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human reproduction **REVIEW** ***Psychology and counselling***

Health-related quality of life in women with primary ovarian insufficiency: a scoping review of the literature and implications for targeted interventions

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STUDY QUESTION: What is known about health-related quality of life (HR-QoL) in women with idiopathic primary ovarian insufficiency (POI)?

SUMMARY ANSWER: Women with POI have a range of unmet psychosocial needs relating to three interrelated themes: ‘diagnostic odyssey’, ‘isolation and stigma’ and impaired ‘ego integrity’.

WHAT IS KNOWN ALREADY: Prior studies have reported increased depressive symptoms, diminished sexual function and altered body image/self-concept in women with POI.

STUDY DESIGN, SIZE, DURATION: A systematic scoping review (11 databases) on HR-QoL in POI including published quantitative, qualitative and mixed-methods studies as well as unpublished gray literature (i.e. unpublished dissertations) through June, 2021.

PARTICIPANTS/MATERIALS, SETTING, METHODS: After removing duplicates, 1244 articles underwent title and abstract review by independent reviewers. The remaining 72 relevant articles underwent dual full text review to determine inclusion criteria yielding 24 articles (100% concordance) for data extraction. Findings were summarized in tables by methodology and recurrent HR-QoL themes/sub-themes were mapped to define key aspects of HR-QoL in POI. Promoters of active coping were charted at the individual, interpersonal and healthcare system levels. Targets for tailored interventions supporting active coping and improved HR-QoL were mapped to the Theory of Planned Behavior (TPB).

MAIN RESULTS AND THE ROLE OF CHANCE: Three interrelated themes affecting HR-QoL in POI emerged from the data synthesis. First, the theme ‘diagnostic odyssey’ comprised sub-themes of uncertainty, lack of control, knowledge gaps, discontinuous care and negative clinical interactions. The second theme ‘isolation and stigma’ included sub-themes of guilt, shame, concealment, feeling labeled as infertile, lack of social support and unsympathetic clinicians. The third theme, impaired ‘ego integrity’ captured sub-themes of decreased sexual function, altered body image, psychological vulnerability and catastrophizing. Targets promoting active coping at the individual ($n = 2$), interpersonal ($n = 1$) and healthcare system ($n = 1$) levels were mapped to the TPB to inform development of tailored interventions supporting active coping and improved HR-QoL in POI (i.e. narrative intervention, co-creating patient-facing materials, peer-to-peer support and provider resources).

LIMITATIONS, REASONS FOR CAUTION: No studies using a POI-specific HR-QoL instrument were identified. No interventional studies aimed at improving HR-QoL in POI were identified. Only articles published in English were included in the study.

WIDER IMPLICATIONS OF THE FINDINGS: Women with POI frequently have impaired HR-QoL related to the life-altering infertility diagnosis. The range of unmet psychosocial needs may be relevant for informing interventions for other populations with infertility.

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Introduction

Primary ovarian insufficiency (POI) is a complicated syndrome characterized by loss of ovarian function by age 40 and has a variable clinical course that includes early onset of menopausal symptoms and infertility. In the literature, POI has been variably termed premature ovarian failure, premature ovarian insufficiency, premature menopause, premature ovarian dysfunction, poor ovarian response and/or diminished ovarian reserve (Welt, 2008). Data suggest that POI affects approximately 1% of women before the age of 40 and roughly 0.1% before 30 years (Coulam *et al.*, 1986). Autoimmune (e.g. autoimmune oophoritis), iatrogenic (e.g. post-chemotherapy, radiotherapy) and genetic factors have been described—including chromosomal abnormalities (e.g. Turner syndrome) and gene variants identified using next generation sequencing (Franca and Mendonca, 2020). However, in most cases, the etiology remains poorly defined, likely related to rare gene variants yet to be discovered or not routinely examined.

In addition to difficulty understanding the cause of POI, patients experience adverse effects from the disorder itself that are challenging to quantify. The European Society of Human Reproduction and Embryology (ESHRE) has developed a guideline to manage the symptoms and complications of POI (European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI *et al.*, 2016). ESHRE guidelines recommend treatment to protect bone health and recommend psychosocial support for women diagnosed with POI (European Society for Human Reproduction and Embryology (ESHRE) Guideline Group on POI *et al.*, 2016). Symptom management and mitigating sequelae is also critical as POI symptoms are caused by low estrogen levels and include hot flashes, night sweats, poor sleep, amenorrhea, sexual dysfunction, sub-/infertility and a range of physical effects including impaired bone health and increased risk of cardiovascular disease as well as diminished quality of life (Li *et al.*, 2020).

Measures of health-related quality of life (HR-QoL) have been constructed to assess the impact of disease (and treatment) on an individual across physical, psychological and social dimensions. A recent systematic review and meta-analysis of 19 studies on women with POI found low to medium effect size on HR-QoL compared to women with normal ovarian function (Li *et al.*, 2020). Importantly however, many validated HR-QoL measures (i.e. SF-36, World Health Organization Quality of Life—Brief (WHO-QOL Bref)) are generic instruments and it remains unclear if such instruments accurately capture disease-specific constructs that women with POI experience. For example, generic HR-QoL instruments may not appropriately assess menopausal symptoms, sexual dysfunction, altered body image, self-esteem and concerns related to infertility that have been reported in POI. Thus, while evidence suggests women with POI experience decreased HR-QoL, a comprehensive, holistic understanding of the challenges faced by women is lacking. The knowledge gap limits the development of targeted interventions that respond to the priority needs of women with POI.

We aimed to conduct a systematic scoping review to synthesize findings from quantitative studies, qualitative inquiry, mixed-methods studies and unpublished gray literature on HR-QoL in POI. Subsequently, we identified factors promoting active coping within a systems perspective (i.e. individual, interpersonal and healthcare system levels). We then mapped identified targets onto the Theory of Planned Behavior (TPB) (Ajzen, 1991) to inform the development of theory-informed interventions to improve HR-QoL in women with POI.

Materials and methods

The project involved three sequential components. First, we performed a systematic scoping review of the literature to identify and synthesize existing data on HR-QoL in women with POI. Second, we identified factors supporting active coping at the individual, interpersonal and healthcare system levels. Finally, we mapped results onto the TPB to identify targets for interventions.

Systematic scoping review

We employed Arksey and O'Malley's (2005) framework that involves five steps.

Identifying the research question: The scoping review process was guided by a single primary question 'what is known about HR-QoL in persons with primary ovarian insufficiency?'

Identifying the relevant literature: We performed a systematic, structured literature search of articles in English (published and grey literature) in 11 electronic databases (Medline, PubMed, Embase, CINAHL, PsycINFO, Web of Science Core Collection, The Cochrane Library, Joanna Briggs Institute EBP Database, ProQuest Dissertations and Theses, TRIP and Greylit.org). Appropriate search terms for each respective database were used related to POI (i.e. primary ovarian insufficiency, premature menopause, premature ovarian insufficiency, primary ovarian failure, premature ovarian failure, diminished ovarian reserve, poor ovarian response) and HR-QoL (quality of life, health-related quality of life, well-being, health outcome). Database search results were exported into Endnote^{TM} (V20, Clarivate, Boston, MA, USA). Additional articles were identified using a 'snowball' technique to review the reference lists of included articles and the publications of frequently cited authors. Articles identified using the 'snowball' approach were added to the list of articles identified in the database search.

Selecting the literature: Literature search results were imported into Covidence online systematic review software (www.covidence.org, Veritas Health Innovation, Melbourne, Australia). After duplicates (n = 762) were removed, two researchers (I.R.M. and A.A.D.) independently reviewed titles and abstracts of the remaining 1244 articles for relevancy and inclusion criteria. Included articles were primary research reports including qualitative, quantitative and mixed-methods studies of HR-QoL in women with idiopathic POI. Studies focusing exclusively on iatrogenic (e.g. post-chemotherapy) or syndromic (e.g. Turner syndrome) forms were excluded as were case reports, review articles, opinion pieces and articles not published in English. Discrepancies were discussed (29/1244, 2%) until consensus was reached regarding relevancy and inclusion. Subsequently, 72 potentially relevant articles were independently reviewed by two researchers (I.R.M. and A.A.D.) to determine relevancy and inclusion/exclusion criteria. No discrepancies were identified between independent reviewers. In total, 24 articles were included for data extraction and analysis. The screening process is summarized in a PRISMA flow chart (Fig. 1).

Charting the data

Data were extracted from articles including study design, inclusion/exclusion criteria, sample size, validated instruments/tools and study findings. Risk of bias was not conducted due to methodological variability of included studies (i.e. only one randomized controlled trial).

Collating, summarizing and reporting results

Extracted data from the 24 articles were organized by study methodology (quantitative, qualitative or mixed methods). Findings were reviewed and analyzed using an iterative process to identify thematic elements (Saldaña, 2021). Briefly, investigators discussed and organized study findings into relevant categorical themes and sub-themes (i.e. dimensions of the categorical theme). Thematic categories were then added to the data extraction summary tables. Additionally, promoters/barriers were organized and grouped according to theme and categorized using a systems perspective (i.e. individual factors, interpersonal influences or healthcare system factors).

Theoretical framework

We used the TPB as a guiding theoretical framework for mapping targets for intervention (Ajzen, 1991). Briefly, the TPB applies to an individual's behavioral intention. The TPB posits that 'intention' precedes action and behavior. The TPB considers that intention is shaped by attitudes, subjective norms and perceived behavioral control—all of which are shaped by prior experience (i.e. behavior beliefs, normative beliefs and control beliefs, respectively). 'Attitudes' reflect an individual's perceptions of a behavior being positive/negative. 'Subjective norms' refer to expectations of family, friends, healthcare providers, etc. (i.e. interpersonal mediating factors). 'Perceived behavioral control' relates to an individual's perceived self-efficacy and agency. An active coping response could be considered an essential component for mitigating factors contributing to impaired HR-QoL in women with POI. Accordingly, we conceptualized behavior in the TPB as an active coping response to receiving a POI diagnosis (facilitating identity integration).

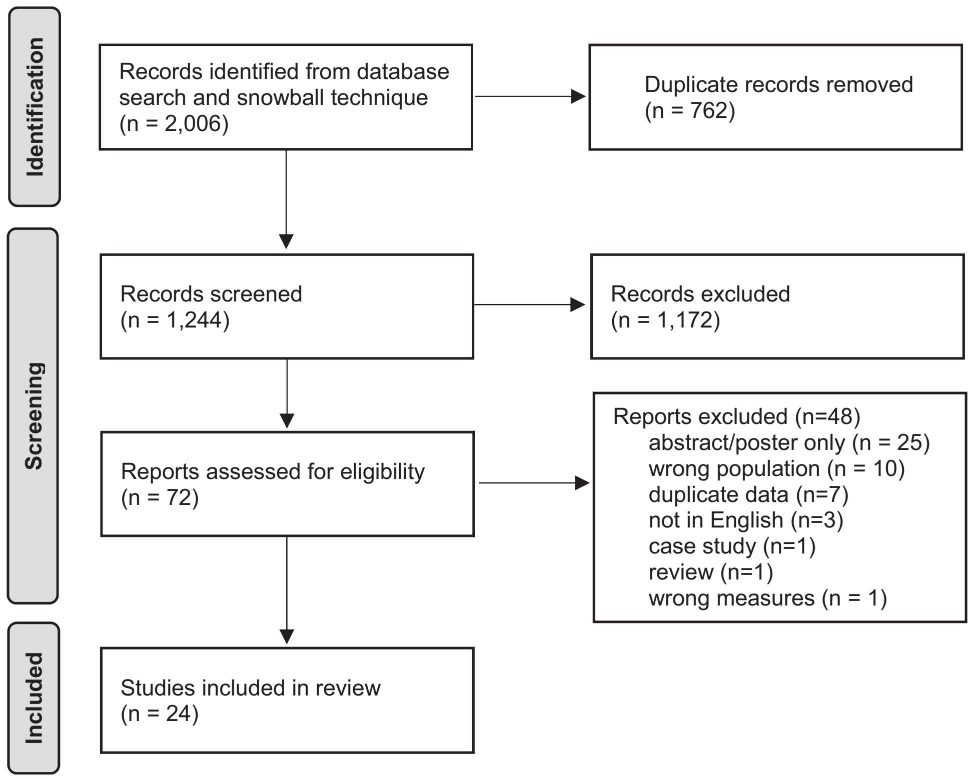

Figure 1. Scoping review PRISMA diagram.

Results

The systematic database search and review of article reference lists identified a total of 2006 articles (Fig. 1). After 762 duplicates were removed, 1244 articles underwent initial title and abstract screening. The remaining 72 articles underwent independent full text review for inclusion criteria and relevance yielding 24 included studies (quantitative (n = 17), qualitative (n = 4), mixed methods (n = 3), 100% concordance between independent reviewers) for data extraction and analysis.

Recurring themes in study findings

After collating study findings, thematic analysis identified several major, recurring themes (Fig. 2a). The overarching theme was 'impaired HR-QoL'—referring to the impact of health status and/or healthcare on physical, mental, social and emotional well-being. Within 'impaired HR-QoL', three distinct, interacting themes were identified relating to the experiences of women with POI. The 'diagnostic odyssey' theme refers to the often-extended journey women experienced in receiving a POI diagnosis. The theme includes several dimensions including feelings of uncertainty, perceived lack of control, knowledge gaps (i.e. not understanding what was wrong), discontinuity of care (i.e. seeing multiple different providers and specialists) and negative clinical interactions with providers. The 'isolation & stigma' theme relates to the social and emotional responses women experienced following diagnosis. Dimensions include feelings of guilt and shame (from peers and providers) resulting in efforts to conceal the diagnosis, feeling labeled (i.e. infertile), lack of social support and perceptions of providers being unsympathetic to their situation. The 'ego integrity' theme refers to the impact the diagnosis and symptoms had on their sense of self and psyche. Dimensions of the theme include decreased sexual function, altered body image, feeling psychologically vulnerable/fragile and the tendency to 'catastrophize' experiences (i.e. any event will be deleterious).

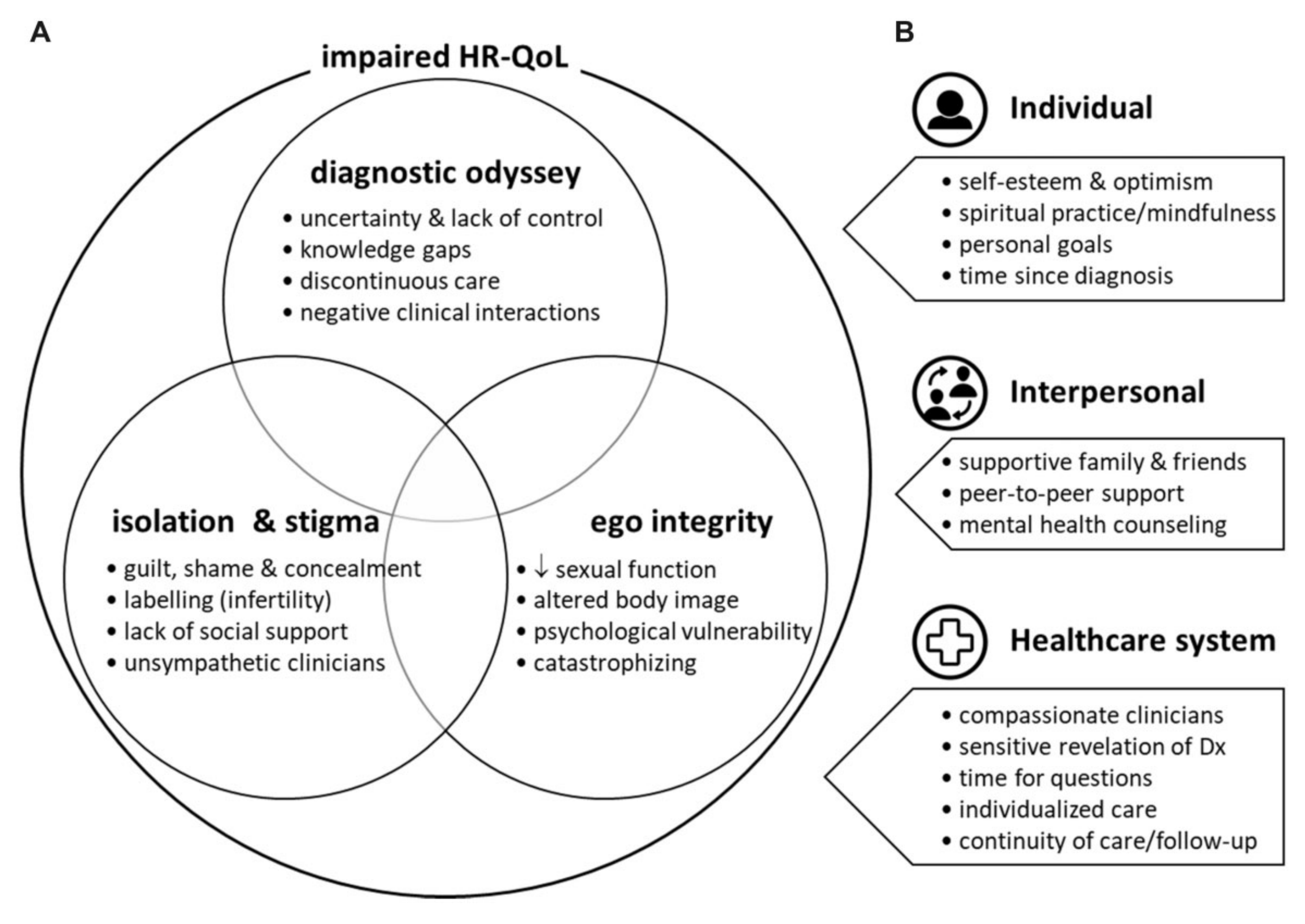

Figure 2. Themes and dimensions related to impaired health-related quality of life (HR-QoL) in women with primary ovarian insufficiency (POI). Synthesizing the results of the scoping review identified potential targets for interventions to improve health-related quality of life (HR-QoL) in women with primary ovarian insufficiency (POI). (**A**) Three interacting themes (bold text in overlapping circles: diagnostic odyssey, isolation and stigma, ego integrity) contributed to impaired HR-QoL in women with POI (i.e. anxiety, depression, psychological distress, diminished health status). Dimensions for each theme are depicted by bullets. (**B**) Several mitigating factors were identified from the literature and are categorized at the individual, interpersonal and healthcare system levels. Protective factors are noted by bulleted points for each respective level. Dx, diagnosis.

Findings from quantitative studies

In total, 17 quantitative research studies were included (Table I). Quantitative study findings most often related to the themes of 'impaired HR-QoL' and 'ego integrity'—noted in 10/17 (59%) articles for each theme. Studies used several validated measures to assess anxiety, depression and psychological distress including the Center for Epidemiologic Studies Depression Scale (CES-D), the State-Trait Anxiety Inventory (STAI) and the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) Structured Clinical Interview (SCID). Several studies noted the high psychological burden associated with a POI diagnosis (Liao *et al.*, 2000; Van Der Stege *et al.*, 2008; Davis *et al.*, 2010; Mann *et al.*, 2012). Studies report that between 64% and 70% of women with POI have been diagnosed with a DSM-IV axis-1 disorder in their lifetime, including major (49–55%) and minor (11–13%) depression (Schmidt *et al.*, 2011; Guerrieri *et al.*, 2014). The Female Sexual Function Index (FSFI) was a validated measure used to assess sexual function. Notably, 5/17 (29%) studies reported impaired sexual function in POI that was distressful or bothersome to women (Kalantaridou *et al.*, 2008; Van Der Stege *et al.*, 2008; Gibson-Helm *et al.*, 2014; Yela *et al.*, 2018; Javadpour *et al.*, 2021). Yela *et al.* (2018) found sexual satisfaction was correlated with all four domains of HR-QoL (physical, psychological, social relationships and environment)—suggesting global effects on wellbeing. Notably, the 'diagnostic odyssey' and 'isolation/stigma' themes were noted less frequently in the quantitative studies (5/17 (29%) and 4/17 (24%), respectively). While few validated scales exist related to the construct of 'diagnostic odyssey', two groups employed the Mishel Uncertainty in Illness Scale to assess uncertainty and lack of control (dimensions of the theme) (Davis *et al.*, 2010; Rivers, 2014; Driscoll *et al.*, 2016).

Findings from qualitative and mixed-methods studies

Four qualitative and three mixed-methods studies were included for data extraction and subsequent thematic analysis (Table II). The 'isolation and stigma' and 'diagnostic odyssey' themes were the most common (both 5/7, 71%) among qualitative and mixed-methods studies. Feelings of isolation and stigma, including the stigma associated with the label of 'infertile', were frequently reported by women with POI. Similarly, feelings of guilt and shame or concealment of their diagnosis were common (Halliday and Boughton, 2009; Singer *et al.*, 2011; Golezar *et al.*, 2020). Women reported that their emotional responses were magnified by interactions with providers they perceived as unsympathetic (Boughton and Halliday, 2008; Halliday and Boughton, 2009) as well as lack of adequate social support (Halliday and Boughton, 2009; Vemuri *et al.*, 2019). Several studies reported women's experiences of negative clinical interactions during clinical encounters (i.e. feeling their symptoms were dismissed/delegitimized because of their young age/non-specific complaints or not receiving enough information about POI from providers) (Boughton and Halliday, 2008; Halliday and Boughton, 2009; Singer *et al.*, 2011; Johnston-Ataata *et al.*, 2020). Such experiences left many women with knowledge gaps about their diagnosis or treatment plans and inadequate support in weighing risks/benefits of hormone therapy (Groff *et al.*, 2005; Halliday and Boughton, 2009; Singer *et al.*, 2011; Johnston-Ataata *et al.*, 2020). Boughton and Halliday (2008) described patients' feelings of undergoing pregnancy tests during the diagnostic process (i.e. evaluating amenorrhea) as a source of both hope and despair—when they ultimately were diagnosed with POI. Singer *et al.* (2011) reported that women with POI may speculate that stress or preceding life events caused POI. For some women, fear of the risks associated with hormone therapy and lack of clinical support contributed to non-adherence and treatment cessation (Johnston-Ataata *et al.*, 2020). The 'ego integrity' theme was prevalent (4/7, 57%) among qualitative and mixed-methods studies. Indeed, several studies found women described altered body image resulting from the POI diagnosis (i.e. felt older, less confident, less feminine) (Groff *et al.*, 2005; Singer *et al.*, 2011; Golezar *et al.*, 2020).

Promoters of effective coping with a POI diagnosis

Among the 24 included studies, many identified promoters/barriers to an active coping response following a POI diagnosis. As the factors were heterogeneous, we clustered them using an ecological (systems) perspective by categorizing factors at the level of the individual, interpersonal level or healthcare system (Fig. 2b). The three levels represent potential targets for intervention to support active coping and help improve HR-QoL in women with POI.

Among quantitative studies, four studies identified mental health counseling as a critical component in managing POI given the high psychological burden (Liao *et al.*, 2000; Davis *et al.*, 2010; Guerrieri *et al.*, 2014; Luiro *et al.*, 2019). Similarly, several studies highlight the importance of social/emotional support for reducing feelings of isolation following diagnosis (Liao *et al.*, 2000; Orshan *et al.*, 2009; Davis *et al.*, 2010; Driscoll *et al.*, 2016). Orshan *et al.* (2009) found a positive association between perceived social support and self-esteem. In line with these findings, Yela *et al.* (2018) identified improving social relationships as a potential target for interventions aimed at improving HR-QoL. Two studies reported that women with POI scored poorly on measures of self-esteem (Orshan *et al.*, 2009; Guerrieri *et al.*, 2014). However, women with POI appear to have different coping trajectories following diagnosis. Higher baseline levels of resilience (e.g. active coping, acceptance, purpose in life, optimism) is positively correlated with well-being, and negatively correlated with distress, at 12 months (Rivers, 2014; Driscoll *et al.*, 2016). Conversely, women with high baseline vulnerability measures (e.g. anxiety, depression, emotionality, interpersonal sensitivity, pessimism) had greater distress and lower well-being at 12 months (Rivers, 2014; Driscoll *et al.*, 2016). Additional factors that may support an effective coping response and adaptation to living with POI include spiritual practice/mindfulness (Ventura *et al.*, 2007; Allshouse *et al.*, 2015), focusing on personal goals (Ventura *et al.*, 2007; Rivers, 2014; Driscoll *et al.*, 2016), and time since diagnosis (Liao *et al.*, 2000). In summary, the quantitative studies point to factors at the individual and interpersonal levels (Fig. 2).

Notably, qualitative and mixed-methods studies also identified many of the same promoters of coping (Fig. 2) among women with POI. Factors including mental health counseling (Groff *et al.*, 2005; Singer *et al.*, 2011), supportive family/friends (Vemuri *et al.*, 2019), focusing on personal goals (Vemuri *et al.*, 2019) and spiritual practice/mindfulness (Groff *et al.*, 2005) were found to support active coping—thereby lending further support for the quantitative findings. Notably, qualitative inquiry (e.g. interviews, analysis of discussion board messages)

Table I Summary of quantitative studies on health-related quality of life in POI (n = 17).

Study information	Measures	Summary findings
Liao *et al.* (2000) UK Cross-sectional (n = 64) mean: 30.8 years range: 19–40 years	– CES-D – Satisfaction with Life Scale – Self-esteem Scale – Perceived Stress Scale – Body Satisfaction Scale – Multidimensional Sexuality Questionnaire	– ↑ burden of psychological distress – 17% currently receiving psychological treatment (23% past) – ↑ depression/stress vs general population – Depression ↓ with time since diagnosis – ↓ life-satisfaction/self-esteem vs general population – relationship status & having children affect satisfaction with life – pre-existing psychological difficulty associated with morbidity Implication: Need for psychological interventions
Ventura *et al.* (2007) USA Cross-sectional (n = 137) median: 32 years range: 18–42 years	– Functional Assessment of Chronic Illness Therapy Spiritual Well-Being Scale – Functional Assessment of Non-Life Threatening Conditions	– 18% were on antidepressants or anti-anxiety medications – spiritual & functional well-being positively correlated – 'meaning/peace' subscale predicts functional well-being – neither age, age at diagnosis, nor time since diagnosis associated with spiritual or functional well-being scores – Women reported searching for meaning as a means of coping Implication: Spirituality may help patients cope with a lack of control & find meaning/purpose
Kalantaridou *et al.* (2008) USA Cross-sectional (n = 143) median: 32.0 years	– Derogatis Interview for Sexual Function	– ↓ sexual cognition/fantasy, orgasm and libido/drive – NO differences in sexual arousal or behavior/experiences – Overall sexual function scores NOT correlated with age, age of onset, time since diagnosis or education level – Only 7% had 'abnormal' composite sexual function scores Implication: POI has significant effects on sexual function/sex life
Van Der Stege *et al.* (2008) Netherlands Cross-sectional (n = 81) median: 37 years	– Screening Sexual Dysfunction Questionnaire – Shortened Fatigue Questionnaire – Symptom Check List-90	– ↑ anxiety, depression, somatization, sensitivity, hostility & psychological distress – ↓ sexual arousal & satisfaction with sex life (distressing) – ↓ frequency of solo sexual activities/fantasies yet similar frequency of desire for & sexual contact with partners Implication: Interventions needed to alleviate psychological distress
Orshan *et al.* (2009) USA Cross-sectional (n = 154) mean: 32.3 years SD: 4.9 years	– Personal Resource Questionnaire 85 – Rosenberg Self-Esteem Scale	– ↓ perceived social support & self-esteem scales – NOT correlated with age, age at diagnosis, time since diagnosis, marital status or children – Perceived social support & self-esteem positively correlated Implication: POI has impact on self-esteem, social support needed
Davis *et al.* (2010) USA Cross-sectional & case control (n = 99) mean: 32.4 years SD: 5.2 years	– CES-D – State-Trait Anxiety Inventory – Positive & Negative Affect Schedule – Positive Mental Well-Being Inventory – Mishel Uncertainty in Illness Scale – Modified Lennon Stigma Scale – Goal Disengagement/Reengagement Scale	– ↑ depression scale, anxiety, negative affect – ↑ rates of medication for depression/anxiety – ↑ rates of psychological counseling – ↑ Illness uncertainty & stigmatization are positive predictors of depression/anxiety – ↑ purpose in life negatively predicts depression/anxiety Implication: Clinicians should provide POI information to ↓ uncertainty, encourage social connections to ↓ stigmatization and facilitate adaptation and provide psychosocial resources & referrals.

(continued)

Table I Continued

Study information	Measures	Summary findings
Benetti-Pinto *et al.* (2011) Brazil Cross-sectional (n = 58) mean: 39.4 years SD: 6.5 years	– WHOQOL-BREF	– No difference in HR-QoL dimensions of social relationships, environment or overall HR-QoL – ↓ HR-QoL in psychological & physical health domains – ↑ negative feelings that life was not meaningful Implication: Both psychosocial and physical support are critical to the care of patients with POI
Schmidt *et al.* (2011) USA Cross-sectional (n = 174) Mean: 31.6 years SD: 5.3 years	– Structured Clinical Interview DSM-IV (SCID)	– 69.5% reported a lifetime history of an Axis I disorder – majority of Dx = mood/anxiety disorders (54.5% = depression) – 22% met criteria for current Axis I Dx – Majority reported depression onset after the onset of menstrual cycle irregularity (yet before POI diagnosis) – ↑ depressive episodes in 3 years prior to POI Dx (vs 3 years post-diagnosis) Implication: Period prior to POI Dx is characterized by uncertainty and psychological distress
Mann *et al.* (2012) UK Cross-sectional (n = 136) Mean: 38.7 years SD: 7.0 years	– Women's Health Questionnaire – General Health Survey (SF-36)	– Neither satisfied/dissatisfied with medical services – positive experiences with Dx predicted satisfaction with medical services (neither age nor time since Dx predicted satisfaction) – ↑ depression, anxiety/fears, sleep problems, memory/concentration difficulties – Emotional role limitations, poor social functioning, ↓ vitality & diminished mental health contributed to ↓ psychosocial well-being & ↓ HR-QOL – Hot flushes/night sweats was correlated with depressed mood, ↓ vitality & ↑ anxiety/fears Implication: POI has wide-ranging effects on HR-QoL
Gibson-Helm (2014) Australia Cross-sectional (n = 25) Median: 36.0 years	– Greene Climacteric Scale	– ↓ interest in sex was 'quite a bit' to 'extremely' distressing – 72% were taking hormone therapy – NO hormone therapy associated with more severe vasomotor & urogenital symptoms – Anxiety/depression/psychological functioning NOT difference vs controls Implication: There is a disconnect between perceived & actual understanding of available treatment options and risks.
Guerrieri *et al.* (2014) USA Randomized control trial (n = 123) Mean: 32.1 years SD: 5.5 years	– Quality of Life Enjoyment & Satisfaction Questionnaire – 10-item Rosenberg Self-esteem Scale – Structured Clinical Interview DSM-IV (SCID) – CES-D – Hamilton Rating Scale for Depression	At baseline: – 13% had major depression, 8% had moderate depression (19% on medication) – 54% had history of major depression – 69% had NO lifetime Dx of an Axis I mood disorder Implication: Women with POI have increased depressive symptoms across multiple instruments.
Rivers (2014) USA Cross-sectional, 2° analysis (n = 99) Mean: 32.4 years SD: 5.2 years	– Fertility Problem Inventory – Life Orientation Test-Revised – Pearlin & Schooler Mastery Scale – CES-D – State-Trait Anxiety Inventory – Mishel Uncertainty in Illness Scale – Lennon Stigma Scale – Goal Disengagement/Reengagement Scale – Positive & Negative Affect Schedule – Positive Mental Well-being Inventory	– ↓ optimism & mastery scores – Optimism & mastery positively correlated with positive affect, purpose in life & goal engagement. – Optimism & mastery negatively correlated with negative affect, anxiety, depression, perceived stigma, illness uncertainty & infertility-related stress. – Optimism, positive affect & goal flexibility predicted emotional well-being over time Implication: Measures of optimism & goal flexibility may be useful for identifying those at risk for poor adjustment/emotional adaptation to guide clinical interventions.

(continued)

Table I Continued

Study information	Measures	Summary findings
Allshouse *et al.* (2015) USA Cross-sectional (n = 160) Mean: 39.3 years SD: 7.3 years	– Menopause-specific QoL questionnaire – Cognitive & Affective Mindfulness Scale Revised – POI symptom-specific questions	– 43% had a history of depression – >50% reported symptoms (joint clicking, cold intolerance, dry eyes, hair loss) – >75% had mood swings & 'mental fog' – Women with >3 severe symptoms had ↓ mindfulness in all domains – QoL & mindfulness measures NOT correlated with time since diagnosis Implication: Symptom checklists created for menopause >40 years do NOT capture the full range of experiences of women with POI.
Driscoll *et al.* (2016) USA Cohort study (n = 102) Mean: 32.0 years SD: 5.4 years	– Big 5 Inventory – Lennon Stigma Scale – Mishel Uncertainty in Illness – Life Orientation Test-Revised – Rosenberg's Self-esteem Scale – Pearlin Mastery Scale – Ego Resilience Scale – Brief COPE – Goal Disengagement/Reengagement Scale – Antoni's 16-item Benefit Finding Scale – CES-D – State-Trait Anxiety Inventory – Positive & Negative Affect Schedule – Positive Mental Well-being Inventory	– Resilience resources (optimism, self-esteem, mastery, ego) were positively correlated with well-being outcomes – Psychosocial vulnerability factors (neuroticism, perceived stigma, illness uncertainty) were positively correlated with distress – Differences in psychosocial vulnerability & avoidant coping at baseline accounted for 19% of variation in distress at 1 year – ↑ psychological vulnerability at baseline predicts ↑ short-term avoidance behaviors and predicts ↑ long-term distress (1 year). – Avoidance mediates long-term distress. – Adaptive coping behaviors include approach coping (planning/support seeking for biological parenting) or letting go/moving on Implication: Women with POI could benefit from interventions supporting adaptive coping.
Yela *et al.* (2018) Brazil Case control (n = 80) Mean: 38.4 years SD: 7.3 years	– Female Sexual Function Index – WHOQoL-BREF	– ↓ physical & psychological QoL & ↓ overall female sexual function index – Overall sexual function scores were positively correlated with self-perceives QoL – Sexual satisfaction was correlated with all QoL domains (social domain = strongest) – Sexual function psychological domains (satisfaction) were stronger predictors of QoL (vs physical domains) Implication: Improving social relationships is a target for improving QoL for POI.
Luiro *et al.* (2019) Finland Case control (n = 22) Median: 51 years Range: 28–70 years	– Beck Depression Inventory – Generalized Anxiety Disorder 7 – Female Sexual Function Index	– The majority of patients had no psychological morbidity – 14% had been diagnosed with a mood disorder (antidepressants & psychotherapy) – 9% had scores consistent with moderate depression – No patients met criteria for generalized anxiety disorder – 41% had 'high' risk for sexual dysfunction Implication: Sexual counseling should be recommended for women with POI.
Javadpour *et al.* (2021) Iran Case control (n = 66) Mean: 37.4 years SD: 3.1 years	– WHOQOL-BREF – Female Sexual Function Index	– 91% reported sexual dysfunction – ↑ sexual dysfunction in ALL domains (↓ lubrication was most common) – ↓ QoL in ALL domains vs controls – Overall sexual function significantly correlated with physical & social QoL domains – libido & arousal sexual function domains were correlated with ALL 4 QoL domains Implication: Sexual dysfunction merits attention and psychological services are integral to the management of POI

CES-D, Center for Epidemiologic Studies Depression Scale; COPE, Coping Orientation to Problems Experienced Inventory; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; fourth edition Dx, diagnosis; HR-QoL, health-related quality of life; POI, primary ovarian insufficiency; QoL, quality of life; WHOQoL-BREF, World Health Organization Quality of Life—Brief.

Table II **Summary of qualitative and mixed-methods studies on health-related quality of life in POI (n = 7).**

Study	Type and methods	Summary findings
Boughton and Halliday (2008) Australia	Qualitative Open-ended interviews (n = 35) Age not reported	– Patients experienced 'uncertainty' due to non-specific physical & psychological symptoms that were often misinterpreted as 'stress-related' – Clinicians 'delegitimized' symptoms because of patient age – Clinicians dismissed patient concerns stating that it was 'all in their heads' – Pregnancy test was stigmatizing, eroded hope and promoted feelings of despair – Clinicians overlooked individual concerns by talking about the 'typical' or 'average' patient Implication: Need to improve patient-provider interactions
Halliday and Boughton (2009) Australia	Qualitative Analysis of online discussion board messages (n = 98) Mean±SD: 34.5 ± 4.3 years	– 'Vague' physical & emotional symptoms were often dismissed by clinicians leaving patients feeling confused & frustrated – Delayed diagnosis associated with a perceived lack of care from clinicians & lack of confidence in clinician knowledge – Emotional response to Dx included feelings of guilt/shame, disrupted sense of self & sexual identity – Patients felt overwhelmed by treatment options & lack of clinician support in decision-making – Feelings of isolation before/after Dx related to lack of clinician/social support – Patients expressed a strong desire to connect with other patients Implication: Need for clinician & social support for patients
Johnston-Ataata *et al.* (2020) Australia	Qualitative Narrative interviews (n = 30) Median: 44 years Range: 28–51 years	– Protracted diagnostic process, misdiagnosis & symptoms being dismissed – Memorable 'diagnostic moment' characterized by feelings of shock, distress, loss and finally 'making sense' of symptoms – Discontinuous care in early adulthood involving multiple clinicians – Fear of risks associated with hormone treatment – Discontinuation of treatment associated with perceived lack of support, gaps in care & perceptions of menopause being a natural (albeit early) process Implication: Need for an individualized approach to Dx & care. Potential role for digital resources.
Golezar *et al.* (2020) Iran	Qualitative In-depth, semi-structured interviews (n = 16) Mean: 36.7 years Range: 28–47 years	– Three major themes: disease effects, distorted self-concept & effects of hormone therapy – Consternation, grief, rage, moodiness, stress & negative feelings were common responses to Dx – Symptoms improved with hormone therapy – Dx was stigmatizing, patients felt judged and tried to conceal their Dx Implication: POI negatively affects QoL, need for support in coping with Dx.
Groff *et al.* (2005) USA	Qualitative 48-question structured interview derived from prior focus groups (n = 100) Median: 33 years Range: 21–43 years	– Lack of information ↓ patients' sense of control & perceived ability to function – 71% dissatisfied with their perception of the Dx – Satisfaction associated with being 'emotionally prepared', knowledgeable & sensitive clinicians & sufficient time with clinician – Anger, depression, feeling less healthy/older/less feminine were common experiences – 8% received a clinician referral for psychological support, 3% had clinician discuss plans for supporting emotional & mental health at Dx – Helpful supports included spirituality, support groups/POI patients & professional counseling Implication: 'Ideal' envisioned support structure would include a forum of patients with POI, network of knowledgeable physicians & reliable medical information.

(continued)

Table II Continued

Study	Type and methods	Summary findings
Singer *et al.* (2011) UK	Mixed-Methods (n = 136) Quantitative – Rosenberg Self Esteem Questionnaire – General Health Survey (SF36) – Sexual Personal Experiences Questionnaire Qualitative Investigator developed open-ended questions Mean±SD: 38.7 ± 7.0 years	– Women perceived stress & earlier life choices contributed to POI – Most felt they were not offered enough information about their Dx – Fertility, diminished sexual function & concerns about therapy were most frequent concerns – Hormone therapy was not associated with satisfaction with medical services – Initial needs = information, understanding & support – Longer-term needs = regular follow-up & psychological support – ↓ mental well-being & sexual satisfaction – 88% reported negative impact on emotional well-being as a long-term consequence of POI – 78% reported POI negatively impacted self-image & confidence Implication: POI negatively impacts psychological wellbeing & sexual satisfaction, need for tailored approach to support patients.
Vemuri *et al.* (2019) USA	Mixed-Methods (n = 26) Quantitative Investigator-designed questionnaire Qualitative Investigator developed open-ended questions Mean±SD: 38.5 ± 5.6 years	– Most common coping strategies included learning about POI, social supports & new hobbies – Negative impact on family & relationships, sexuality, self-esteem & mental health were common – Most valuable aspect of care was finding a clinician with POI expertise & good interpersonal skills Implication: Interactions with skilled, knowledgeable, caring clinicians is important for supporting effective adaptation to living with POI.

Dx, diagnosis; POI, primary ovarian insufficiency; QoL, quality of life.

identified additional factors at the interpersonal and healthcare system levels. Emergent constructs include peer-to-peer support (Groff et al., 2005; Halliday and Boughton, 2009), compassionate clinicians (Groff et al., 2005; Vemuri et al., 2019), a sensitive revelation of POI diagnosis (Groff et al., 2005), individualized care (Vemuri et al., 2019; Johnston-Ataata et al., 2020), adequate time for patient education/questions (Groff et al., 2005) and continuity of care with regular follow-up (Singer et al., 2011).

Discussion

Herein, we report findings from a systematic scoping review of the literature on HR-QoL in women with idiopathic POI. Within the broad umbrella concept of HR-QoL, three key interrelated themes emerged from the quantitative, qualitative and mixed-methods studies: 'diagnostic odyssey', 'isolation and stigma' and impaired 'ego integrity'. First, the 'diagnostic odyssey' theme relates to an extended journey to reach a clinical diagnosis. The diagnostic odyssey is well documented among patients with rare, poorly understood conditions (Bogart et al., 2022). Women with POI frequently report feelings of uncertainty, perceived lack of control, knowledge gaps (i.e. not understanding their health condition) and negative clinical interactions with providers across multiple specialties (i.e. discontinuous care). Findings point to challenges in navigating a complex healthcare ecosystem to reach a diagnosis.

The second interrelated theme 'isolation & stigma' characterizes the emotional coping response of women after being diagnosed with POI. Women often feel labeled as infertile—contributing to guilt and shame. In parallel, negative (unsympathetic) clinical encounters and lack of social support can exacerbate the emotional response to the diagnosis. Many women respond by trying to conceal their diagnosis—an avoidant coping response that can amplify feelings of isolation. These observations point to a need for tailored, person-centered and holistic approaches to care that not only address infertility and hormone replacement, but also the psychosocial impact of receiving a life-altering POI diagnosis.

The third interrelated theme 'ego integrity' refers to the impact the diagnosis and symptoms have on an individual's identity. The theme suggests that acquired POI-related changes like infertility, decreased sexual function and altered body image disrupt the continuity of one's sense of self and threaten ego integrity (Adler et al., 2021). Given the personal and societal value placed on reproductive capacity, infertility is often accompanied by a loss of control and diminished self-worth (Greil, 1997). Individuals who are unable to incorporate the real (physical) and perceived (psychological) changes into their sense of self (i.e. identity integration) can suffer significantly impaired health and well-being (Mitchell et al., 2021).

It is plausible that the personal/societal value placed on reproductive capacity and the protective factor of focusing on personal goals may be linked. Namely, women who are more inclined to focus on personal goals may be less invested in their ability to bear children—and thus relatively insulated from the compromised HR-QoL associated with subfertility/infertility. Reviewing the existing literature we did not identify any clear, direct link between these concepts. However, Liao et al. (2000) noted that already having children was associated with greater life satisfaction—yet not lower rates of depression. Thus, it appears that that individual coping responses appear to be patient-specific and one should be cautious about making sweeping conclusions based on the available data.

It is worthwhile to note that although many women experience psychological distress following a POI diagnosis, other women adjust rather well—indicating variability in coping response to POI. Historically, models examining adaptation to health threats have been unidimensional with a 'negative' focus (i.e. psychological/emotional risk factors, maladaptive coping responses, negative psychosocial outcomes). More recent models embrace a 2-dimensional approach that also includes 'positive' factors like resilience, adaptive (active) coping and positive outcomes (Ryff and Singer, 1998). In one of the few longitudinal studies conducted in women with POI, Driscoll et al. (2016) applied a 2-dimensional model of risk and resilience to examine coping response to infertility. Using confirmatory factor analysis, investigators found that baseline vulnerability and resilience factors predicted distress and well-being respectively at 12 months. Notably, avoidant coping (i.e. refusing to acknowledge diagnosis-related stress) mediated the observed association between baseline vulnerability and distress at 12 months (Driscoll et al., 2016).

Our systematic scoping review did not identify any POI-specific measures of HR-QoL. Importantly, general HR-QoL instruments (e.g. SF-36, WHOQOL-Bref) often do not capture the salient constructs for particular conditions. Thus, general instruments may underestimate the impact of condition-specific symptoms and the degree to which wellbeing is impacted (Ware et al., 2016). Accordingly, future directions could include work to develop and validate a disease-specific POI HR-QoL measure or patient-reported outcome measure (PROM). Our synthesis of existing data in this scoping review could provide foundational insights for developing a POI-specific HR-QoL instrument and could inform the development of PROMs to inform a comprehensive, holistic approach to management of POI. Such disease-specific tools would be a useful addition as they would offer a reliable means to measure changes in response to hormonal and/or psychosocial interventions. We acknowledge that not all people born with ovaries identify as women. As such, additional future directions may include describing the experiences of individuals with POI across the continuum of gender identity. In addition, we did not identify any interventional studies that specifically address the psychosocial wellbeing of women with POI. Coping response (i.e. avoidant vs active) is a critical link between psychosocial traits (i.e. vulnerability, resilience) and outcomes (i.e. distress, wellbeing) (Driscoll et al., 2016). We used an ecological perspective to categorize factors promoting active coping at the level of the individual, interpersonal level or healthcare system. We considered that such targets could be the basis for theory-informed interventions (i.e. TPB) to support active coping and identity integration to foster wellbeing in women with POI (Fig. 3). Notably, a 2021 narrative review conducted to guide the development of models of care for POI identified six key themes: stakeholder engagement, supporting integrated care, evidence-based care, defined outcomes and evaluation, incorporating behavior change methodology and adaptability (Jones et al., 2020). Importantly, stakeholder (patient) engagement was considered central to all of the themes, indicating that there are opportunities to involve patients in the development of models of care and interventions.

At the individual level, narrative interventions (Adler et al., 2016; Mitchell et al., 2021) could help reframe the POI diagnosis and support women in integrating POI into their identity (TPB: behavior beliefs that

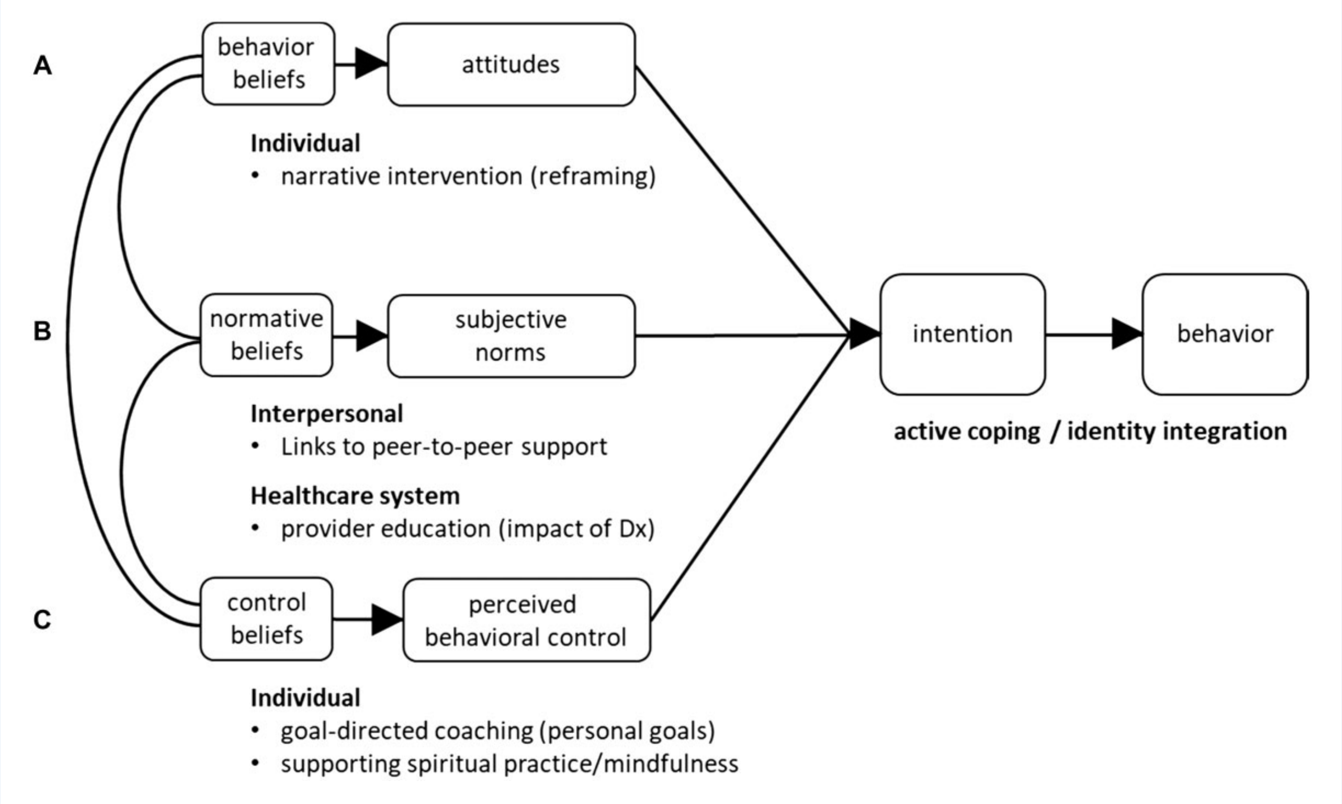

Figure 3. Targets for interventions supporting active coping mapped to the theory of planned behavior. To inform multilevel interventions to support identity integration and active coping (i.e. intention and behavior), we mapped targets from the individual, interpersonal and healthcare system levels to the Theory of Planned Behavior (TPB). (**A**) Factors relating to TPB beliefs/attitudes include narrative interventions to reframe the primary ovarian insufficiency (POI) diagnosis and support individuals in integrating the diagnosis into their identity. (**B**) Factors relating to TPB norms include connecting patients to peer-to-peer support to normalize experiences with other patients and decrease isolation. Educating providers on the psychosocial impact of the POI diagnosis could shift prevailing norms within the healthcare system and support more sensitive patient interactions. (**C**) Factors relating to perceived behavioral control include supporting taking active steps toward personal goals and reinforcing the importance of spiritual/religious practices and mindfulness. Dx, diagnosis.

shape attitudes). Similarly, a positive forward looking approach using goal-directed coaching and supporting spiritual practice/mindfulness could foster and reinforce an internal locus of control over their life (TPB: control beliefs that shape perceived behavioral control). At the interpersonal level, creating patient-facing materials with links to peer-to-peer support could help patients find others to help them normalize their experiences and pierce the veil of isolation and shame (TPB: normative beliefs that shape subjective norms). Peer-to-peer support has proven to be critical for overcoming similar emotional responses among rare disease patient populations (Dwyer *et al.*, 2014). Moreover, a 'design thinking' (i.e. human centered design) approach has been posited for developing more comprehensive, integrated care for POI (Martin *et al.*, 2017). We have previously shown that partnering with patients and using design thinking to co-create patient-facing materials produces high quality, lay language materials that are responsive to patient priorities (COST Action BM1105 *et al.*, 2017; Dwyer *et al.*, 2021). Work is currently underway to engage patients to co-create patient-facing materials for POI. At the healthcare system level, educating providers about the psychosocial aspects of POI and making patient-facing materials freely available online could shift the prevailing norms of providers (TPB normative beliefs that shape subjective norms) (Fig. 3).

Relative strengths of the scoping review include the comprehensive, systematic review of the literature with review by independent investigators (100% concordance) to extract findings from quantitative, qualitative and mixed-methods studies. There are limitations to the scoping review. First, we identified a wide range of validated instruments that were used to study HR-QoL in women with POI. The lack of a validated, disease specific instrument limits our ability to understand the full scope of how POI affects HR-QoL. Second, we did not identify any interventional studies. Thus, the best approach to improving HR-QoL in POI remains unclear. Last, we only included publications in English. As such, it is possible that work published in other languages may add other insights into the experiences of women with POI.

In conclusion, the systematic scoping review found that receiving a POI diagnosis is a watershed moment in a woman's life with significant implications for HR-QoL. We identified three interrelated themes highlighting unmet psychosocial needs of women with POI. The study findings identify targets for theory-informed interventions at the individual, interpersonal and healthcare system levels to support active coping and improve HR-QoL in women with POI. There are opportunities to include patients in designing interventions that respond to high-priority unmet patient needs. Targeted, person-centered interventions are needed to deliver comprehensive, high-quality care for women with POI.

Data availability

No new data were generated or analyzed in support of this research.

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Authors' roles

I.R.M. made significant contributions to data collection, data curation, data validation, formal analysis, writing the original draft, reviewing/editing the manuscript and project administration. C.K.W. made significant contributions to data validation and reviewing/editing the manuscript. A.A.D. made significant contributions to conceptualization, methodology, data validation, formal analysis, creating visualizations, writing the original draft, reviewing/editing the manuscript, supervision, project administration and funding acquisition. All authors have read and approved the submitted manuscript.

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Conflict of interest

The authors declare no conflict of interest or disclosures.

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