* 1995;10(5):1160-1162.
201. Risk factors for pelvic endometriosis in women with pelvic pain or infertility. Gruppo Italiano per lo Studio dell' endometriosi. *Eur J Obstet Gynecol Reprod Biol* 1999;83(2):195-199.
202. 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.

203. Parazzini F, Di Cintio E, Chatenoud L, Moroni S, Mezzanotte C, Crosignani PG, et al. Oral contraceptive use and risk of endometriosis. Italian Endometriosis Study Group. *Br J Obstet Gynaecol* 1999;106(7):695-699.
204. Candiani GB, Danesino V, Gastaldi A, Parazzini F, Ferraroni M. Reproductive and menstrual factors and risk of peritoneal and ovarian endometriosis. *Fertil Steril* 1991;56(2):230-234.
205. Barbieri RL. Stenosis of the external cervical os: an association with endometriosis in women with chronic pelvic pain. *Fertil Steril* 1998;70(3):571-573.
206. Mehio-Sibai A, Feinleib M, Sibai TA, Armenian HK. A positive or a negative confounding variable? A simple teaching aid for clinicians and students. *Ann Epidemiol* 2005;15(6):421-423.
207. Gesink Law DC, Maclehose RF, Longnecker MP. Obesity and time to pregnancy. *Hum Reprod* 2007;22(2):414-420.
208. Kvaskoff M, Mesrine S, Clavel-Chapelon F, Boutron-Ruault MC. Endometriosis risk in relation to naevi, freckles and skin sensitivity to sun exposure: the French E3N cohort. *Int J Epidemiol* 2009;38(4):1143-1153.
209. Slominski A, Tobin DJ, Shibahara S, Wortsman J. Melanin pigmentation in mammalian skin and its hormonal regulation. *Physiol Rev* 2004;84(4):1155-1228.
210. Bai SW, Cho HJ, Kim JY, Jeong KA, Kim SK, Cho DJ, et al. Endometriosis in an adolescent population: the severance hospital in Korean experience. *Yonsei Med J* 2002;43(1):48-52.
211. Engemise S, Gordon C, Konje JC. Endometriosis. *BMJ* 2010;340:c2168.
212. Zhang DK, Qin CR, Yang DZ. [Diagnosis and treatment of endometriosis in adolescents]. *Zhonghua Fu Chan Ke Za Zhi* 2004;39(10):687-689.
213. Frenna V, Santos L, Ohana E, Bailey C, Wattiez A. Laparoscopic management of ureteral endometriosis: our experience. *J Minim Invasive Gynecol* 2007;14(2):169-171.
214. Howard FM. The role of laparoscopy in chronic pelvic pain: promise and pitfalls. *Obstet Gynecol Surv* 1993;48(6):357-387.
215. Hulka JF, Peterson HB, Phillips JM, Surrey MW. Operative laparoscopy. American Association of Gynecologic Laparoscopists 1991 membership survey. *J Reprod Med* 1993;38(8):569-571.
216. Leng JH, Lang JH, Dai Y, Li HJ, Li XY. [Relationship between pain symptoms and clinico-pathological features of pelvic endometriosis]. *Zhonghua Fu Chan Ke Za Zhi* 2007;42(3):165-168.
217. Endometriosis Symptoms [Internet]. [updated 2010/10/06; cited 2010/10/06]. Available from: <http://www.endo-resolved.com/symptoms.html>
218. Hoshiai H, Ishikawa M, Sawatari Y, Noda K, Fukaya T. Laparoscopic evaluation of the onset and progression of endometriosis. *Am J Obstet Gynecol* 1993;169(3):714-719.

219. Gynaecology Clinic - Endometriosis [Internet]. [updated 2010/10/06; cited 2010/10/06]. Available from: <http://www.gynaecologyclinic.com/endometriosis/endometriosis.htm>
220. Infertility: Etiology And Evaluation [Internet]. [updated 2010/10/07; cited 2010/10/07]. Available from: <http://www.dcmsonline.org/jax-medicine/2000journals/may2000/infertility.htm>
221. Araoye MO. Epidemiology of infertility: social problems of the infertile couples. *West Afr J Med* 2003;22(2):190-196.
222. Manderson L, Warren N, Markovic M. Circuit breaking: pathways of treatment seeking for women with endometriosis in Australia. *Qual Health Res* 2008;18(4):522-534.
223. Greene R, Stratton P, Cleary SD, Ballweg ML, Sinaii N. Diagnostic experience among 4,334 women reporting surgically diagnosed endometriosis. *Fertil Steril* 2009;91(1):32-39.
224. Carlson K, Eisenstat S, Ziporyn T, et al. *The new Harvard guide to women's health*. Harvard University Press; 2004. 704 p.
225. Khong SY, Lam A, Luscombe G. Is the 30-item Endometriosis Health Profile (EHP-30) suitable as a self-report health status instrument for clinical trials? *Fertil Steril* 2010;94(5):1928-1932.
226. 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.
227. Seller R. *Differential diagnosis of common complaints*. Philadelphia: Saunders Elsevier; 2007.
228. Husby GK, Haugen RS, Moen MH. Diagnostic delay in women with pain and endometriosis. *Acta Obstet Gynecol Scand* 2003;82(7):649-653.
229. Shah DK, Moravek MB, Vahratian A, Dalton VK, Lebovic DI. Public perceptions of endometriosis: perspectives from both genders. *Acta Obstet Gynecol Scand* 2010;89(5):646-650.
230. Goffman E. *Stigma: Notes on the Management of Spoiled Identity*. New York: Touchstone Books; 1986. 168 p.
231. Denny E, Mann CH. Endometriosis and the primary care consultation. *Eur J Obstet Gynecol Reprod Biol* 2008;139(1):111-115.
232. Petta CA, Matos AM, Bahamondes L, Faúndes D. Current practice in the management of symptoms of endometriosis: a survey of Brazilian gynecologists. *Rev Assoc Med Bras* 2007;53(6):525-529.
233. Marrie RA, Horwitz R, Cutter G, Tyry T, Campagnolo D, Vollmer T, et al. Comorbidity delays diagnosis and increases disability at diagnosis in MS. *Neurology* 2009;72(2):117-124.
234. Arndt V, Stürmer T, Stegmaier C, Ziegler H, Dhom G, Brenner H, et al. Patient delay and stage of diagnosis among breast cancer patients in Germany -- a population based study. *Br J Cancer* 2002;86(7):1034-1040.

235. Samuels TA, Cohen D, Brancati FL, Coresh J, Kao WHL. Delayed diagnosis of incident type 2 diabetes mellitus in the ARIC study. *Am J Manag Care* 2006;12(12):717-724.
236. Fontaine KR, Faith MS, Allison DB, Cheskin LJ. Body weight and health care among women in the general population. *Arch Fam Med* 1998;7(4):381-384.
237. Adams CH, Smith NJ, Wilbur DC, Grady KE. The relationship of obesity to the frequency of pelvic examinations: do physician and patient attitudes make a difference? *Women Health* 1993;20(2):45-57.
238. Lubitz RM, Litzelman DK, Dittus RS, Tierney WM. Is obesity a barrier to physician screening for cervical cancer? *Am J Med* 1995;98(5):491-496.
239. Matsuzaki S, Canis M, Pouly JL, Rabischong B, Botchorishvili R, Mage G, et al. Relationship between delay of surgical diagnosis and severity of disease in patients with symptomatic deep infiltrating endometriosis. *Fertil Steril* 2006;86(5):1314-6; discussion 1317.
240. Martin S, Ulrich C, Munsell M, Taylor S, Lange G, Bleyer A, et al. Delays in cancer diagnosis in underinsured young adults and older adolescents. *Oncologist* 2007;12(7):816-824.
241. Griffin M, Panak WF. The economic cost of infertility-related services: an examination of the Massachusetts infertility insurance mandate. *Fertil Steril* 1998;70(1):22-29.
242. Patrick DL, Bergner M. Measurement of health status in the 1990s. *Annu Rev Public Health* 1990;11:165-183.
243. Sajid MS, Tonsi A, Baig MK. Health-related quality of life measurement. *Int J Health Care Qual Assur* 2008;21(4):365-373.
244. ResearchCore.org - What is "health related quality of life" (HRQOL)? [Internet] [updated 2010/11/20; cited 2010/11/20]. Available from: <http://researchcore.org/faq/answers.php?recID=3>
245. Hickey A, Barker M, McGee H, O'Boyle C. Measuring health-related quality of life in older patient populations: a review of current approaches. *Pharmacoeconomics* 2005;23(10):971-993.
246. Bodner CH, Garratt AM, Ratcliffe J, Macdonald LM, Penney GC. Measuring health-related quality of life outcomes in women with endometriosis--results of the Gynaecology Audit Project in Scotland. *Health Bull (Melb)* 1997;55(2):109-117.
247. 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.
248. Surtees PG, Wainwright NWJ, Khaw KT, Day NE. Functional health status, chronic medical conditions and disorders of mood. *Br J Psychiatry* 2003;183:299-303.
249. Blalock AC, McDaniel JS, Farber EW. Effect of employment on quality of life and psychological functioning in patients with HIV/AIDS. *Psychosomatics* 2002;43(5):400-404.

250. Horner DJ, Wendel CS, Skeps R, Rawl SM, Grant M, Schmidt CM, et al. Positive correlation of employment and psychological well-being for veterans with major abdominal surgery. *Am J Surg* 2010;200(5):585-590.
251. Reisine S, Fifield J, Walsh S, Dauser D. Employment and quality of life outcomes among women with fibromyalgia compared to healthy controls. *Women Health* 2004;39(4):1-19.
252. Bernklev T, Jahnsen J, Henriksen M, Lygren I, Aadland E, Sauar J, et al. Relationship between sick leave, unemployment, disability, and health-related quality of life in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2006;12(5):402-412.
253. O'Neill J, Hibbard MR, Brown M, Jaffe M, Sliwinski M, Vandergoot D, et al. The effect of employment on quality of life and community integration after traumatic brain injury. *J Head Trauma Rehabil* 1998;13(4):68-79.
254. Centers for Disease Control and Prevention (CDC). Social support and health-related quality of life among older adults--Missouri, 2000. *MMWR Morb Mortal Wkly Rep* 2005;54(17):433-437.
255. Sultan S, Fisher DA, Voils CI, Kinney AY, Sandler RS, Provenzale D, et al. Impact of functional support on health-related quality of life in patients with colorectal cancer. *Cancer* 2004;101(12):2737-2743.
256. Colwell HH, Mathias SD, Pasta DJ, Henning JM, Steege JF. A health-related quality-of-life instrument for symptomatic patients with endometriosis: a validation study. *Am J Obstet Gynecol* 1998;179(1):47-55.
257. Laursen BS, Bajaj P, Olesen AS, Delmar C, Arendt-Nielsen L. Health related quality of life and quantitative pain measurement in females with chronic non-malignant pain. *Eur J Pain* 2005;9(3):267-275.
258. Sepulcri RDP, do Amaral VF. Depressive symptoms, anxiety, and quality of life in women with pelvic endometriosis. *Eur J Obstet Gynecol Reprod Biol* 2009;142(1):53-56.
259. Bajaj P, Bajaj P, Madsen H, Arendt-Nielsen L. Endometriosis is associated with central sensitization: a psychophysical controlled study. *J Pain* 2003;4(7):372-380.
260. Neziri AY, Haesler S, Petersen-Felix S, Müller M, Arendt-Nielsen L, Manresa JB, et al. Generalized expansion of nociceptive reflex receptive fields in chronic pain patients. *Pain* 2010;
261. Berkley KJ, Rapkin AJ, Papka RE. The pains of endometriosis. *Science* 2005;308(5728):1587-1589.
262. Oehmke F, Weyand J, Hackethal A, Konrad L, Omwandho C, Tinneberg HR, et al. Impact of endometriosis on quality of life: A pilot study. *Gynecol Endocrinol* 2009;:1-4.
263. Denny E, Mann CH. A clinical overview of endometriosis: a misunderstood disease. *Br J Nurs* 2007;16(18):1112-1116.
264. Ballweg ML. Impact of endometriosis on women's health: comparative historical data show that the earlier the onset, the more severe the disease. *Best Pract Res Clin Obstet Gynaecol* 2004;18(2):201-218.

265. Ferrero S, Remorgida V, Venturini PL. Current pharmacotherapy for endometriosis. *Expert Opin Pharmacother* 2010;11(7):1123-1134.
266. Fourquet J, Gao X, Zavala D, Orengo JC, Abac S, Ruiz A, et al. Patients' report on how endometriosis affects health, work, and daily life. *Fertil Steril* 2010;93(7):2424-2428.
267. van der Kloot WA, Chotkan SA, Kaptein AA, Hamdy NAT. Diagnostic delay in sternocostoclavicular hyperostosis: impact on various aspects of quality of life. *Arthritis care & research* 2010;62(2):251-257.
268. Simoens S, Hummelshoj L, D'Hooghe T. Endometriosis: cost estimates and methodological perspective. *Hum Reprod Update* 2007;13(4):395-404.
269. Gao X, Outley J, Botteman M, Spalding J, Simon JA, Pashos CL, et al. Economic burden of endometriosis. *Fertil Steril* 2006;86(6):1561-1572.
270. Hemp P. Presenteeism: at work--but out of it. *Harv Bus Rev* 2004;82(10):49-58, 155.
271. Fowler JF, Ghosh A, Sung J, Emani S, Chang J, Den E, et al. Impact of chronic hand dermatitis on quality of life, work productivity, activity impairment, and medical costs. *J Am Acad Dermatol* 2006;54(3):448-457.
272. Federal Statistical Office - Basic indicator: Hourly compensation costs in manufacturing [Internet]. [updated 2010/11/19; cited 2010/11/19]. Available from: http://www.destatis.de/jetspeed/portal/cms/Sites/destatis/Internet/EN/Content/Statistics/Internationales/InternationalStatistics/Topic/Tables/BasicData__LaborCosts,templateId=renderPrint.psm
273. Davies L, Gangar K, Drummond M, Saunders D, Beard R. The Economic burden of intractable gynaecological pain. *J Obstet Gynecol* 1992;12(S54-S6)
274. Coco AS. Primary dysmenorrhea. *Am Fam Physician* 1999;60(2):489-496.
275. Kunz K, Kuppermann M, Moynihan C, Williamson A, Mazonson P. The cost of treatment of endometriosis in the California Medicaid population. *Am J Managed Care* 1995;1:25-29.
276. Oehmke F, Weyand J, Hackethal A, Konrad L, Omwandho C, Tinneberg HR, et al. Impact of endometriosis on quality of life: a pilot study. *Gynecol Endocrinol* 2009;25(11):722-725.
277. Missmer SA, Chavarro JE, Malspeis S, Bertone-Johnson ER, Hornstein MD, Spiegelman D, et al. A prospective study of dietary fat consumption and endometriosis risk. *Hum Reprod* 2010;25(6):1528-1535.
278. Vercellini P, Meana M, Hummelshoj L, Somigliana E, Viganò P, Fedele L, et al. Priorities for endometriosis research: a proposed focus on deep dyspareunia. *Reprod Sci* 2011;18(2):114-118.
279. Mbada CE, Adedoyin RA, Ayanniyi O. Socioeconomic status and obesity among semi-urban Nigerians. *Obesity facts* 2009;2(6):356-361.

280. Endometriosis and employment – Is this a contradiction in terms? [Internet] [updated 2010/12/27; cited 2010/12/27]. Available from:
<http://www.bowenworks.org/downloads/endometriosisandwork.pdf>

Appendix 1 - Characteristics of women at recruitment in GSWH

Characteristic	Endometriosis (n=745)	No endometriosis (n=673)			
		Symptomatic (n=587)	P value [‡]	Sterilisation (n=86)	P value [€]
Demographic/ personal					
Age (yrs) [Mean (SD)]	32.5 (6.2)	33.1 (6.4)	0.10	37.2 (5.0)	<0.001
Post-secondary education [% (n)]	69.9 (521)	61.7 (362)	0.004	45.3 (39)	<0.001
In employment [% (n)]	78.5 (585)	71.6 (432)		70.9 (61)	
Paid employment	64.3 (479)	57.6 (338)		61.6 (53)	
Self-employment	14.2 (106)	14.0 (82)		9.3 (8)	
Unemployed	20.3 (151)	22.7 (133)	0.054	29.1 (25)	0.067
Ethnicity [% (n)]					
White	50.1 (373)	45.3 (266)		48.8 (42)	
Asian/Oriental	32.0 (238)	35.4 (208)		8.1 (7)	
Black	7.0 (52)	10.6 (62)		8.1 (7)	
Others	9.7 (72)	6.1 (36)	0.005	33.7 (29)	<0.001
Married or living with partner [% (n)]	73.3 (546)	80.2 (471)	0.002	84.9 (73)	0.017
Body Mass Index (kg/m ²) [Mean (SD)]	22.5 (4.1)	23.4 (4.8)	<0.001	25.2 (4.4)	<0.001
Current smoking [% (n)]	12.9 (96)	10.4 (61)	0.25	26.7 (23)	0.001
Past smoking [% (n)]	13.8 (103)	14.1 (83)	0.66	12.8 (11)	0.79
Never smoked [% (n)]	72.2 (538)	69.7 (409)	0.74	58.1 (50)	0.012
Regular vigorous exercise in last 3 months [% (n)]	27.0 (201)	25.2 (148)	0.86	20.9 (18)	0.54
Clinical					
Age at menarche (Years) [Mean (SD)]	13.0 (1.63)	13.3 (1.7)	0.004	12.8 (1.7)	0.20
Hormonal contraception in past 3 months [% (n)]	23.4 (174)	16.9 (99)	0.004	45.3 (39)	<0.001
Reasons for hormonal contraception [% (n)]					
Contraception/other	58.6 (102)	63.6 (63)		97.4 (38)	
Pelvic pain, irregular or heavy periods	40.2 (70)	35.4 (35)	0.42	2.6 (1)	<0.001
Menstrual cycle length [% (n)]					
≤24 days	16.2 (121)	13.8 (81)		20.9 (18)	
25-32 days	63.2 (471)	60.3 (354)		58.1 (50)	
≥33 days	5.4 (40)	8.5 (50)	0.041	2.3 (2)	0.23
Menstrual duration (days) [Mean (SD)]	4.9 (2.8)	4.9 (2.3)	0.99	4.7 (2.4)	0.63
Parity [Mean (SD)]	0.2 (0.5)	0.5 (1.0)	<0.001	1.8 (1.4)	<0.001
Gravidity [Mean (SD)]	0.5 (0.9)	1.0 (1.4)	<0.001	2.3 (1.6)	<0.001
Subfertility [% (n)]	39.6 (295)	51.8 (304)	<0.001	18.6 (16)	<0.001
Type of symptoms reported [% (n)]					
Pelvic pain, no subfertility	42.7 (318)	29.3 (172)	<0.001	8.1 (7)	<0.001
Pelvic pain and subfertility	17.7 (132)	15.2 (89)	0.21	2.3 (2)	<0.001
Subfertility, no pelvic pain	13.4 (100)	28.6 (168)	<0.001	4.7 (4)	0.02
No pelvic pain, no subfertility	26.2 (195)	27.1 (159)	0.72	84.7 (73)	<0.001
Number of symptoms [Mean (SD)]					
‘Pelvic’ symptoms	1.5 (1.5)	1.0 (1.3)	<0.001	0.3 (0.9)	<0.001
‘Bowel’ symptoms	0.5 (0.9)	0.3 (0.6)	<0.001	0.1 (0.4)	<0.001
‘Urinary’ symptoms	0.2 (0.5)	0.1 (0.4)	0.015	0.0 (0.1)	0.005
‘Pelvic mass’ symptoms	1.3 (0.8)	0.9 (0.8)	<0.001	1.0 (0.4)	0.004
Pelvic pain severity NRS 0-10 [Mean (SD)]	5.6 (2.2)	4.7 (2.2)	<0.001	5.0 (2.5)	0.048
Other pathologies at laparoscopy [% (n)]					
Non-endometriotic adhesions	11.0 (82)	33.7 (198)	<0.001	10.5 (9)	0.002
Non-endometriotic cysts	10.6 (79)	24.2 (142)	0.038	4.7 (4)	0.81
Fibroids	16.0 (119)	21.1 (124)	0.017	3.5 (3)	0.55
Other ^a	2.8 (21)	8.2 (48)	<0.001	1.2 (1)	0.37
Comorbidity [% (n)] ^b					
Cancer	1.5 (11)	1.9 (11)	0.58	2.3 (2)	0.55
Autoimmune/atopic conditions	19.7 (147)	20.1 (118)	0.64	14.0 (12)	0.20
Other	76.9 (573)	60.3 (354)	<0.001	47.8 (41)	<0.001
Any	82.4 (614)	66.3 (389)	<0.001	53.5 (46)	<0.001

[‡] - for endometriosis vs. symptomatic controls; [€] - for endometriosis vs. sterilisation controls; ^a - 'other' pathologies were mainly teratoma and bilateral tubal blockage;

^b - Cancer included breast and ovarian cancer, melanoma and Hodgkins/non-Hodgkin's lymphoma; Autoimmune/atopic conditions included asthma, eczema, Hashimoto's disease, multiple sclerosis, rheumatoid arthritis, Sjogrens syndrome, thyroid disease and systematic lupus erythematosus; 'Other' included chronic fatigue syndrome, deafness, fibromyalgia, depression, diabetes, fibroids, glandular fever, imperforate hymen, migraines, ovarian cysts, polycystic ovarian syndrome, pyloric stenosis, scoliosis and mitral valve prolapse.

Appendix 2 - Unconditional multiple logistic regression models for endometriosis vs. symptomatic controls and endometriosis vs. sterilisation controls

Variables	Logistic regression model Endometriosis vs. symptomatic controls			
	Adjusted OR	p value	95% LCL	95% UCL
<i>Demographic/personal</i>				
Age	1.02	0.58	0.96	1.08
Site	1.08	0.22	0.96	1.21
Post-secondary education	1.62	0.16	0.82	3.21
Ethnicity	1.16	0.44	0.79	1.71
BMI	0.97	0.45	0.90	1.05
Marital status	1.54	0.28	0.70	3.37
<i>Clinical</i>				
Age at menarche	1.04	0.72	0.85	1.27
Hormonal contraception in last 3 months	1.05	0.92	0.40	2.74
Subfertility	1.14	0.36	0.87	1.49
Menstrual duration	0.90	0.28	0.75	1.09
Menstrual cycle length	0.64	0.19	0.33	1.25
Parity	1.45	0.40	0.61	3.43
Gravidity	0.36	<i>0.01</i>	0.16	0.81
Pelvic pain without subfertility	0.73	0.45	0.33	1.64
Subfertility without pelvic pain	0.98	0.97	0.40	2.42
Number of symptoms				
Pelvic symptoms	1.20	0.26	0.87	1.65
Bowel symptoms	1.24	0.63	0.52	2.96
Urinary symptoms	0.49	0.17	0.18	1.34
Pelvic mass symptoms	1.13	0.58	0.72	1.78
Other pathologies at laparoscopy				
Fibroids	0.82	0.59	0.40	1.68
Non-endometriotic adhesions	0.30	<i>0.001</i>	0.15	0.60
Non-endometriotic ovarian cysts	0.77	0.46	0.38	1.56
Pelvic pain severity	1.19	<i>0.04</i>	1.01	1.41
Co-morbidity	1.65	0.19	0.78	3.50

P values in italics for variables identified as important covariates of endometriosis risk (with $p < 0.05$)