ORIGINAL ARTICLE *Gynaecology*

Quality of life outcomes in women with endometriosis are highly influenced by recruitment strategies

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STUDY QUESTION: To what extent are outcome measures in endometriosis-related quality of life studies influenced by the setting in which patient recruitment is performed?

SUMMARY ANSWER: Quality of life outcomes in women with endometriosis are highly influenced by recruitment strategies.

WHAT IS KNOWN ALREADY: Most studies on quality of life in women with endometriosis are conducted in tertiary care centres or patient associations. It is conceivable that the setting in which patient recruitment is performed influences the quality of life results. This has not been investigated before.

STUDY DESIGN, SIZE, DURATION: Retrospective questionnaire based cohort study (part of the World Endometriosis Research Foundation (WERF) EndoCost study). The investigated women were recruited in three settings: a tertiary care centre for endometriosis (n = 135); five secondary care centres (n = 63); an endometriosis patient association (n = 291).

PARTICIPANTS/MATERIALS, SETTING, METHODS: The secondary and tertiary care population included women with a laparoscopic and/or histological diagnosis of endometriosis. The patient association population consisted of women with a self-reported diagnosis of surgically confirmed endometriosis.

MAIN RESULTS AND THE ROLE OF CHANCE: The populations did not differ in terms of age, co-morbidities and education level. Delay of diagnosis was the longest in the patient association (median 7 years) (tertiary care 2 years; secondary care 1.5 years) (P < 0.001). The tertiary care population reported more laparotomies (64%) than the other populations (secondary care 43%; patient association 47%) (P = 0.002). Affected job was least prevalent in the secondary care setting (35%) (patient association 64%; tertiary care 56%) (P < 0.001). Affected relationships were most prevalent in the patient association setting (52%) (tertiary care 38%; secondary care 22%) (P < 0.001). Chronic pain was least prevalent in patients in secondary care (44%) (tertiary care 65%; patient association 61%) (P = 0.009). Substantial differences in quality of life were detected between secondary care (median physical component 50.4, mental component 49.6); tertiary care (physical component 46.2, mental component 46.2) and the patient association (physical component 45.0, mental component 44.6) (P < 0.001, P = 0.018).

LIMITATIONS, REASONS FOR CAUTION: The response rate was relatively low (35%). Analysis of the hospital populations revealed that non-responders and responders did not differ with respect to age or revised American Fertility Society classification, indicating that the non-responder bias is limited. However, other factors, such as social and marital status or symptomatology, might be different for non-responders.

Missing values were analysed as if the symptom was not present. Missing values never exceeded 10%, except for one value. Therefore, it can be expected that the effect of missing data on the outcome is negligible. Twenty-five patients belonged to more than one category. A sensitivity analysis showed that the influence of assigning patients to another category was limited.

WIDER IMPLICATIONS OF THE FINDINGS: Outcomes regarding quality of life are highly influenced by recruitment strategy. None of the groups appeared to be a representative selection of the total population of women with endometriosis. An alternative strategy for creating a

representative population for cost and quality of life studies is probably to recruit women who live in a specific geographic area rather than women that visit a specific hospital or are a member of a patient association.

STUDY FUNDING/COMPETING INTEREST(S): The WERF EndoCost study was funded by the World Endometriosis Research Foundation. The sponsors did not have a role in the design and conduct of this study: collection, management, analysis, interpretation of the data; preparation, review, approval of the manuscript. L.H. is the chief executive and T.M.D. was a board member of WERF at the time of funding. T.M.D holds the Merck-Serono Chair and the Ferring Chair in Reproductive Medicine in Leuven, Belgium and has served as consultant for Merck-Serono, Schering-Plough, Astellas, and Arresto.

TRIAL REGISTRATION NUMBER: Not applicable.

Key words: endometriosis / quality of life / patient association / recruitment strategy / selection bias

Introduction

Endometriosis, defined as the presence of endometrial-like tissue outside the uterus, is one of the most common gynaecological diseases (Eskenazi and Warner, 1997). The chronic, inflammatory reaction, induced by the ectopic endometrial cells, results in a variety of pain symptoms including dysmenorrhoea, dyspareunia, chronic pelvic pain, dysuria and dyschesia, as well as fatigue and infertility (Fauconnier and Chapron, 2005; Dunselman *et al.*, 2014). Treatment options for women with endometriosis are diverse and consist of analgesic therapies, hormonal therapies, conservative or minimal invasive surgery, assisted reproduction, or a combination of these (Dunselman *et al.*, 2014). Treatment has to be customized to the individual needs of the patient (Kennedy, 1991; Dancet *et al.*, 2011). Moreover, endometriosis has been shown to be a disease that cannot be cured easily and therefore can be regarded as a chronic disease in many women (Guo, 2009; Vercellini *et al.*, 2009; Berlanda *et al.*, 2010). The lives of women with endometriosis are characterized by multiple surgeries, hormonal, and fertility treatments (Sinaii *et al.*, 2007; Bernuit *et al.*, 2011; De Graaff *et al.*, 2013). Symptoms such as dysmenorrhoea, dyspareunia and chronic pelvic pain often remain after treatment which result in endometriosis interfering with daily life and work activities, consequently altering women's emotional well-being, and decreasing their quality of life (Fourquet *et al.*, 2010; Nnoaham *et al.*, 2011; Tripoli *et al.*, 2011; Culley *et al.*, 2013; De Graaff *et al.*, 2013).

According to the most recent review on quality of life in women with endometriosis by Culley and co-workers, most studies investigate women recruited in tertiary care centres (defined as an academic hospital or a referral centre according to the material and methods sections of the manuscripts) (Waller and Shaw, 1995; Peveler *et al.*, 1996; Ferrero *et al.*, 2005; Lorençatto *et al.*, 2006; Eriksen *et al.*, 2008; Petrelluzzi *et al.*, 2008; Fagervold *et al.*, 2009; Sepulcri and do Amaral, 2009; Fourquet *et al.*, 2010, 2011; Roth *et al.*, 2011; Tripoli *et al.*, 2011; Chene *et al.*, 2012; Simoens *et al.*, 2012; Culley *et al.*, 2013; De Graaff *et al.*, 2013). Sporadically, patients are recruited in both secondary and tertiary care centres (Nnoaham *et al.*, 2011) (secondary care centre defined as a general hospital, not being a referral centre). Other sources of patient recruitment in studies regarding the effects of endometriosis are patient associations and self-help groups (Hadfield *et al.*, 1996; Ballweg, 2004; Lemaire, 2004; Sinaii *et al.*, 2007; Greene *et al.*, 2009; Gemmill *et al.*, 2010). The number of women surveyed for endometriosis-related issues that are recruited by patient associations is usually large ($n = 218–4334$). Results from these studies do shape to a great extent the general opinion on endometriosis, even though relevant clinical information about the diagnosis and degree of endometriosis is absent in this population.

It is conceivable that the setting where patient recruitment is performed influences the obtained outcome measures. However, this effect has never been investigated before. Therefore we documented and compared in the current study disease severity, medical history, current symptoms, disability, and quality of life in women recruited in three different settings: women treated in a tertiary care centre for endometriosis, women treated in secondary care centres and members of an endometriosis patient association.

Material and Methods

Perspective and setting

The World Endometriosis Research Foundation (WERF) EndoCost Study was conducted to measure costs of illness and health-related quality of life in women with endometriosis. For this purpose a research network, the WERF EndoCost Consortium, was established in 2007 comprising 12 representative tertiary care centres from ten countries. The methods and results of the original WERF EndoCost study are reported in detail elsewhere (Simoens *et al.*, 2011, 2012).

In the current study the WERF EndoCost questionnaires were administered to women treated in five secondary care centres in the Maastricht region and in members of the Dutch endometriosis patient association. The results were compared with earlier obtained results from women recruited in the Maastricht University Medical Centre, as part of the international WERF EndoCost study.

Study population and recruitment

The tertiary care population consisted of the women who were treated for endometriosis in the Maastricht University Medical Centre (MUMC). The participating hospitals were all located in the province of Limburg, which is the residential area of 6.8% of the Dutch population. The secondary care population consisted of women who were treated for endometriosis in one of the five general hospitals in the province of Limburg, the Netherlands: Atrium Medical Centre Heerlen, Laurentius Hospital Roermond, Orbis Medical Centre Sittard, Viecuri Medical Centre Venlo, Sint Jans Gasthuis Weert. The Maastricht Medical Centre acts as a referral centre for endometriosis patients from the mentioned general hospitals. Because the province of Limburg is located on the edge of the Netherlands, it is unlikely that referred patients will go to another hospital than the MUMC. The MUMC is one of the four academic endometriosis referral centres in the Netherlands. However there are patients referred to the MUMC from other parts of the Netherlands than the province of Limburg. The patient association population

consisted of women with endometriosis who are a member of the Dutch endometriosis association.

The secondary and tertiary care population included women with a laparoscopic and/or histological diagnosis of endometriosis, who had at least one contact related to endometriosis-associated symptoms during 2008 with a participating centre. The diagnosis of endometriosis was not necessarily made in this time period, but could have been made earlier. The study excluded women with suspected endometriosis and women with a history of endometriosis who came to the hospital for a clinical problem unrelated to the disease. The patient association population consisted of women with a self-reported diagnosis of endometriosis. Most members of the patient association are women with endometriosis. However, some members do not have the disease and are donors only. All female members received an information letter and consent form in January 2010. Members who were only donors of the association could indicate this on the return form and were excluded. Women with endometriosis who gave their consent were asked to complete the questionnaires at the beginning of March 2010. Members of the patient association who did not have surgically confirmed endometriosis were excluded from the study. The eligible patients from the MUMC received an information letter and consent form in August 2009. If they gave their consent they were asked to complete questionnaires at the beginning of October 2009. The eligible patients from the five general local hospitals received their information letter and consent form in January 2010. If they gave their consent they were asked to complete the questionnaires at the beginning of March 2010.

Ethical approval

Ethical approval was obtained from the ethical committee of the MUMC. The approval of the MUMC ethical committee was adopted by the five general hospitals and the Dutch endometriosis association. Women were required to sign an informed consent form in order to participate in the study.

Questionnaires

The Dutch translation of the original questionnaire of the WERF EndoCost study was used to determine socio-demographic characteristics such as marital status, education, current work situation and medical history such as surgery, fertility treatments and any co-morbidities.

Questions obtained from the WERF Global Study on Women's Health (GSWH) instrument (designed and validated for the WERF Global Study on Women's Health) (Nnoaham et al., 2011) were used to determine the impact of endometriosis on education, work and social well-being from a lifetime perspective, i.e. any impact experienced in the period from first symptoms until completing the questionnaire. Furthermore, questions from the WERF GSWH instrument were used to measure current symptoms, such as dysmenorrhoea, dyspareunia and chronic pelvic pain (recall period 3 months).

The validated Dutch version of the Short Form–36 version 2 (SF36v2) questionnaire was used to measure Health Related Quality of Life (Ware et al., 1993). The SF36v2 is a generic instrument containing eight dimensions of health-related quality of life (recall period 4 weeks) and allows to compare the examined population to a general standard population (Ware et al., 1993, 2000). Norm-based scores in the U.S. general population have a mean of 50 and a standard deviation of 10. Scores around 48 (0.2 SD) indicate that endometriosis has a small effect on quality of life, scores around 45 (0.5 SD) indicate a moderate effect and scores around 42 or lower (0.8 SD) indicate a large effect on quality of life (Cohen, 1988; Contopoulos-Ioannidis et al., 2009).

Disease criteria

For the hospital derived patients (tertiary and secondary care) endometriosis was staged at the time of diagnosis based on hospital records using the revised American Fertility Society (r-AFS) classification: I (minimal), II (mild), III

(moderate) or IV (severe) (American Fertility Society, 1985). Stages I/II and III/IV were analysed together. For the Dutch endometriosis association population self-reported severity of endometriosis was used (minimal-mild or moderate-severe).

Sample size

For this study no sample size calculation was conducted. The sample size was determined by the inclusion period. The inclusion of women was performed during a complete year in order to obtain a sample that includes both women with frequent visits to the hospital and women with only an annual check-up.

Statistical analysis

For statistical analysis patients could be included in only one group. Women who were both seen in a secondary and in a tertiary care centre in the year 2008 were in fact receiving tertiary care. Therefore these women were assigned to the tertiary care population. Women who were a member of the patient association and also visited one of the participating hospitals had a confirmed diagnosis by chart review and their r-AFS scores were available. Therefore these women were assigned to secondary or tertiary care population according to the hospital they visited. A sensitivity analysis was performed to determine the effect of the chosen strategy: all analyses described below were repeated with the women, who fell into more than one category, assigned to the opposite group ($n = 25$).

For categorical data, characteristics were reported as relative frequencies and, for continuous data, as median, minimum, and maximum. Between-groups analyses of categorical and ordinal data were performed by means of Chi-square test. Continuous data were tested for normality with the Kolmogorov–Smirnov test. Because all data, except for one variable were not normally distributed, all continuous data were compared with the Kruskal–Wallis one-way analysis of variance by ranks. For pairwise analysis the Mann–Whitney U-test was used. *Post hoc* pairwise comparisons for categorical, ordinal and continuous data were adjusted for three comparisons (tertiary care population with secondary care population; tertiary care population with patient association; secondary care population with patient association) with use of the Bonferroni correction method. For missing data regarding treatment, medical history, and the effect of endometriosis on education, work, and social well-being, the following approach was chosen: if data were missing they were analysed as if the questioned item was not present, i.e. they were set to zero.

For each SF36v2 dimension, item scores were coded, summed and transformed to T-score based scores (norm-based scores), with higher scores meaning better quality of life. The scorings are standardized across the Short Form family of adult tools using the means and standard deviations from the 1998 US general population (Ware et al., 1993). Calculations were performed using the official QualityMetric Health Outcomes Scoring Software. Missing data were substituted using the QualityMetric's Missing Data Estimator in case at least half of the data in that scale was present (referred to as the 'half-scale rule' of missing data estimation) (Ware et al., 1993, 2000). A sensitivity analysis was conducted where missing data were not substituted and were analysed as being missing (excluded).

A non-responder analysis was conducted comparing age and r-AFS stage between responders and non-responders recruited in the secondary and tertiary care centres.

For statistical analysis the SPSS program version 21 was used.

Results

Of 1402 women, invited to participate in the study, 674 women provided informed consent and had questionnaires posted to them. Of these, 497 returned the questionnaires (overall response rate 35% (497/1402),

tertiary care centre 51% (135/263), secondary care 33% (63/193), and patient association 32% (299/946)). Eight members of the patient association were excluded because they had no surgically confirmed endometriosis (Table I).

The MUMC tertiary care population was a composition of 26% of women who lived in the Maastricht area, which is the direct catchment area of the MUMC, of 56% of women who lived in Limburg, which is the catchment area of the five participating general hospitals and of 17% of women who lived in other parts of the Netherlands. The secondary care population consisted entirely of women who lived in the hospital's catchment area.

The three investigated groups were compared on standard demographic variables of age, education and disease severity (Table I). There was a statistical difference for age (median age tertiary care population 36 years, secondary care population 37 years, patient association population 35 years); however the post hoc pairwise comparisons did not show significant differences. The level of education was not significantly

different between the groups. Moderate to severe endometriosis (r-AFS) was significantly more common in the tertiary care population (78%) than in the secondary care population (59%) (P = 0.004). Self-reported moderate to severe endometriosis was prevalent in 79% of the women of the patient association. For the secondary care population both self-reported severity of the disease and r-AFS by chart review was available. There were 38 women (67%) who reported the same level of severity of endometriosis as determined by r-AFS score based on chart review. There were 12 women (21%) who reported a moderate-severe endometriosis while the r-AFS score was minimal-mild. There were six women (10%) who reported minimal-mild endometriosis, while the r-AFS score was moderate-severe.

In Table II the median delay and median number of physicians and complementary therapists (such as acupuncturists, homeopaths, osteopaths) that were seen before diagnosis are shown. There was a significant difference in median age at first symptoms between the groups. Women recruited from the patient association were significantly younger at first

Table I Demographics and patient characteristics.

Response rate	Tertiary care population n (percentage)	Secondary care population n (percentage)	Patient association population n (percentage)	P-value
Invitation letter sent	263 (100%)	193 (100%)	946 (100%)	
Informed consent provided	177 (67%)	93 (48%)	404 (43%)	<0.001[#,$]
Completed questionnaires	135 (51%)	63 (33%)	299 (32%)	<0.001[#,$]
Included questionnaires	135 (51%)	63 (33%)	291 (31%)	<0.001[#,$]
Characteristic	**Median (min-max)**	**Median (min-max)**	**Median (min-max)**	**P-value**
Age (years)	36 (22−55)	37 (23−59)	35 (20−58)	0.033
Number of co-morbidities	1 (0−6)	1 (0−5)	2 (0−8)	NS
Highest level of education	**n (percentage)**	**n (percentage)**	**n (percentage)**	**P-value**
Primary school	0 (0%)	0	2 (0.7%)	
Lower secondary school	30 (22%)	17 (27%)	44 (15%)	
Upper secondary school	57 (42%)	24 (38%)	101 (35%)	NS
Post secondary, not university	34 (25%)	18 (29%)	105 (36%)	
University/post graduate	11 (8%)	4 (6%)	39 (13%)	
Missing	3 (2.2%)	0	0	
r-AFS stage*				
Minimal-mild (stage I-II)	29 (22%)	24 (38%)	–	0.004
Moderate-severe (stage III-IV)	106 (78%)	37 (59%)	–	
Other**		2 (3%)	–	
Self-reported severity endometriosis*				
Minimal-mild	–	16 (25%)	47 (16%)	
Moderate-severe	–	41 (65%)	229 (79%)	NS
Unknown	–	6 (10%)	14 (5%)	

Percentage of missing values was: 0−9.5%.
*r-AFS stage not available for Dutch Endometriosis Association.
**Umbilicus or Caesarean section scar.
***Self-reported severity endometriosis not available for MUMC.
[#]Significant difference between tertiary care population and secondary care population.
[$]Significant difference between tertiary care population and patient association.

Table II Delay in diagnosis, physicians and complementary therapists consulted.

	Tertiary care population $n = 135$	Secondary care population $n = 63$	Patient association population $n = 291$	
	Median (min-max)	Median (min-max)	Median (min-max)	*P*-value
Age at first symptoms (years)	26 (11−42)	29 (13−51)	21 (6−55)	<0.001[$,@]
Age at diagnosis (years)	31 (19−47)	32 (17−55)	30 (10−55)	0.008[@]
Years since diagnosis (years)	4 (0−20)	3 (1−18)	4 (0−29)	NS
Patient delay (years)	0 (0−16)	0 (0−27)	1 (0−25)	NS
Doctor delay (years)	1 (0−25)	0 (0−19)	3 (0−36)	<0.001[$,@]
Delay total (years)	2 (0−25)	1.5 (0−28)	7 (0−42)	<0.001[$,@]
Number of physicians consulted*	2 (1−10)	2 (1−6)	3 (1−14)	<0.001[#,@]
Number of complementary therapists consulted*	0 (0−4)	0 (0−2)	0 (0−13)	0.025[@]

Percentage of missing values was: 0–9.6%. 'Delay total' in the secondary care population was 11.1% (7/63 missing).
*Number of regular physicians and complementary therapists that a patient consulted before the diagnosis endometriosis was made.
#Significant difference between tertiary care population and secondary care population.
$Significant difference between tertiary care population and patient association.
@Significant difference between secondary care population and patient association.

symptoms (median 21 years, range 6−55) than women recruited in the secondary care (median 29 years, range 13−51) and tertiary care (median 26 years, range 11−42) (*P* < 0.001). Patient delay (time between first symptoms and first visit to a doctor) was comparable between the three groups. Doctors delay (time between first visit to a doctor and diagnosis of endometriosis) was significantly longer in women recruited via the patient association (median 3 years, range 0−36) than in the tertiary care population (median 1 year, range 0−25) and the secondary care population (median 0 years, range 0−19) (*P* < 0.001). The tertiary care population and the patient association population visited significantly more physicians before diagnosis than the secondary care population (tertiary care: median 2, range 1−10; patient association: median 3, range 1−14; secondary care median: 2, range 1−6) (*P* < 0.001). The number of complementary therapists consulted before diagnosis was significantly higher in the patient association than the secondary care population (median 0, range 0−13 versus 0, range 0−2, pairwise *P* = 0.045).

The three groups were asked about their medical history: number of surgeries, medical treatments and fertility treatments (Table III). The tertiary care population reported significantly more laparotomies and major surgeries, while women recruited via the patient association had received most types of hormonal treatments in the past. There was a statistical difference in the frequency of subfertility between the three groups. The *post hoc* pairwise comparisons, however, did not show significant differences. Treatment with IUI was more prevalent in the patient association population than in the secondary care population (23 versus 8%, pairwise *P* = 0.021) and IVF was more prevalent in the patient association population (36%) and the tertiary care population (39%) than in the secondary care population (10%) (*P* < 0.001).

Table IV shows the proportion of women who had ever lost time to their education (changed study, delayed final exam) due to endometriosis-associated symptoms or experienced that endometriosis had a negative effect on work or relationships due to endometriosis-associated symptoms at some time during their life (lifetime perspective). The effect of

endometriosis on daily life was considerably more pronounced in women recruited via the patient association and tertiary care population than in those recruited in the secondary care population. Affected job was more prevalent in patient association members (64%) and women recruited from the tertiary care population (56%) than in women recruited from the secondary care population (35%) (*P* < 0.001). Affected relationships were more prevalent in the patient association (52%) than in the other populations (38% tertiary care and 22% secondary care) (*P* < 0.001).

Women were asked about their current symptoms (recall period 3 months): the prevalence of dysmenorrhoea was comparable between the three groups (Table V). The frequency of dyspareunia differed significantly between the groups, but the *post hoc* comparisons did not show pairwise differences. Pain at other times (chronic pain) was significantly more prevalent in the patient association population (65%) than in the secondary care population (44%) (pairwise *P* = 0.006).

Figure 1 shows the eight domains of the SF-36. *Post hoc* pairwise analysis of the eight domains of the SF-36 shown in Fig. 1 revealed that there were no significant differences between the tertiary care population and the patient association population, except for general health. The tertiary care population scored significantly lower than the secondary care population for the domains physical functioning, physical role limitation, pain, general health and the physical component scale. The patient association population scored significantly lower than the secondary care population for seven of the eight domains and the physical component scale.

Sensitivity analysis

For women who fell into more than one category a sensitivity analysis was conducted. There were five participants who visited both the MUMC and one of the five general hospitals; in the sensitivity analysis they were assigned to the secondary care population. There were 16 participants who visited the MUMC and were a member of the Dutch endometriosis association, in the sensitivity analysis they were assigned to

Table III Surgical and hormonal and fertility treatments (lifetime perspective).

	Tertiary care population n = 135	Secondary care population n = 63	Patient association population n = 291	
Surgeries	**Median (min-max)**	**Median (min-max)**	**Median (min-max)**	**P-value**
Number of laparoscopies	1 (0−8)	1 (0−5)	1 (0−7)	NS
Number of laparotomies	1 (0−6)	0 (0−2)	0 (0−10)	0.001[#,$]
Total number of surgeries	2 (0−11)	2 (0−6)	2 (1−13)	NS
Surgeries*	**n (percentage)**	**n (percentage)**	**n (percentage)**	**P-value**
Laparoscopy	108 (80%)	54 (86%)	260 (89%)	0.033[$]
Laparotomy	87 (64%)	27 (43%)	138 (47%)	0.002[#,$]
Type of surgery unknown	0	2 (3%)	0	
Major surgeries:				
Ovariectomy	48 (36%)	22 (35%)	78 (27%)	NS
Hysterectomy	35 (26%)	11 (18%)	32 (11%)	<0.001[$]
Bowel procedures	62 (46%)	1 (11%)	47 (16%)	<0.001[#,$]
Bladder procedures	24 (18%)	1 (2%)	20 (7%)	<0.001[#,$]
Ureter procedures	14 (10%)	1 (2%)	11 (4%)	0.007[$]
No surgery	6 (4%)	1 (2%)	–	NS
Hormone treatments**				**P-value**
Oral contraceptives	95 (70%)	3 (57%)	216 (74%)	0.025[@]
Progestagen	30 (22%)	18 (29%)	130 (45%)	<0.001[$]
GnRH analogues	77 (57%)	20 (32%)	200 (69%)	<0.001[#,@]
Mirena	20 (15%)	13 (21%)	48 (17%)	NS
Danazol	1 (0.7%)	0 (0%)	15 (5%)	0.017
Not used hormonal treatment	17 (13%)	9 (14.3%)	12 (4%)	0.001[$,@]
	Median (min-max)	**Median (min-max)**	**Median (min-max)**	**P-value**
Median number of different types hormonal treatments	2 (0−4)	1 (0−3)	2 (0−5)	<0.001[$,@]
Fertility treatments	**n (percentage)**	**n (percentage)**	**n (percentage)**	**P-value**
Subfertility	73 (54%)	29 (46%)	181 (62%)	0.036
Fertility treatment	60 (44%)	18 (29%)	129 (44%)	NS
Of which**, hormone treatment	22 (16%)	11 (18%)	31 (11%)	NS
IUI (with or without hormones)	27 (20%)	5 (8%)	67 (23%)	0.026[@]
IVF	53 (39%)	6 (10%)	104 (36%)	<0.001[#,@]

Percentage of missing values was: 0−4.9%.
*Women could have had one or more laparoscopy, laparotomy or both. The same applies for ovariectomy, bowel procedures, etc. Furthermore, women could have had more than one procedure in one surgery, for example both hysterectomy and ovariectomy.
**Women could report more than one type of hormone or fertility treatment.
[#]Significant difference between tertiary care population and secondary care population.
[$]Significant difference between tertiary care population and patient association.
[@]Significant difference between secondary care population and patient association.

the patient association population. There was one participant who visited one of the five general hospitals and was a member of the Dutch endometriosis association, in the sensitivity analysis she was assigned to the patient association population. There were three patients who visited both the MUMC and one of the five general hospitals and were also members of the Dutch endometriosis association, in the sensitivity analysis they were assigned to the patient association population. There were a few differences detected by the sensitivity analysis. The few variables that had a different outcome showed a higher disease burden in the patient association population and lower disease burden in the

Table IV Effect of endometriosis on education, work and social well-being (lifetime perspective).

Effect of endometriosis	Tertiary care population n = 135 n (percentage)	Secondary care population n = 63 n (percentage)	Patient association population n = 291 n (percentage)	P-value
Time lost to education	25 (19%)	5 (8%)	53 (18%)	NS
Affected job	75 (56%)	22 (35%)	185 (64%)	<0.001[#,@]
Affected relationship	51 (38%)	14 (22%)	150 (52%)	<0.001[$,@]

Percentage of missing values was: 0−1.5%.
[#]Significant difference between tertiary care population and secondary care population.
[$]Significant difference between tertiary care population and patient association.
[@]Significant difference between secondary care population and patient association.

Table V Current symptoms.

Dysmenorrhoea	Tertiary care population n = 135 n (percentage)	Secondary care population n = 63 n (percentage)	Patient association population n = 291 n (percentage)	P-value
Dysmenorrhoea	68 (50%)	28 (44%)	139 (48%)	NS
Dyspareunia				
Having intercourse	115 (85%)	46 (73%)	226 (78%)	NS
Dyspareunia: n dyspareunia/n having intercourse (percentage)	65/115 (57%)	25/46 (54%)	157/226 (70%)	0.023
Chronic pelvic pain				
Pain at other times (chronic pain)	82 (61%)	28 (44%)	190 (65%)	0.009[@]

Percentage of missing values was: 0−6.3%.
[@]Significant difference between secondary care population and patient association.

tertiary care population. SF-36v2 domain 'pain' medians: 46.1 for the tertiary care, 50.3 for the secondary care and 46.1 for the patient association ($P = 0.001$). SF-36 domain 'general health' medians: 48.2 for the tertiary care, 50.5 for the secondary care and 38.6 for the patient association ($P < 0.001$). SF-36 domain 'vitality' medians: 48.9 for the tertiary care, 52.1 for the secondary care and 35.9 for the patient association ($P = 0.001$). SF-36 physical component scale medians: 48.3 for the tertiary care, 50.7 for the secondary care and 44.6 for the patient association ($P < 0.001$). All variables that gave a different result in the sensitivity analysis are shown in the Supplementary Table SI.

A second sensitivity analysis was conducted in which missing data for the SF-36v2 were not substituted. Results of this analysis were similar to the analysis in which missing data had been substituted.

Non-responder analysis

Analysis of the non-responders in the secondary and tertiary care centres revealed that there was no difference in age between responders and non-responders. Furthermore there was no difference in severity of the disease (r-AFS) between responders and non-responders in both the secondary care population (non-responders: 41.2% minimal-mild, 55.7% moderate-severe, 3.1% other) and tertiary care population (non-

responders: 15.8% minimal-mild, 80.5% moderate-severe, 3.9% other). Non-responder analysis was not conducted for the patient association population.

Discussion

In this observational study we documented and compared demographics, disease severity, medical history, disability, current symptoms, and quality of life in women recruited in three different settings in order to determine to what extent patient recruitment influences outcome measures.

Similarities and differences in women's characteristics

This study did not reveal considerable differences in age, number of co-morbidities or education between the groups. As can be expected, the percentage of women with moderate-severe endometriosis (r-AFS) was significantly higher in the tertiary care population (78%) than in the secondary care population (59%). Self-reported moderate-severe endometriosis was 79% in the women from the patient association. This
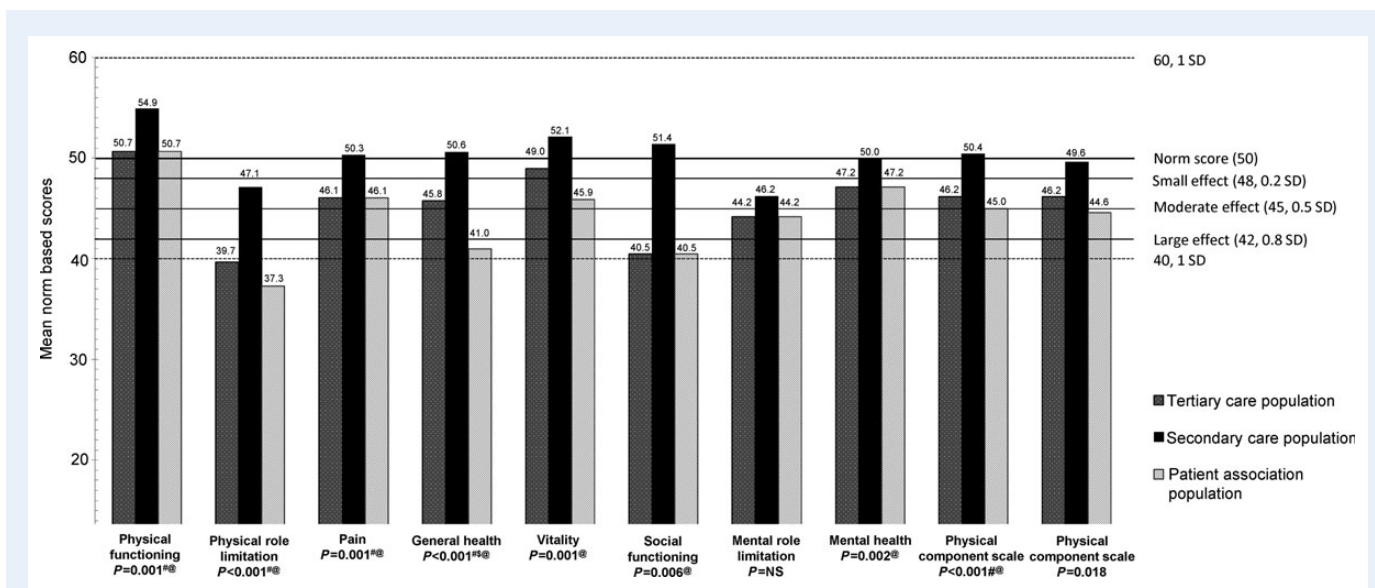
Figure 1 Results of the SF-36v2 HRQoL questionnaire. Percentage of missing values was: 0–8.8%. Number of substituted values varied from 0.2 to 1.8% for the eight domains and 5% for the summary scales. Sensitivity analysis without the substituted data (analysed as being missing) gave the same outcomes. #Significant difference between tertiary care population and secondary care population. $Significant difference between tertiary care population and patient association. @Significant difference between secondary care population and patient association.

percentage is similar to the 78% moderate-severe endometriosis based on r-AFS in the tertiary care population while both are higher than the 59% moderate-severe endometriosis based on the r-AFS score in the secondary care population. However, due to the fact that the r-AFS scores were not available for the patient association population and self-reported severity is not available for the tertiary care population, it is not possible to make an indisputable conclusion regarding the disease severity.

Similarities and differences in disease- and treatment history

The total delay in diagnosis was significantly longer in the endometriosis association population (median 7 years,) compared with delay in both secondary (median 1.5 years) and tertiary care populations (median 2 years). This was the result of the significantly longer doctor's delay in the patient association (median 3 versus 0 and 1 years). It can be speculated that discontented women, due to a long delay in diagnosis, are more likely to join a patient association, which could explain these results. Often cited figures on delay in diagnosis are from the study of Hadfield and co-workers who found a self-reported average delay of 9.4 years in a group of 218 women recruited through endometriosis self-help groups (Hadfield *et al.*, 1996) and Greene and co-workers who found an self-reported average delay of 9.3 years in a group of 4000 members of the American Endometriosis Association (Greene *et al.*, 2009). The results of the current study suggest that it is questionable to use patient association derived figures as absolute references.

The study shows that treatment history differs between the groups: the tertiary care patients did undergo more major surgical procedures than women recruited in the secondary care and the patient association. This is also an indication that women with more severe endometriosis

are more prevalent in the tertiary care population, which might be the result of referral policy.

Similarities and differences in disability, current symptoms and quality of life

This study demonstrates significant differences on key aspects of daily life, current symptoms and quality of life. In short, tertiary care patients and members of the patient association scored similarly on effect on education, work, social well-being and current symptoms, while the secondary care population reported a lower level of disability and fewer symptoms.

For six out of eight domains of the SF-36v2, the secondary care population had scores comparable to those of a normal population indicating that the secondary care population has an almost average quality of life (Fig. 1) (Cohen, 1988; Contopoulos-Ioannidis *et al.*, 2009). On the contrary, endometriosis poses an impressive disease burden on women recruited from the tertiary care population. Similar differences were found by Crook and co-workers who compared persistent pain sufferers treated in a specialty pain clinic with persistent pain sufferers who are treated in a family practice (Crook *et al.*, 1986).

Women recruited from the patient association reported not only significantly lower quality of life for all eight domains of the SF-36v2, but the differences were also considerable compared with the secondary care population. Furthermore the patient association scored comparable or lower than the tertiary care population. Mestre-Stanislas and co-workers found the same remarkable trend when comparing patients with systemic sclerosis recruited from a patient association with sclerosis patients who were hospitalized in a tertiary care centre (Mestre-Stanislas *et al.*, 2010). Conceivably the influence of recruitment strategy is a universal phenomenon and not only restricted to endometriosis or systemic sclerosis.

It would be interesting to link these quality of life outcomes with clinical variables by making use of a conceptual model such as the one developed by Wilson and Cleary (1995). They divided patient outcomes into five levels: biological and physiological factors, symptoms, functioning, general health perceptions, and overall quality of life. However, to link our study outcomes between these different levels is extremely difficult. First, not all levels could be investigated in this study. Secondly, for some levels there is no clear measurement. For instance, the level of biological and physiological factors could be represented by the disease severity. However there is no gold standard for documenting disease severity. The most used measurement is the r-AFS, but this is questionable while the correlation between r-AFS, pain symptoms and quality of life is poor (Vercellini et al., 2007; De Graaff et al., 2013). Third, for this study a cross-sectional design was used with only one point of measurement, which makes it impossible to draw conclusions on causal inference.

There are some potential explanations for the differences that were found between the three settings of recruitment. For example, the main function of a patient association is to provide mutual support to other patients, share information about the disease and treatment options, and help in coping with the difficulties that come with the disease. Therefore, it can be argued that women who experience many symptoms, who are out of treatment options, and who are feeling misunderstood will be more likely to join a patient association and share their experiences with their peers. It is plausible that this self-selection is responsible for the different medical history, higher prevalence of symptoms, effect of endometriosis on daily life, and the profoundly impaired quality of life compared with the hospital populations. In the secondary and tertiary care there is also a form of selection made by the referrers. It is conceivable that women with a more infiltrative form of endometriosis, or women with more symptoms, are more likely to be referred to a tertiary care centre. This could explain the higher prevalence of major surgery, IVF treatments and lower quality of life in the tertiary care population.

Limitations of the study

The response rate in this study is relatively low (35%) (Cummings et al., 2001), but comparable with the WERF EndoCost study (Simoens et al., 2012; De Graaff et al., 2013). This is possibly due to the fact that women were approached through the post rather than during an outpatient contact. The responders and non-responders did not differ in age and r-AFS score in both the secondary and tertiary care. This could indicate that the non-responder bias may be limited (Armstrong and Overton 1977; Cummings et al., 2001). However, it is possible that other factors, such as social and marital status, or symptomatology, are different for non-responders. This leaves some uncertainty regarding the generalizability of the data from responders to non-responders. The relatively low response rate in the patient association could partially be explained by the fact that there were donors among the non-responders. For this reason, it was not possible to conduct a non-responder analysis for the patient association.

For women recruited from the patient association no chart review was available and therefore self-reported endometriosis was used as inclusion criteria, which results in a degree of uncertainty regarding the diagnosis. To diminish this uncertainty, we included only members of the patient association with a self-reported surgically confirmed endometriosis. Furthermore, for women recruited from the patient association it was unknown if they had a hospital contact in the year 2008. For the

hospital population a hospital contact was mandatory, which could influence the quality of life outcomes positively (by getting better care) or negatively (by need for more care).

For missing data for medical history, symptoms and the effect of endometriosis on education, work, and social well-being, the following was chosen: if data were missing, they were analysed as if the questioned symptom was not present. This approach was chosen with the assumption that missing data were not randomly distributed but that answering the question was related to the presence of the questioned treatment and/or symptom. The number of missing values never exceeded the 10% of the population, except for one value ('total delay' in the secondary care population 11.1%). Therefore, we expect that the effect of missing data on the outcome is negligible (Bennett, 2001).

In total there were 25 patients who fell in more than one category. For statistical analysis patients could be included in only one group. The sensitivity analysis did not show many differences compared with the original analysis. The few variables that had a different outcome showed a higher disease burden in the patient association population and lower disease burden in the tertiary care population.

In order to quantify the quality of life of women with endometriosis with a general population, the official norm-based scores derived from the 1998 US general population by Qualitymetric Incorporated were used (Ware et al., 2000). It has to be recognized that these scores were collected 10 years before the current study and only included women from the USA, while the current study included women from the Netherlands. However, the official 1998 US general population scores were not updated and there are no norm-based scores derived from Dutch women available.

Conclusion and wider implications

One of the conclusions that can be drawn from this study is that women recruited from secondary care and women recruited from tertiary care are two different patient populations, which are not comparable in any of the investigated areas. This has important consequences for the interpretation of quality of life studies that have been exclusively conducted in either secondary or tertiary care centres. Indeed, both populations are real, do exist, and both populations contribute to the total endometriosis burden in society. However, both settings contain an unbalanced population. We must recognize that there are women who do not seek help for endometriosis-related symptoms in neither a secondary nor a tertiary care centre, but who still contribute to the total population of women with endometriosis. This group of women is probably not a member of a patient association either, because 97% of the responders in the patient association setting had surgery, which means that they must have been treated in a secondary or tertiary care centre. Therefore, a second conclusion is that women, who are only treated in primary care, are unlikely to be included in studies on disease burden. A third conclusion that can be drawn from this study is that women recruited via a patient association share more similarities with women recruited in tertiary care, than women recruited in the secondary care, and report an even larger disease burden than the investigated tertiary care population. This emphasizes how careful we should be with the interpretation of studies conducted within the sole confines of a disease-specific patient organization.

We propose an alternative strategy for creating a representative study population for cost and quality of life studies, where recruitment is based on women who live in a specific geographic area rather than women that

visit a specific hospital or are a member of a patient association. This recruitment strategy might also have the benefit that it eliminates country-to-country differences in referral policy.

From this study the question arises if the disease burden of endometriosis in general is overestimated. Although it is obvious that a large number of women suffer from severe pain symptoms and decreased quality of life, there is a significant group of women with endometriosis who report less symptoms and a quality of life which is almost similar to that of the general population. Because this group of patients is rarely recruited into the large studies on quality of life that have been published so far, they are less visible and therefore probably underrepresented in the overall perception of the consequences of endometriosis on women's lives. This may contribute to too negative a picture being presented to newly diagnosed women with endometriosis, either by the treating physician or by the information presented on websites of patient organizations.

The current study describes in what direction and to what extent the outcome measures are altered by recruitment strategy. This knowledge will enhance and facilitate the interpretation of quality of life outcomes in studies with different recruitment settings.

Supplementary data

Supplementary data are available at http://humrep.oxfordjournals.org/.

Acknowledgements

Authors' roles

Study design: A.A.D.G., C.D.D., S.S., L.H., T.M.D., G.A.J.D. Study execution: A.A.D.G., S.S., B.D.B., L.H., T.M.D, G.A.J.D. Study analysis: A.A.D.G., C.D.D., G.A.J.D. Manuscript drafting: A.A.D.G., C.D.D., B.D.B., G.A.J.D. Critical discussion: A.A.D.G., C.D.D., S.S., B.D.B., L.H., T.M.D, G.A.J.D.

Funding

Conflict of interest

L.H. is the chief executive and T.M.D. was a board member of WERF at the time of funding. T.M.D. holds the Merck-Serono Chair and the Ferring Chair in Reproductive Medicine in Leuven, Belgium and has served as consultant for Merck-Serono, Schering-Plough, Astellas, and Arresto.

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