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A systematic review to determine use of the Endometriosis Health Profiles to measure quality of life outcomes in women with endometriosis

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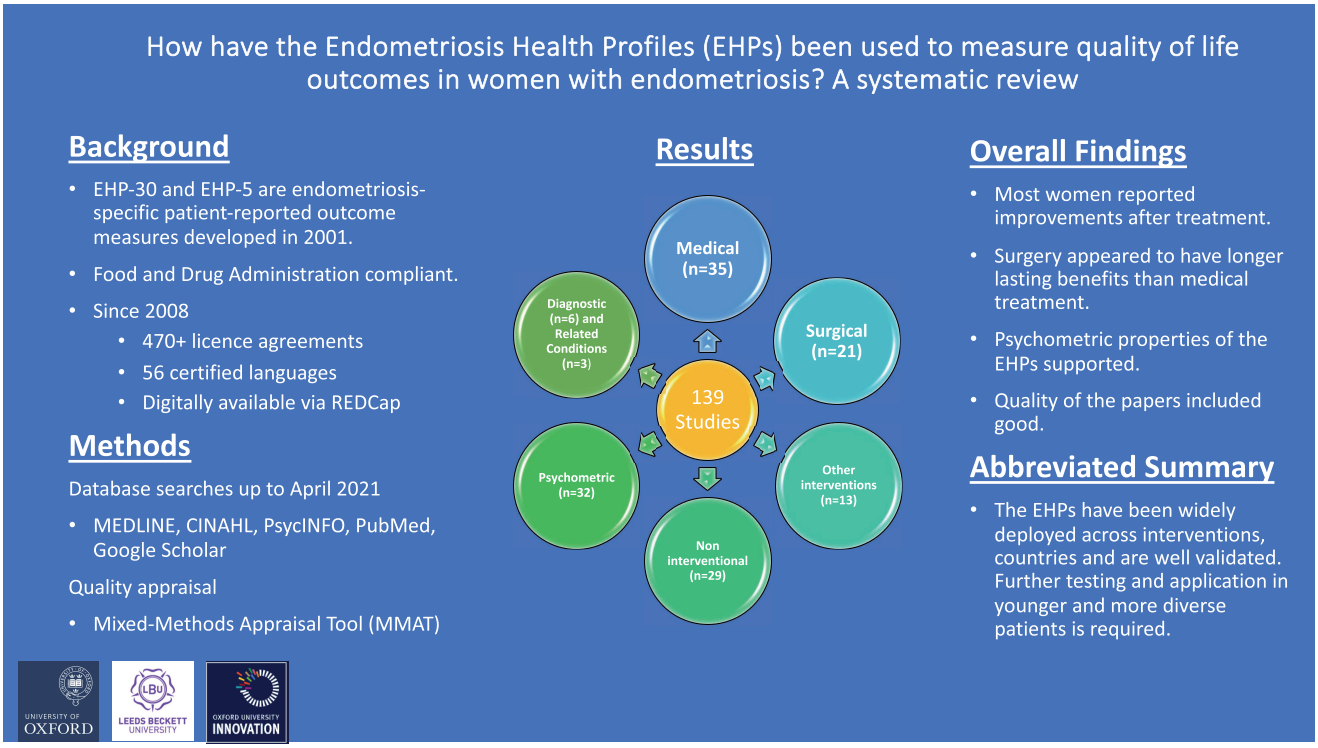
GRAPHICAL ABSTRACT



A summary of Endometriosis Health Profile use.

ABSTRACT

BACKGROUND: The Endometriosis Health Profiles (EHPs), the EHP-30 and EHP-5, are patient-reported outcome measures that were developed to measure the health-related quality of life (HRQoL) of women living with endometriosis. Prior to their development, a systematic review was undertaken which identified that the HRQoL of women living with endometriosis was poorly understood, with only three medical and one surgical study identified.

OBJECTIVE AND RATIONALE: The 20-year anniversary of the EHP-30 provided a timely opportunity to assess how the tools have been used and explore what the findings tell us about the impact of endometriosis and its associated treatments upon women's QoL. Applying robust systematic review methodology, following PRISMA guidelines, we sought to answer: How many studies have used the EHP and for what purpose?; What are the demographic characteristics and international context of the studies?; What is the methodological nature and quality of the studies?; Which interventions have been assessed and what are the reported EHP outcomes?; and Can the EHP outcomes of these interventions be analysed using a meta-analysis and, if so, what do the results show?

SEARCH METHODS: The electronic databases MEDLINE, CINAHL, PsycINFO, PubMed, and Google Scholar were searched from the year the EHP was first published, in 2001 to 26 February 2020 using the search terms 'EHP30', 'EHP5', 'EHP-30', 'EHP-5', 'endometriosis health profile 30', and 'endometriosis health profile 5'. We updated the searches on 9 April 2021. All included studies were quality assessed using the Mixed Methods Appraisal Tool (MMAT).

OUTCOMES: The review included 139 papers. In clinical intervention studies, the EHPs were deployed most frequently to measure the outcomes of medical (n = 35) and surgical (n = 21) treatment. The EHPs were also used in 13 other intervention studies, 29 non-interventional studies, 32 psychometric/cross cultural validation studies; six diagnostic studies, and in three other studies to measure outcomes in related conditions. They were mainly deployed in studies undertaken in Europe and North America. Overall, regardless of the nature of the intervention, most women reported improvements in HRQoL after treatment. Surgical interventions generally resulted in significant improvements for the longest amount of time. There was also evidence that when participants stopped taking medication their EHP scores worsened, perhaps reinforcing the temporary impact of medical treatment. Younger patients reported more negative impact upon their HRQoL. Further evidence using classical test theory to support the EHPs' robust psychometric properties, including acceptability, dimensionality, reliability, validity (including cross-cultural), and responsiveness, was demonstrated, particularly for the EHP-30. Strikingly, using anchor-based methods, EHP-30 responsiveness studies demonstrate the largest mean changes in the 'control and powerlessness' domain post-intervention, followed by 'pain'. MMAT outcomes indicated the quality of the papers was good, with the exception of five studies. A meta-analysis was not undertaken owing to the heterogeneity of the interventions and papers included in this review.

WIDER IMPLICATIONS: Women with endometriosis face a lifetime of surgical and/or medical interventions to keep the condition under control. Less invasive treatments that can lead to improved longer term physical and psycho-social outcomes are needed. The EHPs are reliable, valid, acceptable, and responsive tools, but more assessment of EHP outcomes using modern psychometric methods and in the context of women from ethnically diverse backgrounds and in routine clinical care would be beneficial. Given the brevity of the EHP-5, it may be the most appropriate version to use in routine clinical practice, whereas the longer EHP-30, which provides more granularity, is more appropriate for research.

Keywords: Endometriosis Health Profile 30 / Endometriosis Health Profile 5 / endometriosis / health-related quality of life / patient-reported outcome measures / systematic review / endometriosis treatment

Introduction

Endometriosis, a common gynaecological disease with an estimated prevalence of 10%, is defined as the presence of endometrial-like tissue in extra-uterine locations (Zondervan et al., 2020). It affects women of reproductive age and typically regresses after the menopause. Symptoms include chronic pelvic pain (CPP), painful periods (dysmenorrhoea), pain on defaecation (dyschezia), pain on intercourse (dyspareunia), sub-fertility, and other symptoms such as fatigue (Bulletti et al., 2010). There is no cure and the effectiveness of the limited treatment options varies. Those available focus on symptom control, including pain relief, using analgesics, hormonal therapy, surgery, and, where relevant, fertility treatment. Consequently, endometriosis imposes heavy demands on women and healthcare professionals with resulting high costs.

Recognizing the value of measuring the quality of life of affected women in routine clinical practice and research, the Endometriosis Health Profiles (EHPs) were developed, including the long form version (EHP-30) (Jones et al., 2001) and the shorter EHP-5 (Jones et al., 2004a). Before the EHPs were developed, the impact of endometriosis and associated interventions on women's health-related quality of life (HRQoL) was little understood. For example, a 2002 systematic review identified only four studies (three medical; one surgical) that had assessed treatment outcomes using a patient-reported outcome measure (PROM), all of which were carried out in developed countries (Jones et al., 2002).

The domain and scoring algorithms of the EHPs

Originally developed in English at the University of Oxford, the EHP-30 consists of a core instrument with five scale scores covering: Pain; Control and powerlessness; Social support; Emotional well-being, and Self-image. In addition, six (optional) supplementary modules can be deployed alongside the core instrument covering areas of health status that may not affect every endometriosis sufferer. These cover: Work; Relationship with child/children; Sexual intercourse/functioning; Feelings about medical profession; Feelings about treatment, and Feelings about infertility. Practitioners can choose these modules (in any combination) to assess specific areas of HRQoL that are relevant to their research/clinical practice and the patient.

The core section outcomes can be presented at an individual item level, domain level, or as an overall summary score (i.e. a total score, which includes all 30 items). On the modular section, only the outcomes at an item level or domain level are appropriate. The EHP-30 core and modular sections combined take, on an average, less than 15 min to complete (Nogueira-Silva et al., 2015).

The EHP-5 was developed to provide a briefer version of the tool by taking one item from each of the five core scales (five items) and one from each of six modular scales (six items). The items were chosen based on the highest to total correlation within the scale (Jones et al., 2004a).

The EHPs are compliant with the US Food and Drug Administration's (FDA) recommended guidance for developing PROMs (FDA, 2009). They were developed using data derived from systematic reviews of the literature (Jones et al., 2002) and in-depth interviews with affected women to ensure content validity (Jones et al., 2004b). These measures provided the first psychometrically established instrument, designed specifically to evaluate the impact of endometriosis and its associated treatments, or other related interventions, from the woman's perspective (Jones et al., 2001, 2004c, 2006). This valuable information empowers women to express the impact of the disease on their well-being; it can also help clinical management and decision-making by enabling healthcare professionals to monitor progress.

Portfolio of licence agreements and translations

Since 2008, the EHPs have accumulated over 474 licence agreements through Oxford University Innovation's Clinical Outcomes team, of which 67% have been in publicly funded treatment or academic studies. The remainder is commercial, awarded to privately funded healthcare providers, pharmaceutical companies, or digital platform providers serving commercial users.

The EHPs have 56 certified language versions for use across the globe (i.e. translated and linguistically validated in strict accordance with sector good practices). Some territories have more than one language version covering different populations, e.g. Switzerland: German, French, and Italian, bringing the total number of language versions to 456. There are also eight non-certified language versions (that may not have strictly followed sector good practices), which have been produced by academic or publicly funded groups in close collaboration with the Clinical Outcomes team (Fig. 1).

Modes of EHP administration

The EHPs are available in paper and e-versions. They have been faithfully reproduced into a few eCOA (electronic Clinical Outcome Assessment) libraries and migrated digitally multiple times, most recently into a REDCap friendly survey which is available, subject to licence, to download and install. For each eCOA, the digital reproduction has been assessed by the Clinical Outcomes Team at Oxford to ensure comparability of results acquired from the eCOA modality to the more conventional paper completions. This enables the EHPs to be distributed to patients digitally and provides the functionality to collect and analyse data more easily, especially relevant in routine care. A user manual is freely available from Oxford University Innovation, which guides users on the application and scoring of the EHP measures.

Professional and regulatory endorsement

The American Society for Reproductive Medicine (ASRM) and European Society of Human Reproduction and Embryology (ESHRE) recommend the EHP-30 for use as the secondary outcome measure in clinical trials to assess endometriosis-associated pain (an 11-point numerical rating scale is recommended as the primary outcome) (Vincent et al., 2010). The EHP-30 is also recommended in other national endometriosis guidelines (Grundström et al., 2020a).

Rationale

The 20-year anniversary of the EHP-30 provides an opportunity to assess how the measures have been used globally and explore how endometriosis and its treatments impact upon self-reported quality of life. While other reviews are available, none focus exclusively on the EHP (Bourdel et al., 2019). The new Women's Health Strategy in England acknowledges that still not enough is known about endometriosis and how it impacts affected women (Department of Health & Social Care, 2021). Therefore, this systematic review aims to identify and synthesise the literature relating to the use of the EHP instruments over the last 20 years, and specifically answer the following questions:

- How many studies have used the EHPs and for what purpose?
- What are the demographic characteristics and global context of the studies?

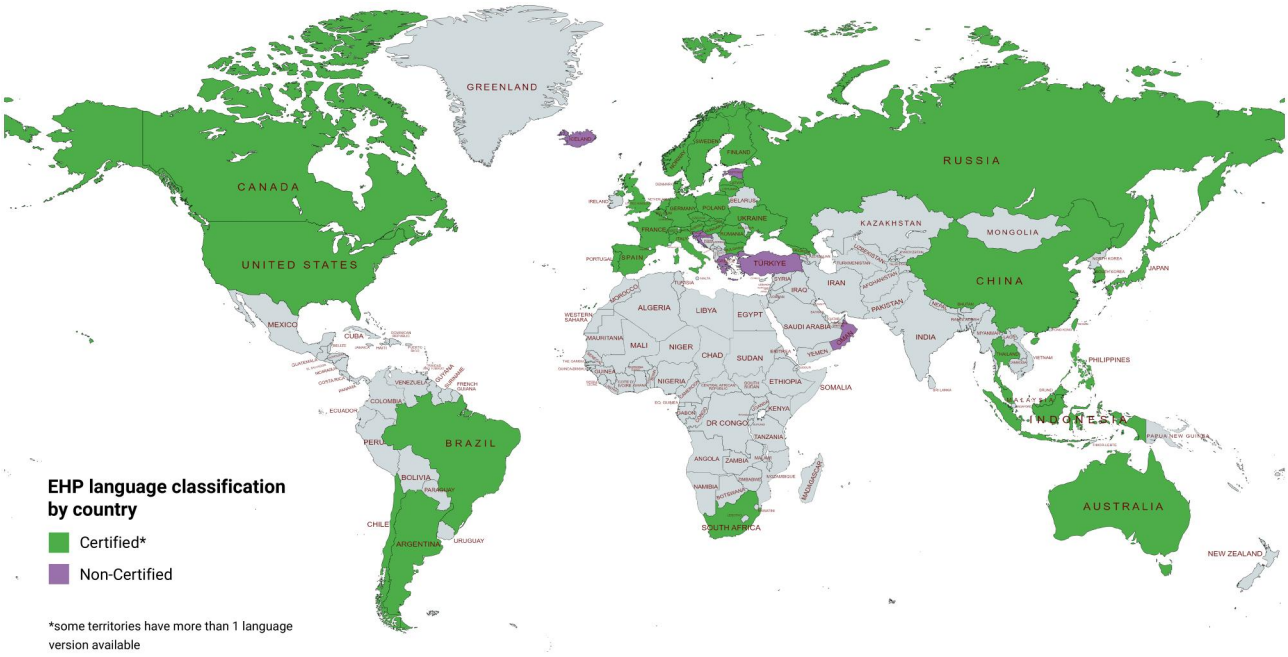


Figure 1. Endometriosis Health Profile language translation map. The Endometriosis Health Profiles (EHPs) have 56 certified language versions for use across the globe. Certified means the EHPs have been translated and linguistically validated in strict accordance with sector good practices.

- What is the methodological nature and quality of the studies?
- What interventions have been assessed and what are the patient-reported EHP outcomes?
- Can the EHP outcomes of these interventions be assessed by meta-analysis and, if so, what do the results show?

Methods

Protocol registration

The protocol for this systematic review was published on Prospero: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021226485.

Search strategy

Publications in all languages in electronic databases (MEDLINE, CINAHL, PsycINFO, PubMed, and Google Scholar) were searched between 2001 (when the EHP was first published) and 26 February 2020, using the search terms 'EHP30', 'EHP5', 'EHP-30', 'EHP-5', 'endometriosis health profile 30', and 'endometriosis health profile 5'. We re-ran the searches on 9 April 2021 to capture any papers published since the initial searches were conducted.

Inclusion and exclusion criteria

The review focuses on a wide range of interventions: surgical (e.g. hysterectomy and laparoscopy), medical (e.g. GnRH analogues, long-acting reversible contraceptives, and the combined oral contraceptive), educational (e.g. self-management interventions), and holistic (e.g. acupuncture, yoga).

We also included studies that have used the EHPs to undertake further psychometric testing, and cross-cultural translation and validation studies. All study types (quantitative, qualitative, and mixed methods) that included empirical EHP data were eligible for inclusion, including but not limited to randomised controlled trials (RCTs), cohort studies, case studies, cross-sectional studies, and qualitative studies. Studies that used the EHPs to measure outcomes in related conditions, such as CPP, were also included but analysed separately.

Literature reviews (e.g. systematic reviews) of the EHPs were recorded separately but were excluded. Studies that mentioned the EHPs but did not report any outcome data were excluded, as were manuscripts written in a foreign language, case reports, opinion pieces, editorials, comments, news, and letters.

Screening and quality assessment

RAYYAN—an online application that facilitates systematic review teams to undertake, organise, and manage screening of literature (Ouzzani *et al.*, 2016)—was used. Titles and abstracts were screened and assessed against the inclusion and exclusion criteria by F.T. Full texts were downloaded and inspected to assess if: the article met the inclusion criteria; or the inclusion/exclusion criteria could not be determined based on the title and abstract alone. If F.T. could not determine the inclusion/exclusion criteria of full text articles, then the team made the final decision after discussion.

Included articles were used to identify additional articles. A standardised data extraction form was created using a Microsoft Excel spreadsheet. The first reviewer read the full text of each included study and extracted the data using a standardised data extraction form; a second reviewer checked the details. A PRISMA flow-diagram to display the screening process was also produced (Fig. 2).

Areas of ambiguity that arose during the screening and data extraction process (e.g. uncertainty around eligibility) or that required further clarification (e.g. nature of the clinical intervention) were resolved in regular weekly meetings involving F.T., K.B., G.L.J., and S.H.K. when clinical endometriosis expertise was needed. Several authors (n = 7) of the included papers were contacted to seek clarity on unreported data or where additional details were needed.

All included studies were assessed for quality using the Mixed Methods Appraisal Tool (MMAT) by K.B. and were discussed during the team meetings if there was any uncertainty (Hong *et al.*,

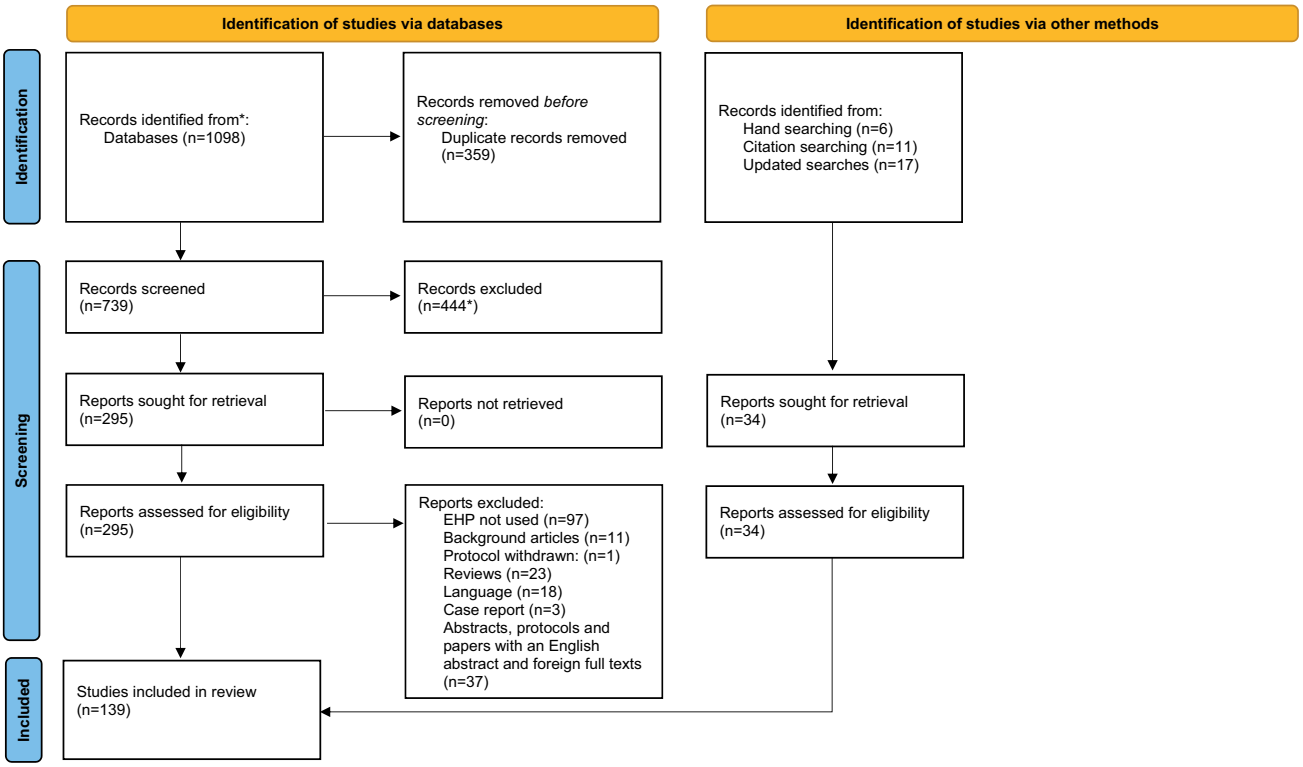


Figure 2. PRISMA flow chart of the selection of studies in a systematic review to determine the use of the Endometriosis Health Profiles to measure quality of life outcomes in women with endometriosis. *Two studies were screened out at the title stage but were later found to be eligible and were put back into the final sample. EHP, Endometriosis Health Profile.

2018). This tool allows most common types of study design and methodology to be appraised, incorporating different sections for each qualitative, quantitative, and mixed methods studies (Hong *et al.*, 2018). The MMAT asks two initial screening questions: whether there are clear research questions, and whether the data collected enable those questions to be answered? Full appraisal of the papers may not be appropriate if these criteria are not satisfied. Abstracts and protocols were not quality assessed. In addition, papers reporting findings of *post hoc* analyses were also not appraised since it is difficult to do so within MMAT, which largely asks questions about the original study design and sample. The MMAT requires the review team to agree on a cut-off value for acceptable complete outcome data and apply this uniformly across the included studies. We determined studies to have complete outcome data where there was a withdrawal/drop-out rate of up to 20% for studies of 12 months or less, or of up to 30% for studies of over 12 months (Dettori, 2011; Viswanathan and Berkman, 2012).

Data extraction and synthesis

Studies that met the inclusion criteria (n = 139) were examined comprehensively. Our standardised data extraction sheet included the categories shown in Tables 1, 2, and 3. We then undertook a narrative synthesis, pooling similar papers, which were described in textual form (Popay *et al.*, 2006; Aromataris and Pearson, 2014). A meta-analysis was not undertaken owing to the heterogeneity of the interventions and papers included.

Results

Study selection

A PRISMA flow diagram (Page *et al.*, 2021) is shown in Fig. 2. The initial database searches produced 1098 papers in total. After removing 359 duplicates, 444/739 (60.1%) papers were excluded at the title and abstract stage leaving 295 papers that were assessed for eligibility against the inclusion/exclusion criteria. A further 153 papers were excluded (Fig. 2), plus 37 abstracts, protocols, and texts with English abstracts but foreign full texts. A further 11 papers, identified from the excluded reviews, were included in the final synthesis. The updated searches (9 April 2021) identified 17 additional eligible papers and six identified by hand searching. One initially included paper was later retracted and therefore excluded (Mira *et al.*, 2015). Thus, in total, 139 papers were included in this review.

Descriptive summary of the studies

The EHPs were deployed most frequently to measure the outcomes of medical (n = 35) (Table 1) and surgical treatment (n = 21) (Table 2). The EHPs were also used in 13 studies to measure the outcomes of other interventions (Supplementary Table S1), in 29 non-interventional studies (Supplementary Table S2), and 32 psychometric/cross cultural validation studies (Tables 3, 4, and 5, and Supplementary Table S3). An additional six studies were diagnostic, and three deployed the EHPs in other related conditions, e.g. CPP and adenomyosis; their findings are not reported in the text but can be found in Supplementary Table S4.

Most studies used the EHP-30, either the core alone (n = 39) or core and all the modular components (n = 34). Seventeen studies used the EHP-30 in addition to specific modular components (e.g. alongside the sexual functioning or work modules). Thirteen studies opted to use specific modules only, without the core measure. Five studies used a modified version of the EHP-30, with a mix/rewording of items/domains taken from the core and modular sections. Seven studies used the EHP-5 (core component only), or core and modular components (n = 13). One study used a modified version of the EHP-5 core and modular sections. The

Table 1. Summary of studies that used the Endometriosis Health Profile in the context of a medical intervention.

Author and year	Country of research	Specific intervention	Study type	Sample size*	Sample mean/median age in years	Sample ethnicity (%)	Stage of endometriosis	EHP measure used	EHP data collection points reported
Medical interventions—GnRH agonists and antagonists									
(Ács *et al.*, 2015)	Bulgaria, Hungary, Poland, Romania, Russia, Ukraine	Elagolix, and Leuprorelin Acetate (LA), and placebo	RCT	174	31.7	White (100)	NR	EHP-5 core section	Baseline, 4, 8, 12, 16, 20, 24 weeks and follow-up.
(Agarwal *et al.* 2020)	Not stated but *post hoc* analysis	Elagolix vs placebo	RCT (*Post hoc* analysis of EM-I and EM-II trials)	1368	32.2	- White (88.4) - Black or African American (8.6) - Multirace (1.3) - Asian (1) - American Indian or Elaskan Native (0.4) - Native Hawaiian or other Pacific Islander (0.3) - Hispanic or Latino (14)	NR	EHP-30 core section and sex module	Original data collected at baseline, month 1, 3, 6, and every 3 months at follow-up.
(Al-Azemi *et al.*, 2009)	UK	Zoladex followed by HRT (tibolone 2.5 mg)	RCT	25 (14 = HRT group; 11 = placebo)	HRT = 34.8 Placebo = 35.9	NR	NR	EHP-30 core section	Baseline, 6, 18, 30 months
(Alshehre *et al.*, 2020)	UK	GnRHa (Triptorelin SR) with add-back therapy (ABT) using Tibolone	Single-arm open-label trial	27	33.35	NR	NR	EHP-30 core and modular sections.	Baseline, 6, 12, 18, 24, 30 months.
(Carr *et al.*, 2013)	USA	Elagolix vs placebo	RCT	137 (Placebo = 69; Elagolix = 68)	For both groups the median = 33years (21–47)	- White (Placebo = 82.62; Elagolix = 80.9) - Black (Placebo = 10.1; Elagolix = 8.8) - Hispanic (Placebo = 7.2; Elagolix = 7.4), - Other (Placebo = 0; Elagolix = 3)	I-IV	EHP-5 core section	Baseline, 8 and 24 weeks.
(Carr *et al.*, 2014)	USA	Elagolix vs subcutaneous depot medroxyprogesterone acetate (DMPA-SC)	RCT	252 (Elagolix 150 mg = 84; Elagolix 75 mg = 84; DMPA-SC = 84)	Elagolix 150 mg = 32.4; Elagolix 75 mg = 31.4; DMPA-SC = 31.6)	- Caucasian (Elagolix 150 mg = 81; Elagolix 75 mg = 83.3; DMPA-SC = 77.4) - African American (Elagolix 150 mg = 7.1; Elagolix 75 mg = 11.9; DMPA-SC = 11.9) - Hispanic (Elagolix 150 mg = 9.5; Elagolix 75 mg = 4.8; DMPA-SC = 7.1) - Other (Elagolix 150 mg = 2.4; Elagolix 75 mg = 0; DMPA-SC = 3.6)	I-IV	EHP-5 core section	Unclear Baseline and 24 weeks
(Diamond *et al.*, 2014)	USA	Elagolix vs placebo	RCT	155 (Placebo = 52; Elagolix 150 mg = 51 Elagolix 250 mg = 52)	Placebo = 31.2 Elagolix 150 mg = 30.9 Elagolix 250 mg = 31.0	- Caucasian (Placebo = 82.7; Elagolix 150 mg and 250 mg = 82.4 and 78.8) - Black (Placebo = 7.7; Elagolix 150 mg and 250 mg = 7.8 and 5.8) - Hispanic (Placebo = 5.8; Elagolix 150 mg and 250 mg = 7.8 and 11.5) - Other (Placebo = 3.8; Elagolix 150 mg and 250 mg = 2 and 3.8)	I-IV	EHP-5 core section	Baseline, 4, 8, 12, 16, 20, 24 and 30 weeks
(Donnez *et al.*, 2020)	USA, Europe	Linzagolix vs placebo	RCT	323 (Placebo = 53; 50 mg = 49;75 mgFD = 56; 75 mgTD = 58; 100 mg = 51;200 mg = 56)	Placebo = 32.4 50 mg = 30.9 75 mgFD = 32 75 mgTD = 31.2 100 mg = 33	- White (Placebo = 92.5; 50 mg = 95.9; 75 mgFD = 91.1; 75 mgTD = 86.2; 100 mg = 94.1; 200 mg = 94.6)	NR	EHP-30 core section	Baseline, 12, 24 weeks

(continued)

Table 1. Continued

Author and year	Country of research	Specific intervention	Study type	Sample size*	Sample mean/median age in years	Sample ethnicity (%)	Stage of endometriosis	EHP measure used	EHP data collection points reported
					200 mg = 30.9	- Black (Placebo = 7.5; 50 mg = 4.1; 75 mgFD = 10.7; 75 mgTD = 13.8; 100 mg = 7.8; 200 mg = 7.1) - Other (Placebo = 0; 50 mg = 2; 75 mgFD = 0; 75 mgTD = 0; 100 mg = 3.9; 200 mg = 1.8)			
(Leyland *et al.*, 2019)	Not stated but *post hoc* analysis	Elagolix vs placebo	RCT (*Post hoc* analysis of EM-I and EM-II trials)	1384 (no dyspareunia = 57; any dyspareunia = 1297)	All = 32.1 no dyspareunia = 32.3; any dyspareunia = 32.1	- White (All = 88; no dyspareunia 83.9; any dyspareunia = 83.8) - Black (All = 8.9; no dyspareunia 13.8; any dyspareunia = 8.6) - Other (All = 3.1; no dyspareunia 2.2; any dyspareunia = 3.2)	NR	EHP-30 sex module	Baseline, 1 month, 3 months, 6 months
(Osuga *et al.*, 2021)	Japan	Relugolix vs placebo or Leuprorelin	RCT	487 (Relugolix 10 mg = 103; 20 mg = 100; 40 mg = 103. Leuprorelin 3.75 mg = 82. Placebo = 99)	Relugolix 10 mg = 35.3; 20 mg= 35.1;40 mg- = 35.6. Leuprorelin = 36.1. Placebo = 35.7	NR	NR	EHP-30 core section	Baseline, week 12 12
(Pokrzywinski *et al.*, 2020c)	EM-I USA and Canada EM-II 5 continents (unspecified)	Elagolix vs placebo	RCT (*Post hoc* analysis of EM-I and EM-II trials)	1686 (EM-I = 871; EM-II = 815)	EM-I = 31.5 EM-II = 33.2	White (EM-I = 87.1, EM-II = 89.2)	NR	EHP-30 core section and sex module	Baseline, 1 month, 3 months, 6 months, 9, 12, 15, 18 months
(Surrey *et al.*, 2018)	USA, Puerto Rico, Canada	Elagolix vs placebo	RCT	569 (EM-III Elagolix 150 mg = 149; 200 mg = 138. EM-IV Elagolix 150 mg = 142; 200 mg = 140)	EM-III Elagolix 150 mg = 32; 200 mg = 31. EM-IV Elagolix 150 mg = 33 200 mg = 34	- White (EM-III Elagolix 150 mg = 89.3; 200 mg = 91.3. EM-IV Elagolix 150 mg = 89.4; 200 mg = 90) - Black (EM-III Elagolix 150 mg = 8.1; 200 mg = 6.5. EM-IV Elagolix 150 mg = 9.9; 200 mg = 8.6) - Other (EM-III Elagolix 150 mg = 2.7; 200 mg = 2.2. EM-IV Elagolix 150 mg = 0.7; 200 mg = 1.4)	NR	EHP-30 core section and sex module	Baseline, 12 months
(Taylor *et al.*, 2017)	EM-I USA and Canada EM-II 5 continents (unspecified)	Elagolix vs placebo	RCT	1686 (EM-I Placebo = 374; Elagolix 150 mg = 249; 200 mg = 248. EM-II Placebo = 360; Elagolix 150 mg = 226; 200 mg = 229)	EM-I Placebo = 31 Elagolix 150 mg = 32; 200 mg = 31. EM-II Placebo = 33 Elagolix 150 mg = 33; 200 mg = 34	- White (EM-I Placebo = 86.4; Elagolix 150 mg and 200 mg = 88.8 and 86.7. EM-II Placebo = 89.4; Elagolix 150 mg and 200 mg = 87.6 and 90.4.) - Black (EM-I Placebo = 8.8; Elagolix 150 mg and 200 mg = 7.6 and 9.7. EM-II Placebo = 8.1; Elagolix 150 mg and 200 mg = 11.1 and 7.9) - Other (EM-I Placebo = 4.8; Elagolix 150 mg and 200 mg = 3.6 and 3.6. EM-II Placebo = 2.5; Elagolix 150 mg and 200 mg = 1.3 and 1.7)	NR	EHP-30 core section and sex module	Baseline, 1 month, 3 months, 6 months
(Taylor *et al.*, 2020)	Not stated but *post hoc* analysis	Elagolix vs placebo	RCT (*Post hoc* analysis of EM-I and EM-II trials)	1686 (Placebo = 734; Elagolix 150 mg = 475; 200 mg = 477)	Placebo = 32.4; Elagolix 150 mg = 32.3; 200 mg = 32.3)	- White (Placebo = 87.9; Elagolix 150 mg and 200 mg = 88.2 and 88.5). - Black (Placebo = 8.4; Elagolix 150 mg and 200 mg = 9.3 and 8.8).	NR	EHP-30 core section and sex module	Baseline, 1 month, 3 months, 6 months

(continued)

Table 1. Continued

Author and year	Country of research	Specific intervention	Study type	Sample size*	Sample mean/median age in years	Sample ethnicity (%)	Stage of endometriosis	EHP measure used	EHP data collection points reported
						- Other (Placebo = 3.7; Elagolix 150 mg and 200 mg = 2.5 and 2.7)			
				Medical interventions—GnRH with contraceptive					
(Crosignani *et al.*, 2006)	Europe, Asia, Latin America (countries not specified) and New Zealand	Injectable contraception (DMPA-SC) vs Leuprolide	RCT	299 (DMPA-SC = 153; Leuprolide = 146)	DMPA-SC = 31.8; Leuprolide = 30.9	- White (DMPA-SC = 56.2; Leuprolide = 64.4) - Black (DMPA-SC = 2.0; Leuprolide = 4.1) - Asian/Pacific Islander (DMPA-SC = 17.6; Leuprolide = 5.5) - Mixed/multiracial (DMPA-SC = 24.2; Leuprolide = 26.0)	NR	EHP-30 core section and sex module	Baseline, 6, and 18 months
(Granese *et al.*, 2015)	Italy	Dienogest and Estradiol Valerate (E2V) vs Leuprorelin Acetate (LA)	RCT	78 (E2V = 39; LA = 39)	E2V = 31.2; LA = 30.5	NR	I-IV	Unclear-EHP-5 used but it's not clear what sections	Baseline, 9 months
(Schlaff *et al.*, 2006)	USA, Canada	Injectable contraceptive (DMPA-SC) vs Leuprorelin Acetate	RCT	274 (DMPA-SC = 136; LA = 138)	DMPA-SC = 29.2; LA = 32.1.	- White (DMPA-SC = 90.4; LA = 82.6) - Black (DMPA-SC = 7.4; LA = 10.9) - Asian or Pacific Islander (DMPA-SC = 0.7; LA = 0.7) - Mixed or multiracial (DMPA-SC = 1.5; LA = 5.8)	NR	EHP-30 core section and sex module	Baseline, 6, 18 months
				Medical interventions—hormonal contraceptive					
(Barra *et al.*, 2020)	Italy	Dienogest (DNG)	Cohort study	83	32.8	NR	NR.	EHP-30 core section	Baseline, 6, 12, 24, 36 months
(Carvalho *et al.*, 2018)	Brazil	Etonogestrel (ENG)-releasing contraceptive implant vs Levonorgestrel-releasing intrauterine system (LNG-IUS)	RCT	103 (ENG = 51; LNG-IUS = 52)	ENG = 33.4 LNG-IUS = 34.7	- White (ENG = 80.8; LNG-IUS = 76.5) - Other (ENG = 19.2; LNG-IUS = 23.5)	I-IV	EHP-30 core and modular sections	Baseline, 6 months
(Ebert *et al.*, 2017)	Germany, Austria, France, Finland, Czech Republic, Spain	Dienogest (DNG)	Open-label single-arm study	111	15.4	- White (94.6) - Black/African American (0.9) - NR (4.5)	NR	EHP-30 core section	Baseline, 12, 24, 52 weeks
(Egekvist *et al.*, 2019)	Denmark	Oral contraceptives, oral gestagens, and/or the levonorgestrel-releasing intrauterine device (LNG-IUS)	Cohort study	80	38.6	NR	NR	EHP-30 core section	Baseline, 6, 12 months
(Ferrero *et al.*, 2020)	Italy	Etonogestrel (ENG)-releasing implant	Cohort study	43	32.8	White (83.7), Other (16.3)	NR	EHP-30 core section	Baseline, 6 months, 12 months, 24 months
(Flores *et al.*, 2015)	Mexico	Levonorgestrel-releasing intrauterine system (LNG-IUS)	Open non-comparative study	29	31.7	NR	II-IV	Modified version of the EHP-30	Baseline, 6 months
(Middleton *et al.*, 2017)	UK	Injectable contraceptive (DMPA) vs Levonorgestrel-releasing intrauterine system (LNG-IUS)	RCT pilot	77	31	- White British (86) - Black/Black British Caribbean (3) -Asian/Asian British Indian (4) - Asian/Asian British Pakistani (1) - Mixed White/ Black Caribbean (3) - Mixed White/Asian (1)	I-IV	EHP-30 pain module only	Unclear

(continued)

Table 1. Continued

Author and year	Country of research	Specific intervention	Study type	Sample size*	Sample mean/median age in years	Sample ethnicity (%)	Stage of endometriosis	EHP measure used	EHP data collection points reported
						- Other mixed background (1)			
(Morotti *et al.*, 2014)	Italy	Dienogest (DNG)	Pilot open-label single-arm trial	25	33.4	NR	NR	EHP-30 core section	Baseline, 6 months
(Scala *et al.*, 2018)	Italy	Norethindrone Acetate (NETA) vs Oral contraception (OC)	Open label comparative study	NETA = 50 OC = 50	NETA = 32.5 OC = 33.1	- Caucasian (NETA = 80; OC = 76) - Afro-Caribbean (NETA = 16; OC = 18) - Asian (NETA = 4; OC = 6)	NR	EHP-30 core section	Baseline, 12 months
(Taniguchi *et al.*, 2020)	Japan	Tokishakuyakusan add-on therapy with low-dose oral contraceptive pills	Open-label single-arm trial	9	31.4	NR	NR	EHP-30 core section	Baseline, following 3 menstrual cycles
(Techatraisak *et al.*, 2019)	Thailand Indonesia Republic of Korea Malaysia Philippines Singapore	Dienogest (DNG)	Cohort study	865	34.4	Asian (100)	I-IV	EHP-30 core and modular sections	Baseline, 6 months
(Yela, 2020)	Brazil	Progestin	Cross-sectional study	58	37.2	- White (75.86), - Non-White (24.14)	NR	EHP-30 core and modular sections	N/A
(Yong, 2020)	Canada	Combined hormonal contraceptive (CHC)	Cross-sectional study	373** (-Cyclic CHC ineffective Yes/No = 103/125 discontinued Yes/No = 94/134. - Continuous CHC ineffective Yes/No = 67/108 discontinued Yes/No = 59/116)	Cyclic CHC ineffective Yes = 31.7/No = 34.5 discontinued Yes = 34.1/No = 32.6 Continuous CHC ineffective Yes = 30/No = 33.8 discontinued Yes = 33.3/No = 31.9	NR	I-IV	EHP-30 pain module	N/A
Other medical interventions									
(Ekin *et al.*, 2021)	Turkey	New Cross linked Hyaluronan Gel (NCH gel) vs sterile saline solution	Pilot RCT	60 (NCH gel = 30 Control = 30)	NCH gel = 34.36 Control = 36.43	NR	NR	EHP-5 core and modular sections	Baseline, 3, 6 months
(Khodaverdi *et al.*, 2021)	Iran	Superior Hypogastric Plexus (SHP) block	Open-label pilot trial	16	33	NR	IV	EHP-5 core and modular sections	Baseline, 1, 4, 12, 24 weeks
(Mathiasen *et al.*, 2019)	Denmark	Assisted reproductive technologies (ART)	Cohort study	154 (-Endometriosis undergoing ART Yes/No = 52/50 -Without endometriosis undergoing ART = 52)	Endometriosis undergoing ART Yes = 32.4/No = 32.7 Without endometriosis undergoing ART = 33.1	NR	NR	EHP-30 core section	Baseline, 28–40 days

(continued)

Table 1. Continued

Author and year	Country of research	Specific intervention	Study type	Sample size*	Sample mean/median age in years	Sample ethnicity (%)	Stage of endometriosis	EHP measure used	EHP data collection points reported
(Van der Houwen, 2014)	Netherlands	Assisted reproductive technologies	Cohort study	75 (IUI = 25; IVF = 25; IVF-Long = 25)	IUI = 32; IVF = 34; IVF-Long = 34	- Caucasian (IUI = 64; IVF = 76; IVF-Long = 80) - Asian (IUI = 12; IVF = 20; IVF-Long = 12) - Mediterranean (IUI = 8; IVF = 4; IVF-Long = 0) - Creole (IUI = 4; IVF = 0; IVF-Long = 4) - Hindu (IUI = 8; IVF = 0; IVF-Long = 4) - Other (IUI = 4; IVF = 0; IVF-Long = 0)	III-IV	EHP-30 core and modular sections	Baseline, 29 days
(Wickström *et al.*, 2013)	Sweden	Lidocaine vs placebo	RCT	42 (Lidocaine = 24; placebo = 18)	(Lidocaine = 33.08; placebo = 33.4)	NR	NR	EHP-30 core section and sex module	Baseline, 6, 12 months

* For consistency, we have cited the sample size upon which age and ethnicity were calculated.
** The women were allocated to more than one group.
NR, not reported; RCT, randomised controlled trial; EHP, Endometriosis Health Profile.

Table 2. Summary of studies that used the Endometriosis Health Profile in the context of a surgical intervention.

Author and year	Country	Specific intervention	Study type	Sample size*	Sample mean/median age in years	Sample ethnicity	Stage of endometriosis	EHP measure used	EHP data collection points
				Hysterectomy					
(De la Hera-Lazaro *et al.*, 2016)	Spain	Hysterectomy, one/two-sided adnexectomy bowel resection, rectum-vaginal nodule resection, bladder resection, vaginal resection	Non-randomised interventional study	46	38.6	NR	IV	EHP-5 core and modular sections	Baseline, 6 months
(Kent *et al.*, 2016)	UK	Laparoscopic surgery	Cohort study	137	36.7	NR	IV	EHP-30 core and modular sections	Baseline, 2 months, 6 months, 12 months
(Sandström *et al.*, 2020)	Sweden	Hysterectomy	Cross-sectional study	137	41	NR	Not staged-IV	EHP-30 core section	37–107 months
(Tan *et al.*, 2013)	UK	Abdominal hysterectomy and bilateral salpingo-oophorectomy	Cohort study	16	38.1	NR	I-IV	EHP-30 core and modular sections	Baseline, 3 months
				Laparoscopic Surgery					
(Barton-Smith, 2010)	UK	Harmonic scalpel excision vs carbon dioxide laser vaporisation	RCT	133 (Excised=66; Vaporised=67)	Excised=33.05 Vaporised=32.74 but on n=66)	NR	I-III	EHP-30 core and sex module	Baseline, 3, 6, 12 months
(Delbos *et al.*, 2018)	France	Simple shaving, shaving exclusively/in part by plasma vaporisation (plasma), or resection.	Cross sectional study	52 (Simple shaving=22 Plasma=13 Resection=17)	Simple shaving=33 Plasma=32 Resection=35	NR	NR	EHP-5 core and modular sections	Collected twice during one interview
(Ekine *et al.*, 2020)	Hungary	Laparoscopic excision	Cohort study	87	34.2	NR	I-IV	Unclear -EHP-36 and modules are unfamiliar.	Baseline, 6, 12, 24 months.
(Gallicchio *et al.*, 2015)	USA	White light imaging+narrow band imaging (WL/NBI) vs white light imaging only (WL/WL)	RCT	148 (WL/NBI=110; WL/WL=38).	WL/NBI=33.2; WL/WL=30.6).	- White (WL/NBI=71.8; WL/WL=76.3) - African American (WL/NBI=18.2; WL/WL=18.4) - Hispanic (WL/NBI=5.5; WL/WL=2.6) - Other (WL/NBI=4.5; WL/WL=2.6)	I-IV	EHP-30 core section	Baseline, 3, 6 months.
(Ghai *et al.*, 2020)	UK	Conservative and radical surgery	RCT (*Post hoc* analysis of two trials)	198 (102 superficial; 96 recto-vaginal endometriosis).	Superficial=NR Recto-Vaginal=37	NR	NR	EHP-30 core and modular sections	Baseline and 12-month post-surgery.

(continued)

Table 2. Continued

Author and year	Country	Specific intervention	Study type	Sample size*	Sample mean/median age in years	Sample ethnicity	Stage of endometriosis	EHP measure used	EHP data collection points
(Meuleman *et al.*, 2009)	Belgium	Laparoscopic excision	Cohort study	56	32	NR	II-IV	EHP-30 core section	Baseline, median follow-up was 29 months (range 6–76 months)
(Meuleman *et al.*, 2011)	Belgium	Bowel resection and reanastomosis at the end of a CO_2 laser laparoscopic radical excision of endometriosis	Cohort study	45	30	NR	III-IV	EHP-30 core section	Baseline, median follow up of 27 months (range: 16–40) months
(Meuleman *et al.*, 2014)	Belgium	Laparoscopic excision of moderate-severe endometriosis in women with and without bowel resection and reanastomosis.	Cohort study	203 (Study group=76; Control=127).	(Study group=32.9 and Control=32.1)	NR	III-IV	EHP-30 core and modular sections	Baseline, 6, 12, 18, 24 months
(Minas and Dada, 2014)	UK	Laparoscopic ablation with and without excision	Cross-sectional study	49	NR	NR	I-IV	EHP-5 core and modular sections	Collected twice post-surgery to ask about pre-and-post-QoL outcomes
(Misra *et al.*, 2020)	UK	Laparoscopic treatment with electrodiathermy vs helium thermal coagulator	RCT	192 (Diathermy=96; Helium=96)	Diathermy=28.9 Helium=29.03	NR	I-III	EHP-30 core section	6, 12, and 36 weeks
(Protopapas *et al.*, 2014)	Greece	Laparoscopic excision	Cohort Study	36	29.2	NR	I-IV	EHP-30—unclear which sections	Baseline, 6, 12, 18, 24 months
(Rindos *et al.*, 2020)	USA	Laparoscopic excision	Cohort Study	46	32.5	- Caucasian (96) - African American (4)	I-IV	EHP-30 core section	Baseline, 1 month, and 2.6- to 6.8-year post-surgery
(Soto *et al.*, 2017)	USA	Laparoscopy (Lap) vs robotic surgery (RS)	RCT	73 (RS=35; Lap=38)	RS=34.3 Lap=34.3	- White/Caucasian (RS=64.7; Lap=76.3) - Hispanic (RS=23.5; Lap=13.2) - Black/African American (RS=5.9; Lap=5.3) - Asian/Pacific Islander (RS=0; Lap=5.3) - Other (RS=5.9; Lap=0)	I-IV	EHP-30 core and modular sections	Baseline, 6 weeks, 6 months

(continued)

Table 2. Continued

Author and year	Country	Specific intervention	Study type	Sample size*	Sample mean/median age in years	Sample ethnicity	Stage of endometriosis	EHP measure used	EHP data collection points
(Tiringer *et al.*, 2020)	Austria	Laparoscopic excision	Cohort study	115	32	NR	NR	EHP-30 core section	Baseline, and 6–10 weeks post-operatively.
(Turco *et al.*, 2020)	Unclear—Italy	Segmental colorectal resection	Cohort study	50	38	NR	III-IV	EHP-30 core and modular sections	Baseline, median follow-up 42.5 months (range 12–157 months)
(Yong *et al.*, 2018)	Canada	Minimally invasive surgery including excision (and other interdisciplinary treatments)	Cohort study	497 (1-year follow-up=278; Lost to follow-up=219)	All=34 1-year follow-up=35 Lost to follow-up=33	NR	I-IV	EHP-30 sex module only	Baseline, 12 months
Medical and surgical interventions									
(Vercellini *et al.*, 2013)	Italy	Second-line conservative surgery (Surgery) at laparoscopy or low-dose progestin treatment (Progestin)	Cohort study	154 (Progestin=103 Surgery=51)	Progestin <30/30+=17/86. Surgery <30/30+=8/43	NR	III-IV	EHP-30 core and modular sections	Baseline, 3, 6, and 12 months

* For consistency, we have cited the sample size upon which age and ethnicity were calculated.
RCT, randomised controlled trial; NR, not reported; EHP, Endometriosis Health Profile.

remaining studies did not clearly report either the EHP measures or domains used (n = 10). Some used the EHPs without the 'not applicable' box for the modular components (Fauconnier *et al.*, 2017).

A cohort study was the most common design for evaluating the impact of a surgical intervention (n = 12), while an RCT was the most used design for medical interventions (n = 20), including two pilot studies and four *post hoc* analyses. The locations where the research was undertaken are shown in Tables 1, 2, and 3 and Supplementary Tables S1, S2, and S4.

In terms of demographic characteristics, 90/139 studies did not report participants' race/ethnicity. Of those that did, 10 simply reported the percentage of 'White' or 'Caucasian' participants: plus 'others' (n = 6), or no information on the remainder (n = 4). Three studies reported including a wholly 'White' (n = 1), 'Asian' (n = 1), or European' (n = 1) sample. Thirty-two studies included a mix of 'White', 'Black', and/or minority ethnic women. One study reported the percentage of 'Black' versus 'non-Black' participants, another Han versus non-Han participants and two more White versus non-White. Finally, the study by Cosma and Benedetto (2020) compared and mapped guidelines on the diagnosis and treatment of endometriosis to develop an algorithm of the endometriosis care pathway; thus, no participants were recruited.

Quality appraisal

Of the 139 studies, 15 were not fully appraised because their design was not MMAT compatible (review, n = 1; review of guidelines to develop a diagnostic/classification system, n = 1; analysis of data previously collected, n = 13). An additional paper was similarly not fully appraised as the research aims were unclear and at odds with the data collection and analysis carried out. Of the 123 fully appraised studies, 90 (73.2%) were of high quality (4–5 criteria satisfied); 29 moderate quality (2–3 criteria satisfied), and four low quality (0–1 criteria satisfied).

What do the EHPs tell us about the impact of medical treatments for endometriosis?

Table 1 shows the impact on HRQoL of medical interventions: GnRH agonists and antagonists (n = 14), GnRH agonists with contraceptives (n = 3), hormonal contraceptives only (n = 13), and other types of medical intervention, for example perturbation with lidocaine (n = 5).

GnRH agonists and antagonists

Three RCTs (Al-Azemi *et al.*, 2009; Donnez *et al.*, 2020; Osuga *et al.*, 2021) and one single-arm open-label trial (Alshehre *et al.*, 2020) were conducted to treat endometriosis-associated pain and/or HRQoL. All four reported improved pain and/or HRQoL following treatment; two (Al-Azemi *et al.*, 2009; Alshehre *et al.*, 2020) found deterioration after treatment cessation.

Most of the studies assessed the efficacy of elagolix in treating endometriosis-associated moderate-to-severe pain. Four Phase II trials using the EHP-5 (Carr *et al.*, 2013, 2014; Diamond *et al.*, 2014; Ács *et al.*, 2015) demonstrated improved HRQoL in all patients that was greatest for those in the elagolix arms. Two subsequent Phase II studies using the EHP-30, plus the modular sexual functioning domain (EM-I and EM-II) (as reported in Taylor *et al.* (2017)), demonstrated significantly improved scores after treatment, although some improvements were dose dependent and differed during follow-up. We refer the reader to the comprehensive review of the EM-I and EM-II trials, including the EHP-30 outcomes (Archer *et al.*, 2020) for further in-depth results and information about the comparators in each study.

There have been two extension studies (EM-III and EM-IV), both using the EHP-30 plus the sexual functioning domain (Surrey *et al.*, 2018), and four *post hoc* studies (Leyland *et al.*, 2019; Agarwal *et al.*, 2020; Pokrzywinski *et al.*, 2020c; Taylor *et al.*, 2020). In the extension studies, there was overall improvement from baseline in HRQoL following 12 months of treatment in both dose groups. Three *post hoc* studies pooled data from EM-I and EM-II to explore whether women with moderate-severe endometriosis-associated pain, randomised to elagolix 150 mg od or 200 mg bd, showed greater clinical and HRQoL improvement compared to placebo (Agarwal *et al.*, 2020; Pokrzywinski *et al.*, 2020c; Taylor *et al.*, 2020). EHP scores improved significantly in women whose dyspareunia (Agarwal *et al.*, 2020) and dysmenorrhoea and non-menstrual pelvic pain (Pokrzywinski *et al.*, 2020c) also improved. Taylor *et al.* (2020) similarly found that treatment was associated in a dose-dependent manner with greater improvements in HRQoL compared with placebo. Leyland *et al.* (2019) pooled EM-I and EM-II data to evaluate the effects of elagolix on endometriosis-associated dyspareunia. Using the EHP-30 sexual functioning domain, they concluded that up to 6 months of treatment improved dyspareunia in a dose-dependent manner.

GnRH agonists with contraceptives

Crosignani *et al.* (2006) and Schlaff *et al.* (2006) found that depot medroxyprogesterone acetate (DMPA-SC 104) reduced endometriosis-associated pain as effectively as leuprolide, but with more bleeding. Granese *et al.* (2015) reported that dienogest plus estradiol valerate and leuprorelin acetate seemed equally efficacious in preventing endometriosis-associated CPP recurrence in the first 9 months after treatment.

Hormonal contraceptives only

Thirteen studies (Table 1) used the EHP-30 to appraise a range of contraceptives including intrauterine devices (levonorgestrel-releasing intrauterine system: LNG-IUS), subdermal implants (etonogestrel (ENG)-releasing contraceptive implant), injectable contraceptives (DMPA), and oral contraceptives (e.g. dienogest, norethindrone acetate: NETA).

Results from two RCTs (Middleton *et al.*, 2017; Carvalho *et al.*, 2018), three open-label single-arm trials (Morotti *et al.*, 2014; Ebert *et al.*, 2017; Taniguchi *et al.*, 2020), one open non-comparative study (Flores *et al.*, 2015), and one open-label comparative study (Scala *et al.*, 2018) demonstrated improvements in all or some of the EHP-30 domains following treatment. However, one study did not calculate domain scores but indicated an increase in the proportion of women selecting 'never' in response to the questions (Ebert *et al.*, 2017). A single-arm pilot trial (Taniguchi *et al.*, 2020) assessed Tokishakuyakusan—a Japanese Kampo medicine—as an add-on therapy to hormonal contraceptives: participants reported some improvement in symptoms and some aspects of HRQoL, which did not reach statistical significance.

Four cohort studies demonstrated improvements in HRQoL with hormonal contraceptives. Barra *et al.* (2020) found significant improvements in EHP-30 scores (with the exception of the self-image and control and powerlessness domains) after 6 months of treatment. Scores further improved at 12 months and stabilised at 24 and 36 months. Ferrero *et al.* (2020) reported improvements in all EHP-30 core domains following 6 months of treatment, with further improvements limited to the pain domain at 12 months and the emotional well-being domain at 24 months. Egekvist *et al.* (2019) found a non-significant improvement in HRQoL across a 12-month follow-up period. In an interim analysis, Techatraisak *et al.* (2019) observed improvements

in EHP-30 core and modular domains 6 months after treatment, especially for pain outcomes.

There were two cross-sectional studies. Despite some inconsistencies in the manuscript and incorrect domain labelling, Yela et al. (2020) reported worse HRQoL in the sexual functioning, emotional well-being, infertility, and social support domains in women treated for deeply infiltrating endometriosis (DIE). Yong et al. (2020) found that women who used combined oral contraception continually (as opposed to cyclically) and discontinued treatment owing to side-effects had poorer HRQoL.

Other medical interventions

Five studies tested the effectiveness of other medical interventions using the EHP (Table 1). Using the EHP-30, Wickström et al. (2013) found, in an RCT of perturbation with lidocaine (local anaesthetic) versus placebo, that only social support had significantly improved for the treatment group at 6 months, which disappeared by 12 months.

Using the EHP-5, significant improvements in HRQoL were observed following superior hypogastric plexus block for endometriosis-associated CPP (Khodaverdi et al., 2021) and New Cross linked Hyaluronan Gel (NCH gel) after laparoscopic surgery for DIE (Ekin et al., 2021). However, in Ekin et al. (2021), it is unclear how the EHP-5 was analysed and whether the results refer to the core or modular components or both.

Two studies used the EHP-30 to assess the effects of ART. Owing to limited sample sizes, van der Houwen et al. (2014) only provided a descriptive analysis of the domain scores pre- and post-ART. Mathiasen (2019) showed that controlled ovarian stimulation during ART did not worsen HRQoL.

What do the EHPs tell us about the impact of surgical treatments for endometriosis?

A range of radical and conservative surgical outcomes have been measured using the EHPs (Table 2). Following hysterectomy, three studies used the EHP-30 (Tan et al., 2013; Kent et al., 2016; Sandström et al., 2020) and one the EHP-5 (De la Hera-Lazaro et al., 2016). Overall, they demonstrated an improvement in HRQoL, although infertility concerns may persist (Tan et al., 2013; Kent et al., 2016) (Table 2). Interestingly, Kent et al. (2016) observed that hysterectomy plus bilateral salpingo-oophorectomy provided significantly better HRQoL at 12 months compared to conservative surgery on all EHP-30 domains scores ($P < 0.05$) with the exception of the modular domains, relationship with children, sex, and feelings about the medical profession ($P > 0.05$).

Laparoscopic surgery

Sixteen papers used the EHPs to measure HRQoL following laparoscopic surgery, i.e. excision, ablation, vaporisation, resection, or shaving (Table 2). Two retrospective cohort studies, both by the same authors, reported improved HRQoL after laparoscopic surgery for DIE with colorectal extension (Meuleman et al., 2009, 2011). However, it is unclear which questionnaire was used as the scales relating to general health, physical health, and quality of professional life are not EHP domains. In a later prospective study, Meuleman et al. (2014) comparing women with and without bowel resection and reanastomosis, all EHP-30 domains 6 months after surgery (except the relationship with children domain, which was not analysed because of small numbers) showed significant improvement, although after 12 months no further improvement was observed.

Among the other 13 studies (Table 2), Protopapas et al. (2014) stated their patients completed the EHP-30 but did not report the pre- or post-surgery scores. In the Ekine et al. (2020) study, it is unclear which measure was used as they referred to the EHP-36 and the description of its content did not clearly match the current EHP domain structure (i.e. it measures demographics, physical, mental, and socioeconomic well-being). All other laparoscopic surgery resulted in HRQoL improvements from baseline in EHP-30 domains (Barton-Smith, 2010; Gallicchio et al., 2015; Soto et al., 2017; Yong et al., 2018; Ghai et al., 2020; Misra et al., 2020; Rindos et al., 2020; Tiringer et al., 2020; Turco et al., 2020) and the EHP-5 (Minas and Dada, 2014; Delbos et al., 2018).

Surgical versus medical interventions

Only one relevant study was found: second-line laparoscopic excision versus low-dose progestin for severe endometriosis-associated deep dyspareunia (Vercellini et al., 2013) (Table 2). At baseline and 3-month follow-up, women treated medically had significantly worse EHP-30 scores than those treated surgically. The surgical group experienced a rapid improvement in HRQoL; however, this declined over time whereas the medical treatment group continued slowly to improve. Consequently, at 12 months all EHP scores had improved for both groups.

What do the EHPs tell us about the impact of other interventions for endometriosis?

Eleven studies used the EHP-30 and two studies the EHP-5 to measure HRQoL following a variety of interventions (Supplementary Table S1): ultrasound therapy (Philip et al., 2020), transcutaneous electrical nerve stimulation (Mira et al., 2020); laser therapy (Thabet and Alshehri, 2018); repetitive transcranial magnetic stimulation (Pinot-Monange et al., 2019); mindfulness (Kold et al., 2012; Hansen et al., 2017); yoga (Gonçalves et al., 2017); acupuncture (Wayne, 2008; Ahn et al., 2009; de Sousa et al., 2016); Chinese herbal medicine (Flower et al., 2011), and educational interventions (Sayed and Aboud, 2018; Simonsen et al., 2020).

What do the EHPs tell us about the impact of endometriosis upon women's quality of life?

Twenty-nine non-interventional studies used the EHP-30 (n = 26) or EHP-5 (n = 3) to explore the impact of endometriosis upon sexual functioning (n = 5) (Shum et al., 2018; Bao et al., 2019; van Poll et al., 2020; Wahl et al., 2020; Martins et al., 2022); psychological well-being (n = 6) (Friedl et al., 2015; Rush and Misajon, 2018; van Aken et al., 2018; González-Echevarría et al., 2019; Roomaney et al., 2020; Škegro et al., 2021); work/productivity (n = 2) (Fourquet et al., 2011; Hansen et al., 2013); pain (n = 5) (Hansen et al., 2014; Stratton et al., 2015; van Aken et al., 2017; de Freitas Fonseca et al., 2018; McPeak et al., 2018); general HRQoL (n = 7) (Matasariu et al., 2017; Soliman et al., 2017, 2020; Verket et al., 2018; Florentino et al., 2019; Ali Nor et al., 2020; Mundo-López et al., 2020); sleep (n = 2) (Leone Roberti Maggiore et al., 2017; Arion et al., 2020), and quality of care (n = 2) (Apers et al., 2018; Ng et al., 2020) (Supplementary Table S2).

Despite the heterogeneity of these studies, some interesting findings emerged. For example, there was some evidence that younger women report poorer HRQoL than older women; that perceptions of medical care are related to psychological well-being and some treatment outcomes, and that symptoms impact functioning at work. The studies also identified factors contributing to poorer HRQoL, such as fatigue or poorer quality of sleep, higher levels of pain, endometriosis severity, greater number of symptoms or symptom severity, and poorer psychological health.

What do we know about the psychometric properties of the EHPs?

Thirty-two studies performed psychometric/cross cultural validation of the EHPs (Table 3). Supplementary Table S3 shows the results of the psychometric tests, and the findings from the responsiveness and/or minimally important difference (MID) analyses are reported separately in Tables 4 and 5.

Cross-cultural adaptation and validation

Four papers from our group concluded that the EHP-30 was reliable, valid, and sensitive to change, and both acceptable and understandable to respondents (Jones *et al.*, 2001, 2004a,b,c, 2006). Nineteen other studies have cross-culturally adapted and validated the EHP in French (Aubry *et al.*, 2017; Chauvet *et al.*, 2017, 2018; Fauconnier *et al.*, 2017); Iranian/Persian (Goshtasebi *et al.*, 2011; Nojomi *et al.*, 2011); Swedish (Wickström *et al.*, 2017; Grundström *et al.*, 2020a,b); Chinese (Jia *et al.*, 2013); Australian English (Khong *et al.*, 2010); Spanish (Marí-Alexandre *et al.*, 2022); Italian (Maiorana *et al.*, 2012); Turkish (Selcuk *et al.*, 2015); Dutch (van de Burgt *et al.*, 2011, 2013); Norwegian (Verket *et al.*, 2018); Portuguese (Nogueira-Silva *et al.*, 2015), and US American (Jenkinson *et al.*, 2008). However, only seven of these related to the EHP-5 (Table 3 and Supplementary Table S3). The EHP-5 has also been translated into Croatian, but validation of the tool was underway at the time of publication (Škegro *et al.*, 2021).

The findings overall supported the psychometric validity of the measures in these languages; however, some recommendations for improvement have been made. For example, Grundström *et al.* (2020a) suggested one question in the Swedish version should be reworded. Maiorana (2012) observed that four items in the Italian version may have been improperly translated making it difficult to differentiate between 'rarely' and 'sometimes'. They also criticised the internal consistency reliability of two domains, social support and self-image, but these achieved alpha values of 0.84 and 0.69 and it appears as though some items may not have been correctly allocated to the pain (n = 7) and control and powerlessness (n = 10) subscales in their analyses, as these should be n = 11 and n = 6, respectively.

Chauvet *et al.* (2018) suggested the French EHP-30 may not capture all relevant issues for women living in France. Some of the issues raised as missing from the EHP (e.g. fatigue) were included during EHP development (Jones *et al.*, 2004b) but were later removed following psychometric testing. Other issues, such as 'thanks' and 'advice', were also identified by Chauvet *et al.* (2018) as missing from the EHP but it is not clear to what extent these would impact upon HRQoL and/or improve the tools.

Dimensionality

To date (with the exception of the study by Maiorana *et al.*, 2012), only classical test theory has been used to explore dimensionality of the EHPs. In some EHP-30 studies, an overall total of the core and/or modular scores was reported; in others, just the domain scores. Most studies included in this review supported the five-factor structure and multi-dimensionality of the EHP-30 core. However, Grundström *et al.* (2020b) proposed four factors with the domains 'social support' and 'self-image' loading together. In the Norwegian version, the results of the factor analysis undertaken by Verket *et al.* (2018) revealed similar findings and, in particular, a lack of validity of the 'self-image' domain. The original structure of the EHP-30 was partially confirmed in another study as factor 5 could not be entirely classified as independent, and the subscale 'pain', which mainly corresponds to factor 1, was also related to other domains, for example 'control and powerlessness' (Marí-Alexandre *et al.*, 2022). The unidimensionality of the EHP-30 core has been demonstrated, supporting the production of a summary score using classical test theory (Jones, 2001; Jenkinson *et al.*, 2008; Nojomi *et al.*, 2011; Nogueira-Silva *et al.*, 2015) but was not when Rasch analysis was undertaken on the Italian EHP-30 core part. A summary score for the EHP-5 is supported by Fauconnier *et al.* (2017) reporting that the 11 EHP-5 items were also unidimensional, although the 'not relevant' boxes were removed during this analysis. Supplementary Table S3 provides further details on rates of data completion and item response distributions (e.g. floor and ceiling effects).

Reliability

All 17 studies that measured the internal consistency reliability of the tools reported Cronbach alpha values >0.7 (except in the study by Maiorana *et al.*, 2012, where self-image was 0.69). Of the six papers that assessed test–retest reliability, three reported intraclass correlation coefficients (ICC) or Spearman's rho correlations exceeding 0.8 (Jones *et al.*, 2001; Selcuk *et al.*, 2015; Grundström *et al.*, 2020b). The ICC agreement in the Van de Burgt *et al.* (2011) study ranged from 0.65 to 0.89. The EHP-30 test–retest reliability was high (>0.8) in the other two studies, except for the domains 'social support' (0.51), and 'infertility' (0.65) (Chauvet *et al.*, 2017), and 'relationship with children' (0.67) (Verket *et al.*, 2018).

Validity

Seven studies used the EHP-5 (Wyrwich *et al.*, 2018; Moradi *et al.*, 2019; Oppenheimer *et al.*, 2019) and EHP-30 (Deal *et al.*, 2010a,b; Roomaney and Kagee, 2018; Pokrzywinski *et al.*, 2020b) as measures of external validity to assess the construct validity of newly developed tools. Pokrzywinski *et al.* (2020b) used the EHP-30 to validate the health-related productivity questionnaire and the remaining studies used existing PROMs including the generic Short Form-36 (SF-36) and the EuroQoL five dimension (EQ-5D) to establish the convergent validity of the EHPs and their translated versions. In a comparison of the EHP-5 and the EQ-5D, the authors found that the EQ-5D had lower construct validity concluding that 'the EHP-5 appears to be a better candidate than EQ-5D' as it is 'simpler and easier to interpret, facilitating evaluation of the baseline quality of life' (Aubry *et al.*, 2017).

Responsiveness and MIDs

As the EHPs have been used in trials to evaluate how treatment outcomes affect subjective health status, their responsiveness and/or MIDs/minimally clinically important differences (MCIDs) have been assessed. Responsiveness is a measure of longitudinal validity, which assesses the ability of a questionnaire to detect a change (if it truly exists) in health status; MIDs/MCIDs base the magnitude of change in health status on small, but to the patient, noticeable amounts. Synthesising the results was difficult because of methodological differences and the range of reported interventions. Sometimes it was unclear how the MID was calculated; in addition, other tools may have been used, not the EHPs, or EHP data were not provided as a contrast for those feeling worse/staying the same (Wickström *et al.*, 2013). However, where synthesis was possible, the findings from external, anchor-based approaches (e.g. using the patients overall self-report of meaningful change), and distribution-based methods, which are based upon statistical indices of the change in QoL scores (e.g. such as effect sizes) (Revicki *et al.*, 2006), are shown in Tables 4 and 5, respectively.

Two studies calculated MIDs using general changes in health status as the anchor (Jones *et al.*, 2004c; van de Burgt *et al.*, 2013)

Table 3. Summary of Endometriosis Health Profile psychometric studies and cross-cultural adaptations.

Author and year	Country	Aim of study	Sample size*	Sample mean/median age in years	Sample ethnicity	Stage of endometriosis	EHP measure used
(Aubry *et al.*, 2017)	France	To compare the French version of the EHP-5 with the EQ-5D.	216	33.2	NR	I-IV	EHP-5 core and modular sections
(Chauvet *et al.*, 2017)	France	To evaluate the French version of the EHP-30.	913	33.4	NR	NR	EHP-30 core and modular sections
(Chauvet *et al.*, 2018)	France	To assess the content validity of the French version of the EHP-30 and SF-36.	913 (Comments Yes=339; Comments No=574)	Comments Yes=34.4. Comments No=32.7	NR	NR	EHP-30 core and modular sections
(Deal *et al.*, 2010b)	USA	To use the EHP-30 core questionnaire during the construct validity testing of the Endometriosis Treatment Satisfaction Questionnaire (ETSQ).	Quantitative study=158	Quantitative study=32.2	-White (81) -Other (19)	NR	EHP-30 core section
(Deal *et al.*, 2010a)	USA	To use the EHP-30 core questionnaire during the construct validity testing of a daily electronic Endometriosis Pain and Bleeding Diary (EPBD).	Quantitative study=128	Quantitative study=33.9	NR	NR	EHP-30 core section
(Fauconnier *et al.*, 2017)	France	To assess the psychometric properties of the French version of the EHP-5.	With endometriosis=125 Controls=80	With endometriosis=34.6 Controls=34.7	NR	NR	EHP-5 core and modular section
(Goshtasebi *et al.*, 2011)	Iran	To develop and validate the Iranian version of the EHP-5.	199	31.4	NR	NR	EHP-5 core section
(Grundström *et al.*, 2020a)	Sweden	To cross-culturally assess the Swedish version of EHP-30 core questionnaire.	18	33.3	NR	NR	EHP-30 core section
(Grundström *et al.*, 2020b)	Sweden	To evaluate the psychometric properties of the Swedish version of the EHP-30.	128	38	NR	NR	EHP-30 core section
(Jenkinson *et al.*, 2008)	USA	To evaluate the EHP-30 in modular and summary form in a USA sample.	225	30.5	-White (83.1) -Asian or Pacific Islander (0.88) -Black (11.6) -Mixed/Multiracial (4.4)	NR	EHP-30 core section
(Jia *et al.*, 2013)	China	To develop a simplified Chinese version of the EHP-30 and evaluate its psychometric properties.	336	33.5	-Han (88.7) -Other (11.3)	NR	EHP-30 core and modular section
(Jones *et al.*, 2001)	UK	To develop the UK version of the EHP-30.	Group A=25 Group B=20 Group C=325 Group D=54 Group E=35	Group C=32.5	NR	NR	EHP-30 core and modular sections
(Jones *et al.*, 2004a)	UK	To develop the UK version of the EHP-5.	Study 1: 325 Study 2: 54	Study 1: 32.5 Study 2: 33.1	NR	NR	EHP 5 core and modular sections

(continued)

Table 3. Continued

Author and year	Country	Aim of study	Sample size*	Sample mean/median age in years	Sample ethnicity	Stage of endometriosis	EHP measure used
			Study 3: As per study 1 and 2	Study 3: As per study 1 and 2			
(Jones *et al.*, 2004c)	UK	To evaluate the sensitivity to change of the UK version of the EHP-30.	40	34.3	NR	NR	EHP-30 core and modular sections
(Jones *et al.*, 2006)	UK	To test the data quality of the UK version of the EHP-30.	610	34.7	NR	NR	EHP-30 core and modular sections
(Khong *et al.*, 2010)	Australia	To evaluate the EHP-30 in an Australian population.	195	34.6	NR	NR	EHP-30 core and modular sections
(Maiorana *et al.*, 2012)	Italy	To evaluate the Italian version of the EHP-30.	98	34.4	NR	NR	EHP-30 core section, unclear if the modular section used
(Marí-Alexandre *et al.*, 2022)	Spain	To evaluate the Spanish version of the EHP-30 core questionnaire.	223 (Histologically confirmed=124; Clinical evidence=99)	All=35.98 Histologically confirmed=36.25; Clinical evidence=35.64)	-Caucasian (Spanish) (All=90.13; HC=90.32; CE=89.90) -Latin Americans (All=6.28; HC=6.45; CE=6.06) -Caucasian (Europeans non-Spanish) (All=2.69; HC=2.42; CE=3.03) -Others (All=0.90; HC=0.81; CE=1.01)	NR	EHP-30 core section
(Moradi *et al.*, 2019)	Australia	To use the EHP-5 (with an altered recall of 12 months) during the concurrent validity testing of the Endometriosis Impact Questionnaire (EIQ).	423	Mean 32.64	NR	NR	EHP-5 core and modular sections
(Nogueira-Silva *et al.*, 2015)	Portugal	To evaluate the Portuguese version of the EHP-30.	152	34.7	-Caucasian (88.2) -Black (7.9) -Other (3.9)	I-IV	EHP-30 core and modular sections.
(Nojomi *et al.*, 2011)	Iran	To evaluate the Persian version of the EHP-30.	100	39.5	NR	NR	EHP-30 core and modular sections
(Oppenheimer *et al.*, 2019)	France	To use the EHP-5 during the construct validity and responsiveness testing of the French version of the Sexual Activity Questionnaire (SAQ).	267 (Completed SAQ at T1 Yes/No=136/131)	All=33.1 SAQ at T1 Yes=33.3 SAQ at T1 No=33.0	NR	I-IV	EHP-5, but sections NR
(Pokrzywinski *et al.*, 2020b)	USA	To use the EHP-30 pain domain to test the convergent validity of the Health-Related Productivity Questionnaire (HRPQ).	1686 (EM-I=871; EM-II=815)	EM-I=31.5 EM-II=33.2	-White (I=87.1; II=89.2) -Black or African American (I=8.7; II=8.8) -Asian (I=1; II=0.9) -American Indian or Alaska Native (I=0.7; II=0.2) -Multi Race (I=2.1; II=0.5)	NR	EHP-30 core section and sex module

(continued)

Table 3. Continued

Author and year	Country	Aim of study	Sample size*	Sample mean/median age in years	Sample ethnicity	Stage of endometriosis	EHP measure used
					-Native Hawaii or Other Pacific Islander (I=0.3; II=0.4) -Hispanic or Latino (I=16; II=13.4) -Not Hispanic or Latino (I=84.0; II=86.6)		
(Pokrzywinski *et al.*, 2020a)	USA	To evaluate the responsiveness and responder thresholds of the EHP-30 core and sexual functioning domain in the context of elagolix for moderate-to-severe endometriosis-associated pain.	As per Pokrzywinski *et al.* (2020b)	As per Pokrzywinski *et al.* (2020b)	As per Pokrzywinski *et al.* (2020b)	As per Pokrzywinski *et al.* (2020b)	As per Pokrzywinski *et al.* (2020b)
(Roomaney and Kagee, 2018)	South Africa	To use the EHP-30 to assess the reliability and validity of the Stellenbosch Endometriosis Quality of life measure (SEQOL).	Pre-pilot=7 Validation=203	Pre-pilot=29 Validation=35	NR	NR	EHP-30 core and work, sex, and infertility
(Selcuk *et al.*, 2015)	Turkey	To test the Turkish version of the EHP-5.	58	33.8	NR	NR	EHP-5 core and modular sections
(van de Burgt *et al.*, 2011)	Netherlands	To test the Dutch version of the EHP-30.	371	NR	NR	NR	EHP-30 core and modular sections
(van de Burgt *et al.*, 2013)	Netherlands	To assess the responsiveness of the Dutch version of the EHP-30.	228	34.5 (18–56)	NR	NR	EHP-30 core and modular sections
(Verket *et al.*, 2018)	Norway	To test the Norwegian (Bokmål) version of the EHP-30.	157	35.2	NR	NR	EHP-30 core and modular sections
(Wickström *et al.*, 2017)	Sweden	To evaluate the responsiveness of the Swedish version of the EHP-30 core section+sexual functioning domain.	42	33.2	NR	NR	EHP-30 core section and sexual functioning module
(Wickström and Edelstam, 2017)	Sweden	To use the EHP-30 to evaluate whether the MIDs generated by an endometriosis VAS scale significantly affected QoL.	37 (>50% on VAS=13; <50% on VAS=23)	All=33.3 >50%=34.1 <50%=33.0	NR	NR	EHP-30 core section and sexual functioning module
(Wyrwich *et al.*, 2018)	USA	To use the EHP-5 to validate the Endometriosis Daily Pain Impact Diary (EDPID).	126	33.0	-Caucasian (81.7) -Black (10.3) -Hispanic (6.3) -American Indian/Alaska Native (0.8)	NR	EHP-5 core and modular sections

* For consistency, we have cited the sample size upon which age and ethnicity were calculated.
EHP, Endometriosis Health Profile; VAS: Visual analogue scale.

(Table 4). Jones *et al.* (2004c) found that the effect sizes were larger in magnitude for the EHP-30 core domains in patients who reported feeling better after conservative surgery (–0.6 to –2.3) compared to the group overall (–0.2 to –1.1) and those who reported no change (+0.1 to –0.3). A similar trend was observed for the modular section. They also observed that, with the exception of the social support domain, a small improvement in well-being following conservative surgery is equivalent to a mean score change of between –7.6 and –35.2 units. van de Burgt *et al.* (2013) observed smaller changes, i.e. that a small improvement in HRQoL is equivalent to a mean score change of between –3.2 and –12.5 units, depending on the EHP core domain but this was expected as the study was not intervention specific.

Other studies used a specific pain question as the anchor (Table 5). Pokrzywinski *et al.* (2020a), who assessed the EHP-30's responsiveness in the context of the EM I and EM II trials, observed similar findings to those of Jones *et al.* (2004c). They noted moderate to large effect sizes on the EHP-30 core and sexual functioning domains (EM-I range –0.59 to –1.80; EM-II range –0.52 to –1.59), and improved well-being equivalent to mean score changes, depending on the EHP-30 domain, of –20.3 to –40.8 (EM I), and –17.8 to –36.0 (EM II). EHP-30 thresholds of meaningful change for these domains ranged from –20 to –35, with greater changes indicating greater improvement in health status. The authors suggested that the EHP-30 should have domain-specific responder threshold values rather than a 'one number fits all' value, and that clinicians should individualise treatment goals by EHP-30 domain and track changes (Pokrzywinski *et al.*, 2020a).

Wickström *et al.* (2017) evaluated the responsiveness and calculated the MIDs of the Swedish version in their perturbation with lidocaine study. On the core and sexual functioning domains, an improvement in HRQoL was equivalent to a mean score change of between –7.3 and –28.3, with effect sizes ranging from –0.30 to –1.24.

Interestingly, using any anchor-based methods, all five studies demonstrated that improvements in HRQoL were largest in the 'control and powerlessness' domain post-intervention, followed by 'pain'. This pattern was also observed in the effect sizes for the better groups (i.e. for those patients that said they had improved following an intervention), with the exception of van de Burgt *et al.* (2013) who showed the effect sizes for the 'pain' and 'control and powerlessness' domains were the same.

Aubry *et al.* (2017) evaluated the EHP-5's responsiveness and MCIDs before and 12 months after medical or surgical treatment using the Clinical Global Impression-Improvement scale as the 'anchor', which includes seven responses (much better, better, somewhat better, no change, somewhat worse, worse, and much worse), and compared the EHP-5 findings with those for the EQ-5D descriptive system and a visual analogue scale (VAS). The effect sizes demonstrated that for the better group overall, both the EHP-5 and EQ-5D had equivalent responsiveness for the treatment group overall and the surgical treatment group. However, only the EHP-5 was responsive to changes in quality of life after medical treatment ($P = 0.014$) compared to the EQ-5D descriptive system ($P = 0.064$) and VAS ($P = 0.437$). Improvement (somewhat better and better) on the EHP-5 was equivalent to a score change of –4.5. While the analysis included patients both medical and surgical treatments, the EHP-5 was more sensitive than the EQ-VAS and EQ-5D index, that had score changes of 10.2 and 0.26, respectively. Wyrwich *et al.* (2018) also used the EHP-5 but only as a measure of external validity when determining the responsiveness of another tool.

Discussion

This systematic review, which aimed to identify and synthesise the literature describing the use of EHPs over the last 20 years, found 139 relevant publications. The questionnaire has mostly been deployed in clinical trials (particularly RCTs) demonstrating its value in assessing the outcomes of interventions from the patient's perspective. Overall, regardless of the nature of the intervention, most women reported improvements in HRQoL after treatment.

Clinical findings

In general, surgical interventions resulted in significant improvements in HRQoL for the longest amount of time and EHP scores worsened when women stopped medication, perhaps reinforcing the temporary impact of medical treatment. Our review also highlights: that less-invasive treatments, which can improve longer term outcomes, are needed; how the condition and its symptoms impact adversely on all areas of women's lives (including work); and the importance of research involving younger patients who may be experiencing more negative impact upon their HRQoL and psychological well-being, based upon their EHP scores.

Many women currently require multiple surgical and/or medical interventions to control symptoms; hence, more effective therapies have long been needed. Encouragingly, since undertaking the review, the US FDA has approved a combination of relugolix, estradiol, and norethindrone acetate (Myfembree) for moderate-severe endometriosis-associated pain (https://www.pfizer.com/news/press-release/press-release-detail/myovant-sciences-and-pfizer-receive-us-fda-approval) (Giudice *et al.*, 2022). In the company's FDA submission, the EHP-30 pain domain was used as a secondary outcome to measure the impact on daily activities.

Reporting of ethnicity was a major limitation of most of the studies included in the review because of failure to provide the information, or the use out-of-date terminology and definitions, e.g. 'White/Non-White', which led to difficulty understanding the full impact of the EHP scores that can only be improved by better reporting of ancestry/ethic origins (Flanagin *et al.*, 2021). In addition, the EHPs have rarely been used to assess the HRQoL of women residing in Africa and the Middle East for complex reasons: (https://archive.discoversociety.org/2020/06/03/quality-of-life-measurement-in-women-living-with-endometriosis-observations-from-the-use-of-the-endometriosis-health-profile-around-the-world). Hence, efforts to facilitate more assessments of endometriosis-associated HRQoL in women from ethnically diverse backgrounds would be beneficial, as would data from transgender and non-binary patients. Lastly, EHP data from routine clinical practice are lacking. We believe the measures would be of value to clinicians and patients if deployed more widely at aggregate level; however, evidence regarding the meaningfulness of individual scores is uncertain and more research is needed in this area.

Methodological findings

Most of the psychometric studies concluded that the EHPs are reliable, valid, acceptable, and responsive tools and the results of the psychometric analyses appear to support deriving a summary score for the EHP-30 core domain and EHP-5, as previously highlighted by Jones (2001). Given the EHP-5's brevity, and recent evidence that the core and modular sections are unidimensional and thus efficient to score (Fauconnier *et al.*, 2017), it may be the most appropriate version to use in routine clinical practice,

Table 4. Comparison of the Endometriosis Health Profile-30 responsiveness/MCID results using a subjective 'general health status' anchor-based method question following an intervention.

	Jones et al. (2004c) Surgery (conservative)*					van de Burgt et al. (2013) Mixed (medical and surgical)**				
	Mean score change (n)		Effect size (n)			Mean score change (n)		Effect size (n)		
	Somewhat better	About the same	Overall group	Better group	No change group	Somewhat better	About the same	Overall group	Better group	No change group
EHP-30 Core Domains										
Pain	−24.8	−5.6	−0.9 (39)	−1.8 (19)	−0.2 (17)	−11.5 (29)	−3.3 (86)	−0.4 (227)	−1.1 (80)	−0.1 (87)
Control and powerlessness	−35.2	−7.6	−1.1 (39)	−2.3 (19)	−0.3 (17)	−12.5 (29)	−3.9 (87)	−0.4 (228)	−1.1 (80)	−0.1 (87)
Emotional well-being	−7.6	−1.5	−0.5 (38)	−1.1 (18)	−0.1 (17)	−5.5 (29)	−1.6 (87)	−0.3 (228)	−0.9 (80)	−0.1 (87)
Social support	1.7	−2.9	−0.2 (38)	−0.6 (19)	−0.1 (17)	−10.0 (28)	−0.8 (86)	−0.3 (226)	−0.8 (79)	0.0 (86)
Self-image	−9.9	1.85	−0.3 (39)	−0.9 (19)	0.1 (18)	−3.2 (29)	−5.0 (86)	−0.3 (227)	−0.6 (80)	−0.2 (86)
EHP-30 Modular Domains										
Work	—	—	−0.6 (35)	−1.6 (15)	0.0 (17)	−5.7 (23)	−2.3 (68)	−0.2 (180)	−0.7 (57)	−0.1 (68)
Children	—	—	−0.7 (10)	−1.4 (6)	0.0 (4)	−17.5 (5)	−5.9 (32)	−0.5 (65)	−1.1 (17)	−0.2 (32)
Sexual functioning	—	—	−0.4 (32)	−1.1 (13)	0.1 (16)	−4.4 (23)	−8.4 (64)	−0.3 (190)	−0.6 (62)	−0.3 (64)
Medical profession	—	—	−0.4 (26)	−0.7 (10)	−0.3 (7)	2.5 (17)	−2.6 (49)	−0.2 (145)	−0.3 (43)	−0.1 (49)
Treatment	—	—	−0.2 (18)	−0.4 (3)	−0.1 (6)	−7.8 (15)	0.2 (51)	−0.2 (147)	−0.4 (39)	0.0 (51)
Infertility	—	—	0.1 (19)	−0.5 (8)	0.5 (8)	2.2 (13)	1.3 (36)	−0.1 (117)	−0.6 (34)	0.1 (36)
SF-36 Domains										
Pain	11.1	3.1	0.5 (40)	1.0 (19)	0.1 (18)	/	/	/	/	/
Energy/vitality	10.5	2.7	0.5 (39)	1.3 (19)	0.2 (17)	/	/	/	/	/
General health	2.4	−2.2	0.1 (39)	0.4 (19)	0.0 (17)	/	/	/	/	/
Mental health	8.7	1.0	0.4 (39)	0.9 (19)	0.2 (17)	/	/	/	/	/
Physical	8.6	0.6	0.3 (38)	0.7 (19)	0.1 (17)	/	/	/	/	/
Role (emotional)	3.0	11.1	−0.3 (40)	0.5 (19)	0.3 (18)	/	/	/	/	/
Role (physical)	22.7	−2.8	0.3 (40)	0.9 (19)	0.0 (18)	/	/	/	/	/
Social functioning	22.2	5.6	0.4 (40)	1.1 (19)	0.2 (18)	/	/	/	/	/

Jones et al. (2004c) and van de Burgt et al. (2013) reported the improvement in score and for the purposes of showing consistency across other studies, we've reversed the sign to show the absolute change in score because in the EHP, low is better. Other indicators of responsiveness have also been used (e.g. the standardised response mean in Jones et al., 2004c).
EHP: 0 = best health status, 100 = worst health status.
SF-36: 0 = worst health status, 100 = best health status.
* Four months after conservative surgery based upon the global health perception question in the SF-36.
** Six months after any treatment (could have been medical or surgical) using the same anchor question as reported in Jones et al. (2004c).
- Not calculated due to the small number of responses.
/ Not reported.
MCID, minimally clinically important difference; EHP, Endometriosis Health Profile.

whereas its longer form (EHP-30), which provides more granularity, is more appropriate for research.

While a summary score for the EHP-30 is also possible, its responsiveness has not yet been established and recent evidence suggests the five-domain structure is more robust (Hansen et al., 2022). In addition, providing EHP-30 data at domain, rather than summary, level has been recommended for clinical trials (Vincent et al., 2010). Although we would recommend including the 'not applicable' boxes, researchers may sometimes think they are inappropriate and omit them. However, this complicates scoring and interpretation of the EHP data: those patients for whom the EHP domain/item is not relevant may choose not to respond or tick 'never', when the issue was actually not relevant.

Most importantly, the responsiveness of the EHP-30 has been demonstrated and emerging evidence suggests the EHP-5 is also responsive. Strikingly, using anchor-based methods, all five EHP-30 studies showed the largest mean changes in the 'control and powerlessness' domain post-intervention, followed by 'pain'. This suggests that women experience the greatest improvements in these domains regardless of the intervention/s. Our findings support the direction of responder thresholds proposed by Pokrzywinski et al. (2020a) of 'control and powerlessness' as the largest (-35), followed by 'pain' (-30). However, the magnitude of the thresholds differed between studies. The thresholds for comparing medical treatment versus placebo suggested by Pokrzywinski et al. (2020a) seem appropriate; however, these may need to be reduced in the context of other interventions (e.g. surgery), or those samples which include mixed interventions.

The rather surprising finding that 'control and powerlessness' is a more salient domain than 'pain' perhaps reflects how pain reduction can result in an even greater improvement in patients' sense of control and power over their endometriosis. Hence, our synthesis concurs with the recommendation of other authors, such as Pokrzywinski et al. (2020a), to strengthen efforts to measure and address the psychological impact of endometriosis. While the EHP-30 pain domain is sometimes chosen as the primary outcome measure in research, we advocate that the 'control and powerlessness' domain should be included as a secondary outcome measure in future trials (ideally with other relevant modules). If researchers prefer the brevity of the EHP-5 for clinical trials, we recommend reporting the scores for 'pain' and 'control and powerlessness' at item level.

The only direct comparisons with generic measures showed that the EHP-30 is overall more responsive than the SF-36 (Jones et al., 2004c) and the EHP-5 more consistently detects treatment changes than the EQ-5D (Aubry et al., 2017). The ASRM and ESHRE currently recommend an 11-point numerical rating scale as the primary outcome in clinical trials assessing endometriosis-associated pain (Vincent et al., 2010). However, some studies continue to use a VAS to measure pain despite recent FDA guidelines (FDA, 2022). Interestingly, all the studies included used (with the exception of Maiorana et al., 2012) classical

Table 5. Comparison of the Endometriosis Health Profile-30 responsiveness/MCID results using a subjective 'pain' anchor-based question following an intervention.

	Pokrzywinski *et al.* (2020a) Elagolix and placebo*				Wickström and Edalstam (2017) Pertubation + lignocaine and placebo**		Wickström *et al.* (2017) Pertubation + lignocaine and placebo***				
	Improved		No change/worsened		Improved	Not improved	Better or pain free		Worse or same		Somewhat better^****
	Mean score change (n)		Mean score change (n)		Median score change (n)	Mean score change (n)	Mean score change (n)	Effect size	Mean score change (n)	Effect size	Mean score change (n)
	EM-I	EM-II	EM-I	EM-II							
EHP-30 Core											
Pain	−31.1 (564)	−30.8 (544)	−5.5 (151)	7.3 (152)	−21.6 (12)	0 (19)	−22.0 (19)	−1.22	−1.7 (13)	−0.09	−19.9 (17)
Control and powerlessness	−40.8 (566)	−36.0 (551)	−8.8 (153)	−8.6 (154)	−33.3 (12)	0 (20)	−28.3 (19)	−1.24	−2.1 (14)	−0.10	−25.7 (17)
Emotional well-being	−21.1 (566)	−18.9 (546)	−6.3 (154)	−4.9 (153)	−8.3 (11)	0 (19)	−18.1 (17)	−1.04	7.1 (13)	0.35	−13.9 (15)
Social support	−22.8 (574)	−20.6 (551)	−0.7 (156)	−1.9 (154)	−9.4 (12)	−6.3 (19)	−16.8 (19)	−0.84	−3.8 (13)	−0.17	−12.9 (17)
Self-image	−20.3 (569)	−17.8 (550)	−1.0 (155)	−2.6 (153)	−16.7 (12)	0 (19)	−8.8 (19)	−0.51	1.9 (13)	0.11	−6.9 (17)
EHP Modular											
Work	/	/	/	/	/	/	/	/	/	/	/
Children	/	/	/	/	/	/	/	/	/	/	/
Sexual functioning	−22.1 (400)	−21.9 (393)	−2.5 (119)	−4.9 (104)	−20 (9)	5 (17)	−7.3 (16)	−0.30	5 (10)	0.15	−4.5 (14)
Medical profession	/	/	/	/	/	/	/	/	/	/	/
Treatment	/	/	/	/	/	/	/	/	/	/	/
Infertility	/	/	/	/	/	/	/	/	/	/	/
Work	/	/	/	/	/	/	/	/	/	/	/
Children	/	/	/	/	/	/	/	/	/	/	/
Sexual functioning	/	/	/	/	/	/	/	/	/	/	/
Pain VAS (mm)	/	/	/	/	Somewhat better −38.6 (18)	Same −7.4 (11)	/	/	/	/	/

EHP: 0 = best health status, 100 = worst health status.
VAS: Visual analogue scale (pain only); 0 mm=no pain, 100 mm=worst pain imagined.
* Three months after treatment with elagolix. Patient Global Impression of Change (seven response categories) was used to estimate changes in pain intensity. Improved, Very much improved, much improved, minimally improved; No change or worse, No change, minimally worse, much worse, very much worse.
** Four/six months following treatment with perturbation with lignocaine using an anchor measure derived from a VAS.
*** Six months after treatment with perturbation with lignocaine. Modified version of the general quality of life question on the SF-36 (five response categories) to estimate changes in pain intensity. Better or pain free, Somewhat better, much better; Worse or same, Somewhat worse, much worse, about the same.
**** Effect sizes not reported.
^ These MIDs were also reported in Wickström *et al.* (2013).
/ Not relevant.
MCID, minimally clinically important difference; EHP, Endometriosis Health Profile.

test theory and not modern psychometric methods, such as Rasch analysis and Item Response Theory. We are re-analysing the EHP-30 using such modern methods to strengthen the psychometric properties of the EHPs, with a focus on the 'pain' domain given the FDA's recommendation regarding VAS.

We identified new instruments specifically designed to measure PROs in endometriosis. Some are disease-specific and the EHP was used as the measure of external validity to aid their development: the Endometriosis Treatment Satisfaction Questionnaire (Deal *et al.*, 2010b); Endometriosis Pain and Bleeding Diary (EPBD) (Deal *et al.*, 2010a); Sexual Activity Questionnaire (SAQ) (Oppenheimer *et al.*, 2019); Endometriosis Daily Pain Impact Diary (Wyrwich *et al.*, 2018); Endometriosis Impact Questionnaire (EIQ) (Moradi *et al.*, 2019), and Stellenbosch Quality of Life questionnaire (Roomaney and Kagee, 2018). The generation of these measures and wide use of the EHP tools possibly reflect best practice guidance over the last 20 years to measure PROs. Other generic PROMS have also been widely used in endometriosis research, e.g. SF-36 (Bourdel *et al.*, 2019; Sima *et al.*, 2021).

The EHPs have also been adapted to measure outcomes for related conditions, such as CPP (e.g. Cheong *et al.*, 2014) and adenomyosis (Andersson *et al.*, 2019), and non-endometriosis treatments such as ART. van der Houwen *et al.* (2014) suggest changing the header question to 'how often did you …' instead of 'because of your endometriosis, how often did you …' to facilitate completing the questionnaire in these circumstances, and we are open to modifying the EHPs on reasonable request. However, the FDA may not recognise results derived from a questionnaire that is not designed for the patient group in question. PROMs for these conditions may, therefore, be needed.

Some commentators consider the EHP-30 takes too long to complete (Wickström and Edelstam, 2017; Roomaney and Kagee, 2018). We find this difficult to understand as, on an average, it takes less than 15 min to complete the EHP-30 long form version (core and modular sections) (Nogueira-Silva *et al.*, 2015) and the overall completion rates in the studies identified are high. Other concerns expressed relate to the lack of a domain on 'vitality' or 'support', and that the EHP pain scale is only symptom-based (Roomaney and Kagee, 2018). In fact, the items are not purely symptom-based as they also reflect the impact that endometriosis-associated pain may have upon day-to-day functioning: for example, attending social events, undertaking jobs around the home, leisure activities or exercising, sleeping, and other daily-life activities.

Limitations

We have attempted to identify and synthesise the EHP literature since the measure was first published in 2001. Whilst we have tried to be as comprehensive as possible, it is possible that some literature was missed—particularly as one paper that did not mention the EHP in the title or abstract was later identified as relevant to the review (Roomaney and Kagee, 2018). Conversely, some papers that used an EHP were not included because the full text was unavailable in English. Thus, the total number of studies that have used the EHP exceeds 139, which is reflected in the larger number of EHP licences granted. It is also important to mention that the original EHP authors were members of the team that undertook this review: clearly their papers were included. To overcome any potential biases that might have ensued during the quality appraisal process, K.B. who had no prior knowledge or affiliation to the EHP measures undertook this process independently.

In recent years, standards and frameworks for appraising the measurement properties of PROMS have been developed, most notably by the COSMIN (COnsensus-based Standards for the selection of health Measurement INstruments) group (e.g. Mokkink *et al.*, 2018). As the purpose of this review was to gather and synthesise the literature to-date on the EHP tools generally (not just their measurement properties), we have described the key psychometric properties using the COSMIN taxonomy as a guide, but we have not applied their risk of bias tool to assess the quality of the studies. This is a similar approach to that undertaken in other recent reviews of quality-of-life measures in endometriosis (Bourdel *et al.*, 2019). We recognise this is an important next step and are currently undertaking such an analysis, using the COSMIN risk of bias framework.

However, we did undertake a thorough review of the responsiveness studies, comparing data based not only on type of approach (anchor and distribution-based) but also on the specific nature of the anchor question (general health status vs pain), which is seldom done. We also quality appraised all the studies using the MMAT. While 97% of the studies exceeded the threshold of a low-quality paper, some caution when interpreting the results is needed. Owing to the considerable heterogeneity across the papers, many of the manuscripts did not fit easily into the MMAT predefined categories (e.g. pilot and feasibility studies). It was also difficult to interpret data from some studies because of the non-standardised interpretation of the scoring. In an attempt to decipher the data, the corresponding authors were contacted and asked to clarify their reporting of the EHP data. One author responded and six authors did not respond. Finally, for studies of 12 months or more, we applied a 30% cut-off as our acceptable level. However, among these studies, there was considerable variation in follow-up times with some studies following up for 36 months or longer. As higher drop-out levels are to be expected in studies with lengthier follow-up periods, the MMAT results on this metric should be interpreted with caution.

Conclusions and implications for future research

The EHP measures have been deployed widely since they were first developed in 2001 and further robust psychometric testing continues to support their reliability, validity, responsiveness, and acceptability. While the EHPs have 56 certified translations with others ongoing, further testing of items in the translated (particularly Italian and Norwegian) versions would be beneficial. Testing should also be extended to samples of younger women and those from ethnic minorities and different populations, especially in Africa. The EHPs' digital availability via REDCap may help such testing and implementation. Future developments by the EHP authors are focusing on undertaking modern psychometric tests on the tools—specifically to improve measurement of endometriosis-associated pain.

Supplementary data

Supplementary data are available at *Human Reproduction Update* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Authors' roles

All the authors contributed to writing the manuscript. G.L.J.: conceived the idea, and assisted with protocol development, data extraction, and analysis. K.B.: undertook the MMAT, and assisted

with protocol development, data extraction, and analysis. F.T.: undertook the literature searches and data extraction, and assisted with protocol development. D.M.: assisted with data extraction and analysis. J.R.: assisted with data extraction and analysis. D.C.: assisted with protocol development. S.H.K.: assisted with protocol development, data extraction, and analysis. C.J.: assisted with protocol development, data extraction, and analysis.

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Conflict of interest

G.L.J., S.H.K., and C.J. are the original developers of the EHP instruments. They receive royalties from commercial licensing, which are facilitated by Oxford University Innovation Limited (a wholly owned subsidiary of the University of Oxford) of which J. R. is an employee. D.C. was also an employee at Oxford University Innovation Limited at the time of working on and producing this review. K.B., D.M., and F.T. have no conflicts of interest to declare.

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