Fertility Quality of Life Tool: Update on Research and Practice Considerations

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Abstract

The 36-item Fertility Quality of Life (FertiQoL) tool is increasingly used in research and practice. It measures quality of life in four personal domains (emotional, social, relational, mind/body) and two treatment domains (tolerability, environment). A literature review of published empirical research using FertiQoL was undertaken to provide an overview of this research base. Five databases were searched using "~~the key word~~ FertiQoL" and its variant. In total, 41 published articles from 35 independent samples in 23 countries involving 16,315 participants, mainly in clinical settings, were reviewed. FertiQoL was used for three main purposes. First, to assess quality of life and FertiQoL measurement properties (especially Core FertiQoL) ~~)~~ ~~in new populations~~ using cross-sectional designs. Second, to identify correlates, predictors and consequences of fertility quality of life. ~~These also~~ Some included international comparisons. Finally, to assess the effect of psychological interventions on fertility quality of life. The range of median FertiQoL Core, Treatment and subscale (scaled) scores in 31 samples was between 60 and 75. Poorer fertility quality of life was ~~most~~ consistently associated with being a woman, longer duration of infertility, poorer psychological functioning and lower patient-centered care. Some FertiQoL subscale scores ~~were shown to~~ improved after psychological interventions. Future research should address measurement issues and ~~provide more in-depth understanding of~~examine reported associations with fertility quality of life.

Keywords: infertility; fertility

Introduction

FertiQoL is an international instrument to measure quality of life in individuals experiencing fertility problems (Boivin, Takefman, & Braverman, 2011). As defined by the World Health Organization, quality of life encompasses: "…individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns." (World Health Organization, p. 1403). It is important to measure quality of life (QoL) of individuals experiencing fertility problems because infertility and fertility care have an impact on it (Aarts et al., 2011; Boivin et al., 2011; Huppelschoten et al., 2013b; Kitchen, Aldhouse, Trigg, Palencia, & Mitchell, 2017), and, conversely, QoL is linked to patient behaviour and clinical outcomes (Domar, Gross, Rooney, & Boivin, 2015; Gameiro, Canavarro, & Boivin 2013; Kitchen et al., 2017). The measurement structure of FertiQoL was proposed to include a Core FertiQoL component with subscales that measure the impact of fertility problems on emotional (e.g., 'Do you feel able to cope with your fertility problems?'), mind-body (e.g., 'Are you bothered by fatigue because of fertility problems?'), relational (e.g., 'Do you find it difficult to talk to your partner about your feelings related to infertility?'), and social (e.g., 'Are you socially isolated because of fertility problems?') domains of quality of life. The FertiQoL structure also includes the Treatment FertiQoL that measures treatment quality of life via the treatment environment (e.g., 'Do you feel the fertility staff understand what you are going through?') and tolerability (e.g., 'Are you bothered by the physical side effects of fertility medication and treatment?') subscales. A higher score on all subscales (and total scores) means more quality of life. The FertiQoL was a collaborative effort among the European Society of Human Reproduction and Embryology (ESHRE), American Society for Reproductive Medicine (ASRM), Merck-Serono, Geneva Switzerland (part of Merck, Darmstadt Germany) and Cardiff University to address the unmet need for a more standardised approach to fertility specific quality of life measurement for patient understanding, service evaluation, and research.

FertiQoL added to existing fertility distress tools by measuring the broader concept of quality of life, involving fertility patients in its development and validating it with a large international sample.

FertiQoL has now been translated into 48 languages and used extensively (see Boivin et al., 2011 and www.fertiqol.com for more detailed information about the tool, available translations, scoring methods). Potential users must strictly adhere to the Terms of Reference. Items should not be altered. FertiQoL is judged to perform well in reviews of patient reported outcomes (Kitchen et al. 2017; Pedro et al. 2016) but findings using FertiQoL have not yet been reviewed in depth despite a large number of studies using FertiQoL. The purpose of the literature review was to identify all research using FertiQoL to date, to consolidate and summarize what has currently been reported using it, and to identify areas for future study. A review of this nature would enable us to show progress in understanding of fertility quality of life, how FertiQoL has been (and could be) used in patient-oriented work (clinical care or research-based), and identify potential directions for future research about fertility quality of life (e.g., causes and consequences of poor fertility quality of life, the effectiveness of clinical care strategies and psychological interventions in improving fertility quality of life, and the effect of fertility quality of life on treatment trajectories) or on FertiQoL itself. This paper presents the characteristics of the studies reviewed, a thematic summary of what the results show about fertility quality of life, and offers suggestions for future directions for research.

Material and Methods

Search Procedure and Study Selection

The search strategy covered FertiQoL studies to November 4, 2017. Online databases including Ovid Medline, EMBASE, PsychINFO, CINAHL, and Cochrane were searched between 2002 (the year FertiQoL was released) and November 2017 (see Supplementary Table 1). Search terms included 'Fertility OR Infertility' and 'FertiQoL OR Fertility quality of life'. The search strategy was crosschecked with three key studies (Aarts et al., 2011; Boivin et al., 2011; Gameiro et al., 2013). Reference lists of included articles were manually searched. Studies identified in all searches were included if they were published empirical research collecting FertiQoL data. Review papers, study protocols, studies not using FertiQol, conference abstracts, non-English articles and duplicates were excluded. Two researchers

screened the titles, abstracts, and full-text articles independently and any disagreements were resolved with discussion. Overlapping studies using a portion or all of same sample were accepted if the article reported on different outcomes (von Elm, Poglia, Walder, & Tramer, 2004). For these studies, psychometric properties on the largest sample with available data for subscales (i.e., mean, standard deviation, reliability) were reported. Studies were identified as overlapping in Tables and in text where relevant. No ethics approval was sought.

Data Extraction and Synthesis

EK extracted the following from the included studies: authors; publication date; country; study design; purpose; sample size; population (gender) and treatment (i.e., type of treatment); recruitment source (in clinic, online); when FertiQoL measured (e.g., pre-treatment, during treatment, post-treatment); response rate; and results (scaled scores, effect sizes or p-values). In the present study we report FertiQoL scaled scores, which range from 0 to 100 with higher scores indicating higher quality of life (see http://sites.cardiff.ac.uk/fertiqol/scoring/ for more details about scoring). Each study's purpose and results were reviewed and grouped into themes according to commonalities across studies. A summary for each theme and subthemes was developed.

Quality Appraisal

EK assessed study quality of articles available in English using an adapted Newcastle-Ottawa quality assessment scale (Wells, 2010) and the Critical Appraisal Skills Program checklist (CASP, 2016). Quality criteria included the representativeness of the sample, comparability based on control of confounders, validity of aims, hypotheses, and methods, adequacy of outcome measures, and quality of outcome reporting. The overall quality was the sum of all points where 1-2 points was considered low quality; 3-5 points moderate quality; and 6-7 points high quality scores. Intervention studies were evaluated based on the Specialist Unit for Review Evidence (SURE, 2013) criteria for experimental studies with and without control groups. These studies could receive up to 8 points. Only one quality

assessment was done per sample. In overlapping studies, quality assessment was informed by all reports where relevant (e.g., when an outcome was reported in a later article). Supplementary Tables 2 to 4 provide detail of the quality appraisal and point system.

Results

Figure 1 shows the flowchart for study selection. After exclusion, 41 included studies were reviewed and critically appraised (from 35 independent samples).

Characteristics of Included Studies

The 41 included studies were drawn from 35 independent samples (16,315 participants) in 23 countries. Five clusters of studies using overlapping samples were identified (characteristics of largest sample reported in this section: Aarts et al., 2011; Gameiro et al., 2013; Huppelschoten et al., 2013b; Maroufizadeh, Ghaheri, Amini, Omani Smani, 2017a; Sexty et al., 2016).

Overall the majority of included studies were cross-sectional (26 studies, 74.3%), with remaining studies being pre to post designs (4 studies, 11.4%) or prospective or longitudinal designs (5 studies, 14.3%). The largest number of studies pooled participants at different treatment stages (13 studies, 37.1%) but some sampled patients exclusively pre-treatment (7 studies, 20%), during treatment (8 studies, 19.4%), or post treatment (4 studies, 11.4%). Overall 21 studies recruited individuals (60%) and 14 (40%) couples. The majority of included studies (28, 80%) used non-systematic methods of recruitment in clinics (e.g., convenience sampling) with few studies recruiting consecutive patients (4 studies, 11.4%), or using random sampling (3 studies, 8.6%). All but one study sampled patients in treatment (97.1%), most commonly undergoing assisted reproductive technology (ART) treatment cycles (28 studies, 80%). The median sample size across included studies was 301 participants (range 18 to 3,088), and the female to male ratio was close to 4:1 in individual, non-couple studies. The participation rate averaged across included studies was 70% (range 41 to 92.5%). Quality assessment of included papers (overlapping

samples included once) indicated 11 studies were of high quality (31.4%), 23 of moderate quality (65.7%) and one low-quality (2.9%),

We grouped the results of the included studies into the three broad themes their data addressed (see Supplementary Tables 5 to 10 for study details). A summary of what the results show about fertility quality of life is provided for each theme. One included study was not considered further (Hsu, Lin, Hwang, Lee, & Wu, 2013) because several subscales showed a likely error in scoring that had previously been communicated to the authors (personal communication via email from J Boivin, 6 August 2013).

1. What are the psychometric properties of FertiQoL as a measure of fertility quality of life?

a) Confirmatory factor analysis of FertiQoL measurement structure

As noted, FertiQoL was conceptualised as measuring quality of life in four Core personal domains (Emotional, Mind/Body, Relational, Social) and two Treatment domains (Environment, Tolerability). Donarelli et al. (2016) and Maroufizadeh et al. (2017a) both reported best-fit indices that were within satisfactory standards indicating observed data in Italy and Iran (respectively) with the proposed FertiQoL Core conceptual model, and Treatment (Maroufizadeh et al., 2017a) only).

b) Internal consistency of FertiQoL

See Supplementary Table 11 for summary of Cronbach coefficient alpha for each study providing these data and Supplementary Table 12 for specific details of each subscale. Reliability is generally considered satisfactory when $\geq$ .70 (Peterson, 1994). For all studies, reliability for the Core FertiQoL was > .80. Further, satisfactory reliability was reported for the Emotional, Mind/Body and Social subscales (> .70) with one exception for social domain (Sexty et al., 2016). In contrast, the Relational subscale generally showed unsatisfactory reliability with most studies reporting alpha coefficients between .60 and .70. The Treatment Module reliability was > .70 as was its two subscales (Environment and Tolerability) in all but one study from Iran (Maroufizadeh et al., 2017a) and one study from Turkey (Kahyaoglu Sut &

Balkanli Kaplan, 2015). The Total FertiQoL reliability coefficient was > .90 in all five studies reporting it.

c) Construct validity of FertiQoL

In all cases, construct validity was measured by correlating FertiQoL scores with cognate measures in which scores should be associated in predictable ways (i.e., convergent validity; e.g., depression scale and FertiQoL Emotional subscale should be positively correlated). Results suggested convergent validity. For example, lower FertiQoL scores were associated with higher anxiety and depression scores in a sample of Dutch women accessing fertility treatment (Aarts et al., 2011) and in Turkish infertility patients (Kahyaoglu Sut & Balkanli Kaplan, 2015). The FertiQoL Relational subscale and scores on a relationship adjustment scale were positively correlated in an Italian sample of couples awaiting a first ART cycle (Donarelli et al., 2016). Women with a high level of marital distress reported significantly lower relational quality of life than women not distressed (Chan, Lau, Tam, & Ng, 2016). Similarly, in a Hong Kong study the Relational subscale showed the highest correlation with sexual dysfunction and those experiencing sexual dysfunction had significantly lower Relational FertiQoL scores than those without such problems (Lo & Kok, 2016). Higher Treatment FertiQoL scores were associated with measures of better patient centered care in cross-sectional studies (Aarts et al., 2012; Pedro, Canavarro, Boivin, & Gameiro, 2013; Holter et al., 2014). Finally, the disease-specific FertiQoL was compared to a global quality of life tool (Short Form-36; SF-36) in a prospective study of 41 Spanish women undergoing fertility treatment (Heredia et al., 2013). Results showed positive and significant correlations between FertiQoL scores and the majority of SF-36 mental dimensions (vitality, social functioning, mental health and emotional role functioning). See Supplementary Table 11 for summary of studies measuring construct validity.

2. What has been learnt about fertility quality of life from using FertiQoL?

a) Average fertility quality of life scores (including International Comparisons)

Figure 2 shows that median scores across FertiQoL subscales, Core, Treatment and Total were in the range of 60 to 75 (n=31 independent samples, overlapping samples counted once, Hsu et al. (2013) not included). Figure 3 shows Core FertiQoL mean scores across country. Supplementary Table 13 presents descriptive data (means and standard deviations) for included studies. Core and Treatment FertiQoL scores were moderately correlated within included studies ($r(22)=.574$, $p \leq .011$).

Four cross-sectional studies (moderate quality) did comparative analyses. Jordanian couples were shown to have poorer emotional, relational and mind-body quality of life than did German and Hungarian couples (Cserepes et al., 2014; Sexty et al., 2016) but after controlling for group differences on socio-demographic and fertility variables the Jordanian group differed only on emotional quality of life. Chi et al. (2016) found lower Core subscale scores in a Korean sample compared to the FertiQoL development sample (i.e., Boivin et al. 2011). Valsangkar, Bodhare, Bele, and Sai (2011) found similar results in comparison between the FertiQoL development sample and an Indian sample. Madero and colleagues (2017) compared FertiQoL scores in men and women from Germany, Italy and France undergoing cross-border oocyte donation in Spain. French patients showed poorer emotional and mind-body quality of life than Italians, whereas both French and German patients showed lower relational quality of life than Italian patients. However, Italian patients had lower social quality of life than Germans.

FertiQoL was used to examine the QoL of specific infertile populations. The studies were of moderate quality. In one prospective, controlled cohort study, infertile women with and without endometriosis were found to have similar FertiQoL scores except that women with endometriosis had lower QoL in the Mind-Body domain (Santulli et al., 2015). In a longitudinal study (Jarvholm, Johannesson, Clarke, & Brannstrom, 2015), nine women undergoing uterine transplant were shown to have higher FertiQoL scores than that reported for general infertile populations (e.g., Aarts et al., 2011). In another prospective study, Santoro and colleagues (2016) reported that women with polycystic ovary syndrome (PCOS) had lower FertiQoL scores than women with unexplained infertility (except for Relational domain). However, additional analyses showed that this difference was explained by differences in features of disease (i.e., greater weight and hirsutism in PCOS group). Partners of these

women showed a reverse pattern namely, men partnered with women having PCOS had higher QoL (except relational) than partners of women with unexplained infertility (Santoro et al., 2016).

b) Clinically important thresholds

To identify level of quality of life associated with distress three studies determined the FertiQoL scores corresponding to cut-offs for depression and anxiety on validated measures (no corresponding Supplementary Table as studies reported in other sections). In a Dutch sample, the total FertiQoL scores that corresponded to the clinical cut off for anxiety and depression were 59 and 52, respectively (Aarts et al., 2011). Using similar methodology, cut offs of 55 and 52, respectively, were reported for women in Turkey (Dural et al., 2016) whereas another study of Turkish women found the same cut offs as the Dutch sample (Kahyaoglu Sut & Balkanli Kaplan, 2015). In an Italian study, FertiQoL Relational scores below around 74 corresponded to marital dysfunction on dyadic adjustment questionnaire (range 74 to 84, depending on measure, Donarelli et al., 2016).

c) Variables that co-vary with fertility quality of life

Eighteen cross-sectional studies (moderate to high quality) investigated correlates of fertility quality of life (see Supplementary Table 7). This research was primarily conducted using convenience samples with women recruited through infertility clinics completing FertiQoL prior to or during treatment. There were mixed results for demographic variables. Gender was the strongest predictor across studies, with women consistently showing poorer quality of life than men. Huppelschoten et al. (2013b) reported that 28% of variability in Core FertiQoL was due to gender. Unemployment was associated with lower FertiQoL scores in one study (Keramat et al., 2014) but not in two others (Goker, Yanikkerem, Birge, & Kuscu 2017; Heredia et al., 2013). Higher income level was associated with better quality of life in five studies (Karaca et al., 2016; Keramat et al., 2014; Namavar, Mansouri, Forouhari, Poordast, & Salehi, 2018; Steuber and High, 2015; Santoro et al., 2016), but not in three others (Hasson et al., 2017; Karabulut, Ozkan, & Oguz, 2013; Karabulut, Demirtas, Sonmez, Karaca, & Gok, 2017). Higher

education was associated with better quality of life in three studies (Karabulut et al., 2013; Keramat et al., 2014; Namavar et al., 2018), and lower quality of life in two studies (Hasson et al., 2017; Porat-Katz, Paltiel, Kahane, Eldar-Geva, 2016) and no association in four others (Kahyaoglu Sut & Balkanli Kaplan, 2015; Karabulut et al., 2017; Maroufizadeh, Ghaheri, & Omani Samani, 2017b; Santoro et al., 2016). Older age was correlated to higher FertiQoL scores in five studies (Asazawa & Mori, 2015; Goker et al., 2017; Karabulut et al., 2013; Porat-Katz et al., 2016; Santoro et al., 2016) but not in five others (Heredia et al., 2013; Kahyaoglu Sut & Balkanli Kaplan, 2015; Karabulut et al., 2017; Keramat et al., 2014; Maroufizadeh et al., 2017b). Marital status was not associated with quality of life in two studies (Hasson et al., 2017; Porat-Katz et al., 2016). Longer marital duration was associated with higher quality of life in one study (Goker et al., 2017) but not in another (Keramat et al., 2014).

Characteristics of the infertility or treatment experience were also associated with fertility quality of life, but not consistently. Time trying to conceive was associated with lower FertiQoL scores in one study (Kahyaoglu Sut & Balkanli Kaplan, 2015). A longer duration of infertility was associated with poorer quality of life in five of seven studies (Karabulut et al., 2013; Karaca et al., 2016; Keramat et al., 2014; Namavar et al., 2018; Santoro et al., 2016) as was unexplained infertility (Heredia et al., 2013; Maroufizadeh et al., 2017b). In contrast secondary infertility was associated with better quality of life than primary infertility (Karabulut et al., 2013). Being in treatment or having had a consultation for infertility was associated with lower quality of life in one study (Namavar et al., 2018). A greater number of treatment attempts was associated with lower quality of life in one study (Kahyaoglu Sut & Balkanli Kaplan, 2015) but not in two others (Heredia et al., 2013; Smith, Madeira, & Millard, 2015). Cycle cancellation in ART was associated with lower FertiQoL scores compared to a completion cycle (whether pregnant or not; Heredia et al., 2013). The partner accompanying the patient at clinic was associated with higher quality of life (Heredia et al., 2013). Use of complementary medicine was associated with higher Relational quality of life and lower Social quality of life in one study (Porat-Katz et al., 2016). One study reported that higher BMI and more hirsutism were associated with lower FertiQoL scores (Santoro et al., 2016).

Indicators of psychological vulnerability were more consistently associated with poorer quality of life. Specifically, higher depression (Chan et al., 2016; Kahyaoglu Sut & Balkanli Kaplan, 2015; Maroufizadeh et al., 2017b), anxiety (Chan et al., 2016; Kahyaoglu Sut & Balkanli Kaplan, 2015; Maroufizadeh et al., 2017b), desire for psychological support (Karabulut et al., 2013), lower marital and sexual satisfaction (Keramat et al., 2014), lower sexual functioning (Lo & Kok, 2016; Smith et al., 2015) decisional conflict (Chan et al., 2016), and use of indirect forms of communication to disclose fertility problems (e.g., email or jokes; Steuber & High, 2014) were all related to poorer quality of life.

FertiQoL subscales were correlated with cognate measures of psychological and interpersonal functioning. For example, three showed that higher depression and anxiety were related to lower FertiQoL scores (Aarts et al., 2011; Chi et al., 2016; Dural et al., 2016). Some of the associations between psychological vulnerability and FertiQoL were mediated by other variables. For example, in a cross-sectional American sample perceived social support accounted for the benefit of direct forms of disclosing fertility problems (e.g., face-to-face) on quality of life (Steuber & High, 2014). One cross-sectional study tested a 'partnership causal model' for couples undergoing fertility treatment in Japan (Asazawa & Mori, 2015) and showed that higher emotional support from partner was positively associated with higher FertiQoL scores for both genders. Importantly, support from medical professionals (e.g., doctors and nurses) at the clinic was associated with better quality of life through strengthening the partner relationship during treatment (Asazawa & Mori, 2015).

Only three studies examined correlates of fertility quality of life for men and women separately (Goker et al., 2017; Karabulut et al., 2017; Namavar et al., 2018). Two studies found shorter duration of education was associated with lower FertiQoL scores in men (Goker et al., 2017; Namavar et al., 2018) but only one of the studies found this association in women (Namavar et al., 2018). Unemployment was associated with poorer quality of life for men but not women in one study (Karabulut et al., 2017). One cross-sectional study examining FertiQoL in Turkish couples found that lower education, living in a town/village, and having primary infertility was associated with poorer QoL for men but correlates of low FertiQoL in women were being of middle/lower income and having undergone previous treatment. Being

younger, in their first marriage, in an arranged marriage, having a shorter duration of marriage (under 10 years), and being childless for more than 5 years was associated with poor QoL for both sexes (Goker et al., 2017).

There is evidence that correlates may differ according to FertiQoL domain scores. For example, Goker et al. (2017) found that for men education predicted lower Emotional, Mind-body and Tolerability domains, shorter marriages additionally predicted Social domains whereas being in an arranged marriage predicted Relational and Environment domains. Similarly, Hasson et al. (2017) found immigration status predicted all FertiQoL domains except Relational and Treatment Tolerability domains.

d) Associations with fertility quality of life over time

Of the studies reviewed, six provided longitudinal or prospective data about fertility quality of life over time. Jarvholm et al. (2015) assessed FertiQoL prior to and 3, 6 and 12 months after uterine transplant in nine Swedish women and their partners. Scores were stable over time for women and men. Chan et al. (2016) assessed FertiQoL (Core, Treatment) immediately after learning of ART treatment failure, two to three weeks later when couples decided about further treatment, and three months hence (Hong Kong sample). Descriptive statistics were reported showing little change over time in FertiQoL. Correlations showed that FertiQoL scores at each assessment were highly predictive of scores at the next assessment ($r > .70$). Chan et al. (2016) also found that Core and Treatment FertiQoL were predictive of each other across time (correlations .30 to .50).

A few studies explored whether FertiQoL scores could predict future outcomes. In the Chan et al. (2016) study lower Core and Treatment FertiQoL immediately after a failed cycle predicted higher decisional conflict at post-treatment consultation two to three weeks later (regardless of decision). Additionally, Treatment quality of life predicted decisional regret three months later. Three studies predicted dropout from pre-treatment scores. Huppelschoten et al. (2013a) assessed Core FertiQoL within three months of a treatment cycle and found it did not predict treatment discontinuation at 12-month follow-up. Domar et al. (2015) reported that Emotional FertiQoL assessed within a month of the start of

an ART cycle did not predict dropout at 12 months, and this lack of association was observed in patients randomised and not randomised to a coping intervention. Finally, Santoro et al. (2015) reported that pre-treatment FertiQoL scores did not predict dropout over a five-month treatment protocol. Santoro et al. (2015) also reported on pregnancy rates. It was found that lower pre-treatment Emotional FertiQoL predicted lower pregnancy and live-birth rate in women with PCOS whereas lower Mind-Body FertiQoL predicted higher pregnancy in women with unexplained infertility. The authors argued that results in PCOS were due to cofounding effects of BMI that were related to both Emotional FertiQoL and treatment outcomes.

Heredia et al. (2013), Li, Long, Liu, He, and Li (2016), and Oron et al. (2015) also had a prospective design but none of the analyses provided data on FertiQoL associations over time.

3. Is fertility quality of life responsive to psychological interventions?

a) Intervention Studies

Four intervention studies (moderate to high quality) used FertiQoL as an outcome measure to determine whether fertility quality of life was responsive to psychological interventions. A partnership program in Japan did not affect FertiQoL scores compared to controls, except for improved Mind-Body scores (Asazawa, 2015). In the United States, a cognitive behavioural intervention (coping and relaxation) administered for the two-week waiting period was associated with increased FertiQoL Core scores especially in the Emotional domain compared to a routine care control group (Domar et al., 2015). In China, an increase in all FertiQoL subscales and Total score was observed for women randomised to a mindfulness intervention group versus control (Li et al., 2016). Finally, improvement in the Emotional and Mind-Body subscales was found after a 6-week yoga program in Canada (pre to post design without control group, Oron et al., 2016).

b) Evaluations of Treatment Service

Three cross-sectional studies in Portugal (using overlapping samples, Gameiro et al., 2013; Lopes, Canavarro, Verhaak, Boivin, & Gameiro, 2014; Pedro et al., 2013) found that higher scores on the Patient-Centredness Questionnaire (PCQ) (communication, competence, accessibility and continuity of care) were indirectly associated to patient wellbeing via increased treatment tolerability as measured by FertiQoL Tolerability subscale (n= 433; Gamerio et al., 2013). Higher Tolerability for treatment was associated to increased likelihood of persisting with treatment (n=348; Pedro et al., 2013). Aarts and colleagues (2012) showed that higher perceived patient centered care was correlated with higher FertiQoL subscale scores in a Dutch sample.

Discussion

The studies reviewed sampled more than 16,000 men and women in 23 countries. Results of the literature review provide evidence that FertiQoL is useful in understanding fertility quality of life. It shows the general psychometric soundness of the FertiQoL in measuring fertility quality of life (satisfactory internal consistency, model fit, and correlation with cognate measures) but also demonstrates that many factors (e.g., gender, culture, psychological vulnerability) are likely to be causes, consequences, mediators or moderators of fertility quality of life. The goal of future research should be to better understand these associations ~~in order~~ to identify those at risk of poorer fertility quality of life. Some additional challenges in FertiQoL's use need to be addressed, namely the lower reliability of the Relational subscale, ~~and~~ the lack of clinically meaningful thresholds (and critical differences between groups) and, robustness of translations and invariance across groups. The evidence reviewed supports continued international efforts to understand fertility quality of life and the use of FertiQoL in research and practice.

Results of this literature review should be examined in light of strengths and limitations in the literature review process and included studies. We excluded conference abstracts and non-English studies and only reported on main study findings due to resource considerations (e.g., searching grey literature, cost of translations). These decisions were motivated by the fact that conference abstracts often did not include complete data (e.g., all subscales, population characteristics, study design) and few sub-analyses

were theoretically motivated. Further, data extraction and study selection was performed by one person, but discussed with other authors when uncertainty arose. These decisions mean that our literature review may lack the rigor associated with systematic reviews. Limitations in primary studies were over-reliance on convenience sampling, cross-sectional studies, bivariate tests that rarely took account of confounders. The studies that did carry out confounder analyses showed that quality of life has multiple determinants best understood using multifactorial models (e.g., see model testing; Asazawa & Mori, 2015). As the FertiQoL research base gains momentum we expect methodological rigour to improve both for the review process and primary research.

FertiQoL has largely satisfactory psychometric properties at the subscale and summed score level (Core, Treatment) for the measurement of multi-dimensional construct of fertility quality of life. This conclusion is consistent with recent reviews of patient-reported outcomes in infertility (Kitchen et al., 2017; Pedro et al. 2016) and other studies examining the factor structure of FertiQoL (Pedro et al. 2016; Melo et al. unpublished results). There was also evidence of construct validity because of correlations between FertiQoL subscales and cognate measures of psychological and interpersonal functioning. However, there is a need for further investigation of measurement properties and users are urged to consider the following in using FertiQoL. The Relational subscale has poorer reliability than other subscales. Similar relational scales in other quality of life measures also show less reliability (e.g., World Health Organization quality of life, reliability coefficients .60 to .70, factor loadings < .50, see Skevington, Lotfy, & O'Connell, 2004). These measurement issues are often attributed to clinical characteristics, for example functional status (Schuler et al., 2016). Our analysis suggests, however, potential conceptual and cultural underpinnings. For example, the items with lowest factor loadings on the social subscale required the individual to have informed others of their fertility problems (i.e., 'Are you satisfied with support you receive from friends…', 'Do you feel your family can understand what you are going through?'). Many infertile people do not disclose their infertility to others. In-depth multi-country analyses would help determine best course of action to address these measurement issues (e.g., re-word item, remove item, use total scores, drop subscale). The Core and Treatment subscales should be

reported separately and not combined into a Total score because the reliabilities of the Core and Treatment FertiQoL is better as individual totals. Finally, studies on the factorial validity of the FertiQoL though promising are scarce as is the test of measurement invariance. As such caution should be exercised in using FertiQoL until further psychometric studies have been carried out.

The median subscale scores indicate that fertility problems have a moderate impact on quality of life, with some domains impacted more than others. The lack of a clinically meaningful threshold is an issue for the interpretation of FertiQoL scores, as has been noted in another review (Kitchen et al., 2017). Determining what is an [sub-] optimal FertiQoL score is a challenge (e.g., Aarts et al. 2011; Donarelli et al. 2016), and in particular what score is indicative of individuals needing additional support. One approach would be to use the median scores obtained thus far in published studies (see Figure 2 median FertiQoL scores in the range of 60 to 75 across 31 independent samples) or to use reports of the FertiQoL scores that correspond to cut-off scores for clinical levels of depression and anxiety on validated 'gold standard' measures such as the HADS (FertiQoL Core scores below 52 to 59, see Aarts et al., 2011, Dural et al., 2016, Kahyaoglu Sut & Balkanli Kaplan, 2015). However, comparisons to median scores or HADS scores must be made with caution because the studies reviewed were not designed to establish normative or reference scores (Kendall, Marrs-Garcia, Nath, & Sheldrick, 1999; Kendall & Sheldrick, 2000). Derivation of reference values requires a standardised protocol (e.g., population, recruitment) applied consistently across the settings contributing to norms, which has not yet been done but could be a next step in FertiQoL development. Such data would facilitate comparisons of FertiQoL across person, place and time and would facilitate translating research findings into clinical application. It is also possible that FertiQoL scores are used purely descriptively for profiling individual patients for clinical meetings, case histories, discussions with patients themselves and so on. ~~However, based on the medians (see Figure 2), w~~We offer an illustrative description of a typical research (patient) participant willing to complete FertiQoL during treatment based on results from Figure 2. This illustrative profile was derived ~~(using~~ by using the median scores to pinpoint the median of the response scale for each item in the FertiQoL subscales~~median scores, response scale, and item content~~. Note this profile is illustrative only~~)~~,

with the caveat that there may be differences in how these issues manifest or are described according to gender and culture. If the Figure 2 medians were scores from a ~~n the typical patient~~patient then the profile could be described as ~~participant~~:

> Emotional quality of life appears to be impacted the most with individuals often experiencing feelings of grief and loss, jealousy and resentment and occasionally feeling sad, depressed and angry. They often fluctuate between hope and despair however they generally feel able to cope with their fertility problems. There is less impact on the cognitive and physical quality of life. Individuals generally experience a small amount of fatigue, pain and discomfort, and their attention and concentration, energy level and ability to meet their day-to-day obligations rarely impacted. They occasionally feel their fertility problems make them inferior to others with children and experience some pressure to have children. However, they generally feel understood and satisfied with the support they receive from family and friends and feel comfortable attending social situations that could involve families and children. The relational quality of life domain appears to be impacted the least with individuals feeling satisfied with their relationship and believing that their fertility problems have strengthened their commitment to each other. They may find it difficult at times to talk to their partner about their fertility problems. In terms of the treatment experience, the median scores suggest that individuals feel understood by fertility staff and feel satisfied with the quality of services, treatment and information they receive and their interactions with fertility staff while in treatment. They are seldom bothered by the physical side effects or the impact of treatment on their lives in general and do not find the procedures or details required by treatment to be very complicated.

The included research showed that fertility quality of life could be predicted with women, those with psychological vulnerability and those with longer duration of infertility reporting poorer quality of life. These findings are consistent with previous research in infertile populations showing these to be risks for depression and anxiety (e.g., Verhaak et al., 2007) and poorer quality of life using other measures (e.g., Chachamovich et al., 2010). Separate gender analyses suggest men from lower socioeconomic backgrounds (less education, unemployed) may also be at greater risk for poor quality of life. As many studies were cross-sectional the direction of causation remains to be established. However, the literature review also provides promising evidence that fertility quality of life could be improved through targeting modifiable risk factors for poor FertiQoL or enhancing protective factors (e.g., through interventions such as a cognitive behavioural intervention; Domar et al., 2015).

There is evidence that FertiQoL could be useful in practice. Poorer quality of life of some patient groups could be better understood (e.g., patients with endometriosis, PCOS). Treatment quality of life predicted decisional conflict and regret and intentions to persist with treatment (Gameiro et al., 2013) though not actual dropout (Huppelschoten et al., 2013a). Pre-treatment FertiQoL scores also predicted pregnancy and live birth in some groups (Santoro et al., 2016). More studies are needed to clarify these relationships because confounder analyses and prospective studies suggested such prediction could be due to the multiple determinants of quality of life (e.g., obesity, longer duration of infertility, greater treatment attempts) that could also impact on treatment outcomes. FertiQoL could also be useful in practice to identify aspects of treatment that could improve quality of life. For example, the review suggested that patient centered care was associated with better quality of life, as was support from medical professionals (e.g., doctors and nurses) in strengthening the partner relationship (Asazawa & Mori, 2015).

To date very few of the FertiQoL studies examined how quality of life predictors differed across groups (e.g., gender, treatment status, country). Understanding more deeply international variations in FertiQoL scores is an important future research goal. FertiQoL has been translated (see www.fertiqol.com for translations) using a consistently applied process (see Boivin et al., 2011) that involves a cooperative exchange between a professional translator and bilingual fertility experts in psychology and medicine in the country requesting the translation. This co-production is important because it helps ensure that the translation has high fidelity to the English version but is also culturally tailored (Kreuter, Lukwago, Bucholtz, & Clark, 2003). This quality control does not necessarily prevent threats to validity. According to Herdman, Fox-Rushby, and Badia (1998) a true translation also implies that the meaning of FertiQoL items is equivalent across translations. As noted, we lack at present in-depth cross-cultural psychometric and qualitative studies to confirm validation in the ‘meaning’ of items. Continued research could help disentangle cultural from methodological difference. The use of the COSMIN checklist (COnsensus-based Standards for the selection of health Measurement Instruments; Mokkink et al., 2010) and qualitative research into item meaning can help in this endeavour.

Conclusion

This literature review presented a consolidation and summary of research using the FertiQoL to date and presented considerations for future research. The review showed FertiQoL is a reliable and valid measurement tool for quality of life among people with fertility problems showing promise in multiple settings for a range of research and practical goals. Methodological and conceptual challenges remain, but these are being addressed. Future efforts with FertiQoL should aim to better understand some measurement issues (e.g., reliability of relational subscale, invariance of FertiQoL across samples), generate valid population normative scores, extend clinical application (e.g., identify clinically meaningful thresholds) and extend understanding of reported associations with fertility quality of life through more rigorous research designs (e.g., prospective studies).

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Dr. Janet Takefman is a reproductive health and clinical psychologist. She is the coordinator of psychological services & research at the MUHC Reproductive Centre and holds joint assistant professorships at the Departments of Obstetrics & Gynecology and Psychology at McGill University, Montreal, Canada.

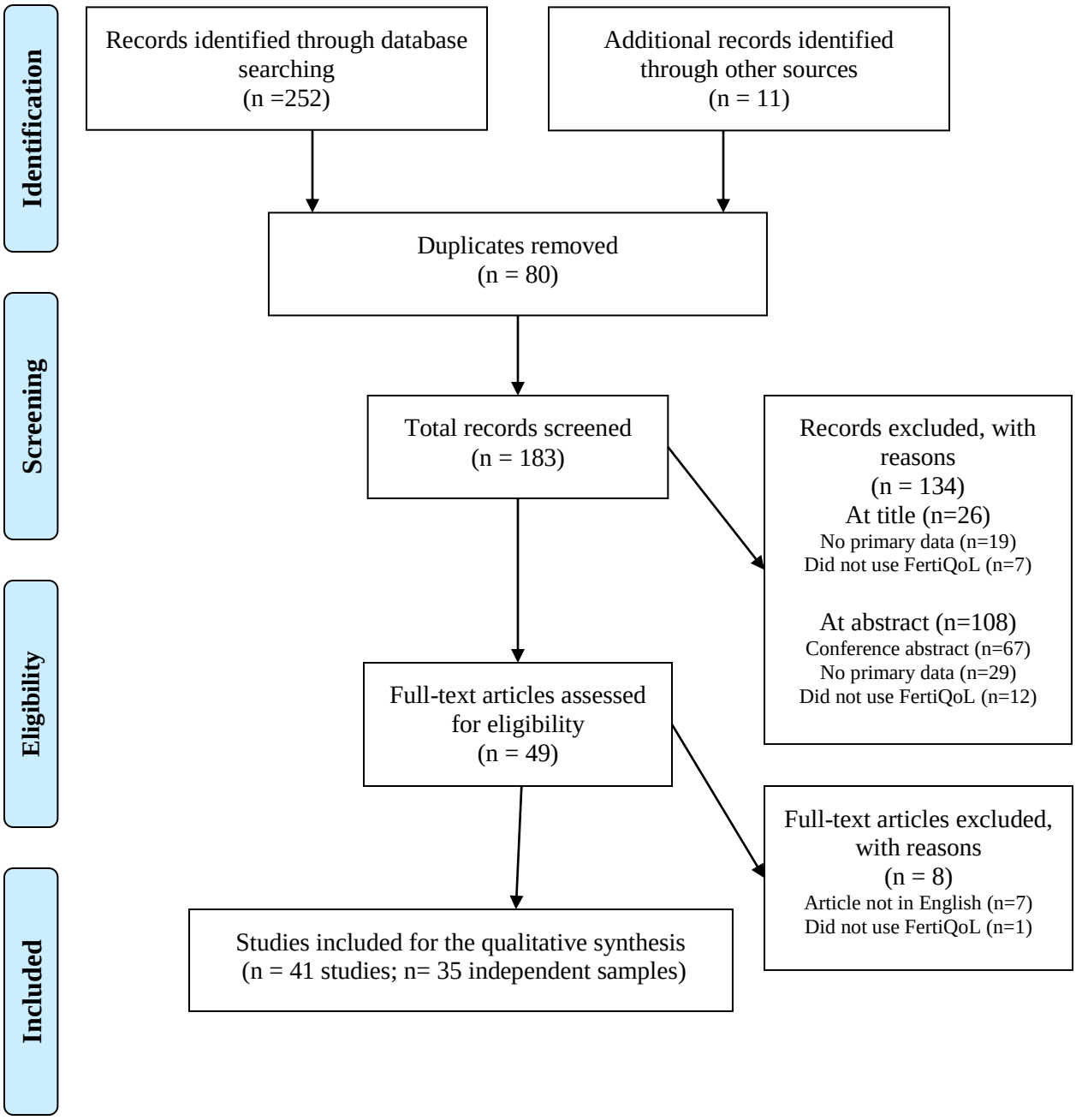
She is considered a leader in her field and has co-authored over 100 monographs, grants, book chapters, research studies and peer review articles and has been an invited speaker more than 50 times for medical conferences around the world. She is the co-creator of the FertiQoL the only international validated quality of life measure for the infertile population. She provides counselling and therapy.

Professor Jacky Boivin:

Professor Jacky Boivin is a Professor of Health Psychology and Chartered Health Psychologist in the School of Psychology, Cardiff University.

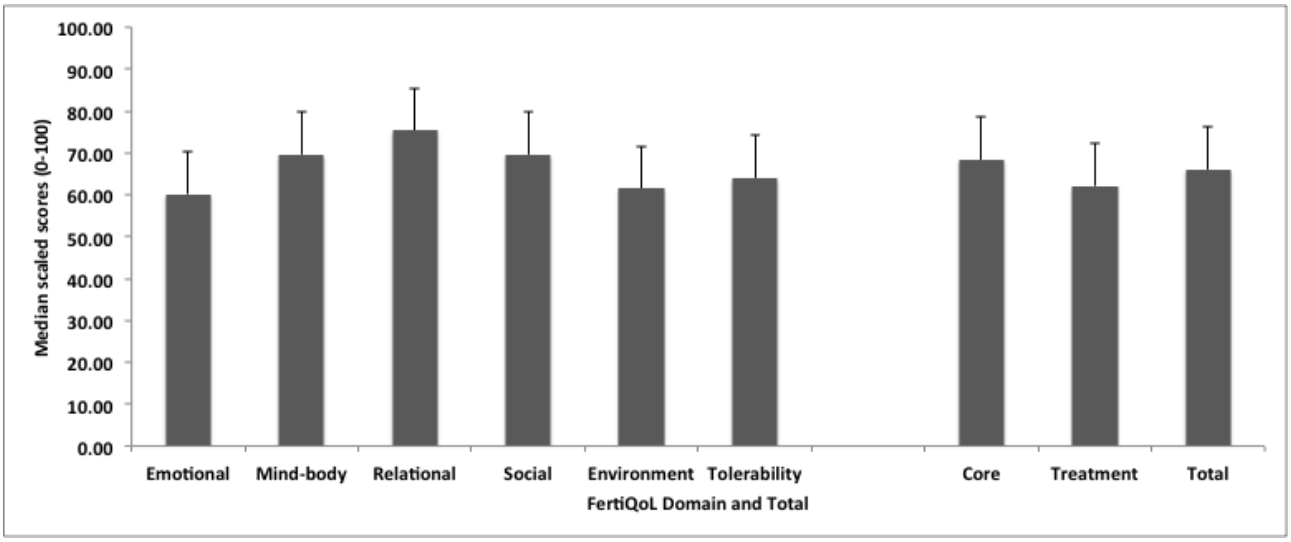
Prof. Boivin's most important contribution to the field of reproductive health has been to bring about a more systematic and research oriented perspective to the investigation of psychosocial issues in reproductive health. She is the co-creator of the FertiQoL.

Figure 1: Flowchart for study selection



Note: PRISMA Diagram from reference Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Medicine*, *6*, e1000097.

Figure 2: Average FertiQoL median scores (and standard deviations) from selected studies

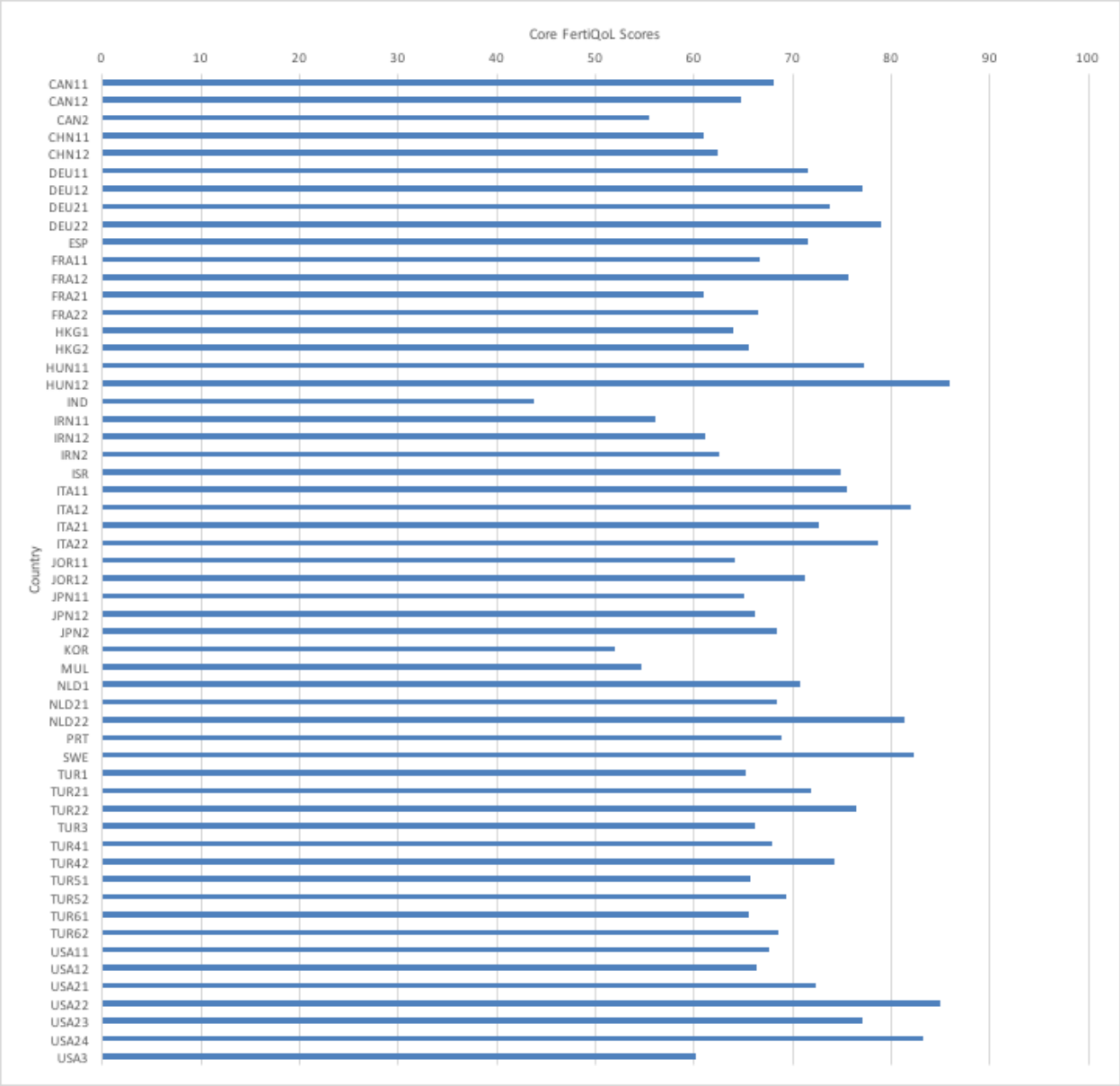


Note. Sample size varies according to domain or total score.

N=31 only independent samples included; mean scores from all studies ranged from 42.1 – 91.7, medians for each subscale ranged from 59.80 - 75.42.

The scores shown in the graph are the medians of the distribution of mean subscale scores for the selected studies (from Supplementary Table 13)

Figure 3: Mean Core FertiQoL scores by country from selected studies



Note. Three-letter country abbreviations used. First number after abbreviation is used when multiple studies for a country (studies numbered alphabetically) and second number is used when multiple independent groups within a study.
N=31 only independent samples included.
CAN=Canada, CNH=China, DEU=Germany, ESP=Spain, FRA=France, HKG=Hong Kong, HUN=Hungary, IND=India, IRN=Iran, ISR=Israel, ITA=Italy, JOR=Jordan, JPN=Japan, KOR=Korea, MUL=Multiple countries combined, NLD=Netherlands, PRT=Portugal, SWE=Sweden, TUR=Turkey, USA=United States.

See Supplementary Table 13 for list of mean Core scores by country.