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

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## 22 Abstract

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

39  
40 **Keywords:** infertility; fertility

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## Introduction

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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.

68 FertiQoL has now been translated into 48 languages and used extensively (see Boivin et al., 2011 and  
69 [www.fertiqol.com](http://www.fertiqol.com) for more detailed information about the tool, available translations, scoring methods).

70 Potential users must strictly adhere to the Terms of Reference. Items should not be altered. FertiQoL is  
71 judged to perform well in reviews of patient reported outcomes (Kitchen et al. 2017; Pedro et al. 2016)  
72 but findings using FertiQoL have not yet been reviewed in depth despite a large number of studies using  
73 FertiQoL. The purpose of the literature review was to identify all research using FertiQoL to date, to  
74 consolidate and summarize what has currently been reported using it, and to identify areas for future  
75 study. A review of this nature would enable us to show progress in understanding of fertility quality of  
76 life, how FertiQoL has been (and could be) used in patient-oriented work (clinical care or research-  
77 based), and identify potential directions for future research about fertility quality of life (e.g., causes and  
78 consequences of poor fertility quality of life, the effectiveness of clinical care strategies and psychological  
79 interventions in improving fertility quality of life, and the effect of fertility quality of life on treatment  
80 trajectories) or on FertiQoL itself. This paper presents the characteristics of the studies reviewed, a  
81 thematic summary of what the results show about fertility quality of life, and offers suggestions for future  
82 directions for research.

83

## 84 **Material and Methods**

### 85 **Search Procedure and Study Selection**

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

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

100

### 101 *Data Extraction and Synthesis*

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

110

### 111 *Quality Appraisal*

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

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

123

124

## Results

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

127

### Characteristics of Included Studies

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

133 Overall the majority of included studies were cross-sectional (26 studies, 74.3%), with remaining  
 134 studies being pre to post designs (4 studies, 11.4%) or prospective or longitudinal designs (5 studies,  
 135 14.3%). The largest number of studies pooled participants at different treatment stages (13 studies,  
 136 37.1%) but some sampled patients exclusively pre-treatment (7 studies, 20%), during treatment (8 studies,  
 137 19.4%), or post treatment (4 studies, 11.4%). Overall 21 studies recruited individuals (60%) and 14  
 138 (40%) couples. The majority of included studies (28, 80%) used non-systematic methods of recruitment  
 139 in clinics (e.g., convenience sampling) with few studies recruiting consecutive patients (4 studies, 11.4%),  
 140 or using random sampling (3 studies, 8.6%). All but one study sampled patients in treatment (97.1%),  
 141 most commonly undergoing assisted reproductive technology (ART) treatment cycles (28 studies, 80%).  
 142 The median sample size across included studies was 301 participants (range 18 to 3,088), and the female  
 143 to male ratio was close to 4:1 in individual, non-couple studies. The participation rate averaged across  
 144 included studies was 70% (range 41 to 92.5%). Quality assessment of included papers (overlapping

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

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

152

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

#### 154 *a) Confirmatory factor analysis of FertiQoL measurement structure*

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

160

#### 161 *b) Internal consistency of FertiQoL*

162 See Supplementary Table 11 for summary of Cronbach coefficient alpha for each study providing  
 163 these data and Supplementary Table 12 for specific details of each subscale. Reliability is generally  
 164 considered satisfactory when  $\geq .70$  (Peterson, 1994). For all studies, reliability for the Core FertiQoL was  
 165  $> .80$ . Further, satisfactory reliability was reported for the Emotional, Mind/Body and Social subscales ( $>$   
 166  $.70$ ) with one exception for social domain (Sexty et al., 2016). In contrast, the Relational subscale  
 167 generally showed unsatisfactory reliability with most studies reporting alpha coefficients between  $.60$  and  
 168  $.70$ . The Treatment Module reliability was  $> .70$  as was its two subscales (Environment and Tolerability)  
 169 in all but one study from Iran (Maroufizadeh et al., 2017a) and one study from Turkey (Kahyaoglu Sut &



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

172

### 173 *c) Construct validity of FertiQoL*

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

193

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

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

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

201 Four cross-sectional studies (moderate quality) did comparative analyses. Jordanian couples were  
 202 shown to have poorer emotional, relational and mind-body quality of life than did German and Hungarian  
 203 couples (Cserepes et al., 2014; Sexty et al., 2016) but after controlling for group differences on socio-  
 204 demographic and fertility variables the Jordanian group differed only on emotional quality of life. Chi et  
 205 al. (2016) found lower Core subscale scores in a Korean sample compared to the FertiQoL development  
 206 sample (i.e., Boivin et al. 2011). Valsangkar, Bodhare, Bele, and Sai (2011) found similar results in  
 207 comparison between the FertiQoL development sample and an Indian sample. Madero and colleagues  
 208 (2017) compared FertiQoL scores in men and women from Germany, Italy and France undergoing cross-  
 209 border oocyte donation in Spain. French patients showed poorer emotional and mind-body quality of life  
 210 than Italians, whereas both French and German patients showed lower relational quality of life than  
 211 Italian patients. However, Italian patients had lower social quality of life than Germans.

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

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

224

225 *b) Clinically important thresholds*

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

235

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

237 Eighteen cross-sectional studies (moderate to high quality) investigated correlates of fertility  
 238 quality of life (see Supplementary Table 7). This research was primarily conducted using convenience  
 239 samples with women recruited through infertility clinics completing FertiQoL prior to or during  
 240 treatment. There were mixed results for demographic variables. Gender was the strongest predictor  
 241 across studies, with women consistently showing poorer quality of life than men. Huppelschoten et al.  
 242 (2013b) reported that 28% of variability in Core FertiQoL was due to gender. Unemployment was  
 243 associated with lower FertiQoL scores in one study (Keramat et al., 2014) but not in two others (Goker,  
 244 Yanikkerem, Birge, & Kuscu 2017; Heredia et al., 2013). Higher income level was associated with better  
 245 quality of life in five studies (Karaca et al., 2016; Keramat et al., 2014; Namavar, Mansouri, Forouhari,  
 246 Poordast, & Salehi, 2018; Steuber and High, 2015; Santoro et al., 2016), but not in three others (Hasson et  
 247 al., 2017; Karabulut, Ozkan, & Oguz, 2013; Karabulut, Demirtas, Sonmez, Karaca, & Gok, 2017). Higher

248 education was associated with better quality of life in three studies (Karabulut et al., 2013; Keramat et al.,  
 249 2014; Namavar et al., 2018), and lower quality of life in two studies (Hasson et al., 2017; Porat-Katz,  
 250 Paltiel, Kahane, Eldar-Geva, 2016) and no association in four others (Kahyaoglu Sut & Balkanli Kaplan,  
 251 2015; Karabulut et al., 2017; Maroufizadeh, Ghaheri, & Omani Samani, 2017b; Santoro et al., 2016).  
 252 Older age was correlated to higher FertiQoL scores in five studies (Asazawa & Mori, 2015; Goker et al.,  
 253 2017; Karabulut et al., 2013; Porat-Katz et al., 2016; Santoro et al., 2016) but not in five others (Heredia  
 254 et al., 2013; Kahyaoglu Sut & Balkanli Kaplan, 2015; Karabulut et al., 2017; Keramat et al., 2014;  
 255 Maroufizadeh et al., 2017b). Marital status was not associated with quality of life in two studies (Hasson  
 256 et al., 2017; Porat-Katz et al., 2016). Longer marital duration was associated with higher quality of life in  
 257 one study (Goker et al., 2017) but not in another (Keramat et al., 2014).

258         Characteristics of the infertility or treatment experience were also associated with fertility quality  
 259 of life, but not consistently. Time trying to conceive was associated with lower FertiQoL scores in one  
 260 study (Kahyaoglu Sut & Balkanli Kaplan, 2015). A longer duration of infertility was associated with  
 261 poorer quality of life in five of seven studies (Karabulut et al., 2013; Karaca et al., 2016; Keramat et al.,  
 262 2014; Namavar et al., 2018; Santoro et al., 2016) as was unexplained infertility (Heredia et al., 2013;  
 263 Maroufizadeh et al., 2017b). In contrast secondary infertility was associated with better quality of life  
 264 than primary infertility (Karabulut et al., 2013). Being in treatment or having had a consultation for  
 265 infertility was associated with lower quality of life in one study (Namavar et al., 2018). A greater number  
 266 of treatment attempts was associated with lower quality of life in one study (Kahyaoglu Sut & Balkanli  
 267 Kaplan, 2015) but not in two others (Heredia et al., 2013; Smith, Madeira, & Millard, 2015). Cycle  
 268 cancellation in ART was associated with lower FertiQoL scores compared to a completion cycle (whether  
 269 pregnant or not; Heredia et al., 2013). The partner accompanying the patient at clinic was associated with  
 270 higher quality of life (Heredia et al., 2013). Use of complementary medicine was associated with higher  
 271 Relational quality of life and lower Social quality of life in one study (Porat-Katz et al., 2016). One study  
 272 reported that higher BMI and more hirsutism were associated with lower FertiQoL scores (Santoro et al.,  
 273 2016).

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

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

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

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

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

308

309 *d) Associations with fertility quality of life over time*

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

319 A few studies explored whether FertiQoL scores could predict future outcomes. In the Chan et al.  
 320 (2016) study lower Core and Treatment FertiQoL immediately after a failed cycle predicted higher  
 321 decisional conflict at post-treatment consultation two to three weeks later (regardless of decision).  
 322 Additionally, Treatment quality of life predicted decisional regret three months later. Three studies  
 323 predicted dropout from pre-treatment scores. Huppelschoten et al. (2013a) assessed Core FertiQoL within  
 324 three months of a treatment cycle and found it did not predict treatment discontinuation at 12-month  
 325 follow-up. Domar et al. (2015) reported that Emotional FertiQoL assessed within a month of the start of

326 an ART cycle did not predict dropout at 12 months, and this lack of association was observed in patients  
 327 randomised and not randomised to a coping intervention. Finally, Santoro et al. (2015) reported that pre-  
 328 treatment FertiQoL scores did not predict dropout over a five-month treatment protocol. Santoro et al.  
 329 (2015) also reported on pregnancy rates. It was found that lower pre-treatment Emotional FertiQoL  
 330 predicted lower pregnancy and live-birth rate in women with PCOS whereas lower Mind-Body FertiQoL  
 331 predicted higher pregnancy in women with unexplained infertility. The authors argued that results in  
 332 PCOS were due to confounding effects of BMI that were related to both Emotional FertiQoL and treatment  
 333 outcomes.

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

336

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

#### 338 *a) Intervention Studies*

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

349

#### 350 *b) Evaluations of Treatment Service*

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

### 359 Discussion

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

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



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

385 FertiQoL has largely satisfactory psychometric properties at the subscale and summed score level  
386 (Core, Treatment) for the measurement of multi-dimensional construct of fertility quality of life. This  
387 conclusion is consistent with recent reviews of patient-reported outcomes in infertility (Kitchen et al.,  
388 2017; Pedro et al. 2016) and other studies examining the factor structure of FertiQoL (Pedro et al. 2016;  
389 Melo et al. unpublished results). There was also evidence of construct validity because of correlations  
390 between FertiQoL subscales and cognate measures of psychological and interpersonal functioning.  
391 However, there is a need for further investigation of measurement properties [and users are urged to](#)  
392 [consider the following in using FertiQoL](#). The Relational subscale has poorer reliability than other  
393 subscales. Similar relational scales in other quality of life measures also show less reliability (e.g., World  
394 Health Organization quality of life, reliability coefficients .60 to .70, factor loadings < .50, see  
395 Skevington, Lotfy, & O'Connell, 2004). These measurement issues are often attributed to clinical  
396 characteristics, for example functional status (Schuler et al., 2016). Our analysis suggests, however,  
397 potential conceptual and cultural underpinnings. For example, the items with lowest factor loadings on  
398 the social subscale required the individual to have informed others of their fertility problems (i.e., 'Are  
399 you satisfied with support you receive from friends...', 'Do you feel your family can understand what you  
400 are going through?'). Many infertile people do not disclose their infertility to others. In-depth multi-  
401 country analyses would help determine best course of action to address these measurement issues (e.g.,  
402 re-word item, remove item, use total scores, drop subscale). [The Core and Treatment subscales should be](#)

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

407 The median subscale scores indicate that fertility problems have a moderate impact on quality of  
 408 life, with some domains impacted more than others. The lack of a clinically meaningful threshold is an  
 409 issue for the interpretation of FertiQoL scores, as has been noted in another review (Kitchen et al., 2017).  
 410 Determining what is an [sub-] optimal FertiQoL score is a challenge (e.g., Aarts et al. 2011; Donarelli et  
 411 al. 2016), and in particular what score is indicative of individuals needing additional support. One  
 412 approach would be to use the median scores obtained thus far in published studies (see Figure 2 median  
 413 FertiQoL scores in the range of 60 to 75 across 31 independent samples) or to use reports of the FertiQoL  
 414 scores that correspond to cut-off scores for clinical levels of depression and anxiety on validated ‘gold  
 415 standard’ measures such as the HADS (FertiQoL Core scores below 52 to 59, see Aarts et al., 2011, Dural  
 416 et al., 2016, Kahyaoglu Sut & Balkanli Kaplan, 2015). However, comparisons to median scores or  
 417 HADS scores must be made with caution because the studies reviewed were not designed to establish  
 418 normative or reference scores (Kendall, Marrs-Garcia, Nath, & Sheldrick, 1999; Kendall & Sheldrick,  
 419 2000). Derivation of reference values requires a standardised protocol (e.g., population, recruitment)  
 420 applied consistently across [the](#) settings contributing to norms, which has not yet been done but could be a  
 421 next step in FertiQoL development. Such data would facilitate comparisons of FertiQoL across person,  
 422 place and time and would facilitate translating research findings into clinical application. [It is also](#)  
 423 [possible that FertiQoL scores are used purely descriptively for profiling individual patients for clinical](#)  
 424 [meetings, case histories, discussions with patients themselves and so on. However, based on the medians](#)  
 425 [\(see Figure 2\), w](#)~~We~~ offer an illustrative description of a typical research (patient) participant willing to  
 426 complete FertiQoL during treatment [based on results from Figure 2. This illustrative profile was derived](#)  
 427 [\(using by using the](#) median scores [to pinpoint the median of the response scale for each item in the](#)  
 428 [FertiQoL subscales](#)~~median scores, response scale, and item content.~~ Note this profile is illustrative only),

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

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

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

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

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

486

**487 Conclusion**

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

497

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501

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514

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683 **Biographical Notes:**684 **Dr. Emily Koert:**

685 Dr. Emily Koert is a Registered Psychologist and Adjunct Professor at the University of British  
 686 Columbia, Vancouver, British Columbia, Canada. Her research and clinical work focuses on fertility-  
 687 related issues such as consequences of delayed childbearing, the psychosocial impact of recurrent  
 688 pregnancy loss and infertility, and fertility awareness and decision-making.

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691 **Dr. Janet Takefman:**

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

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

702

703 **Professor Jacky Boivin:**

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

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

709 **Figure 1: Flowchart for study selection**

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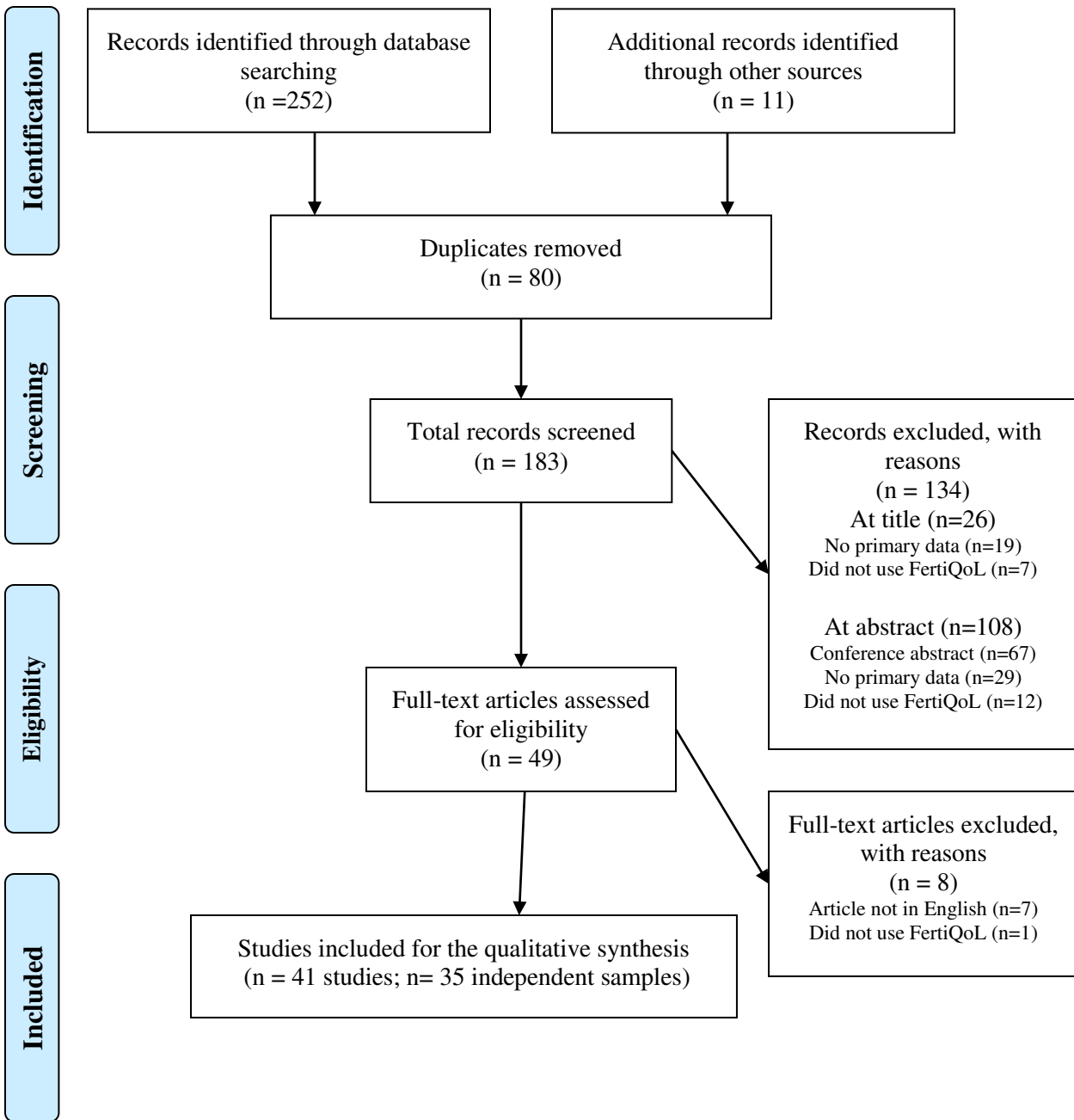
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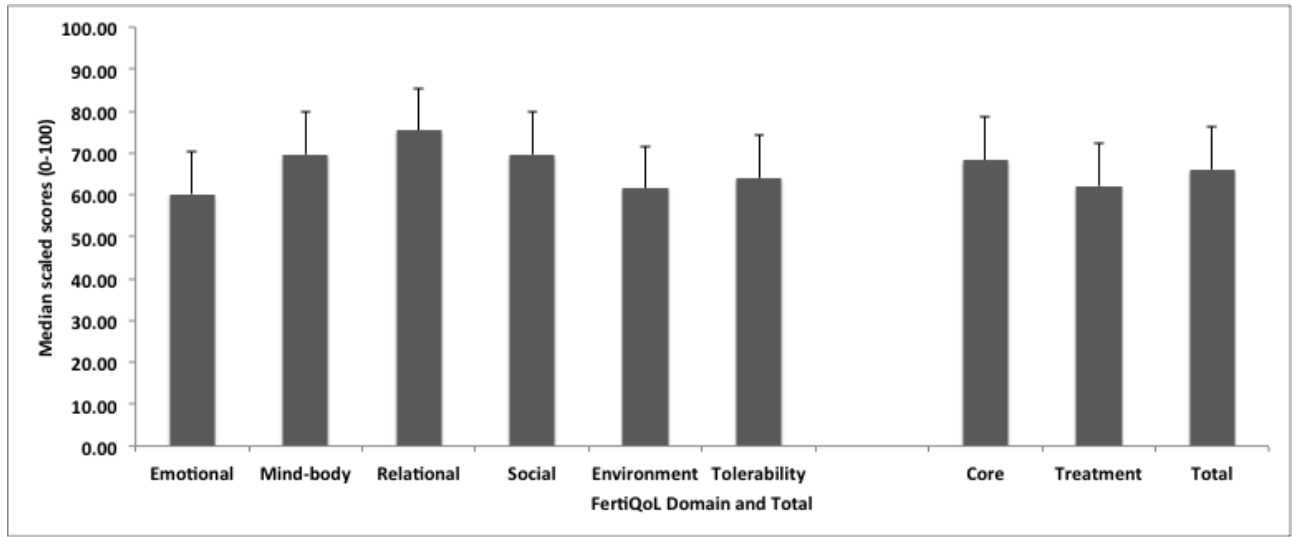
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**Note:** PRISMA Diagram from reference Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.

*PLoS Medicine*, 6, e1000097.

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



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

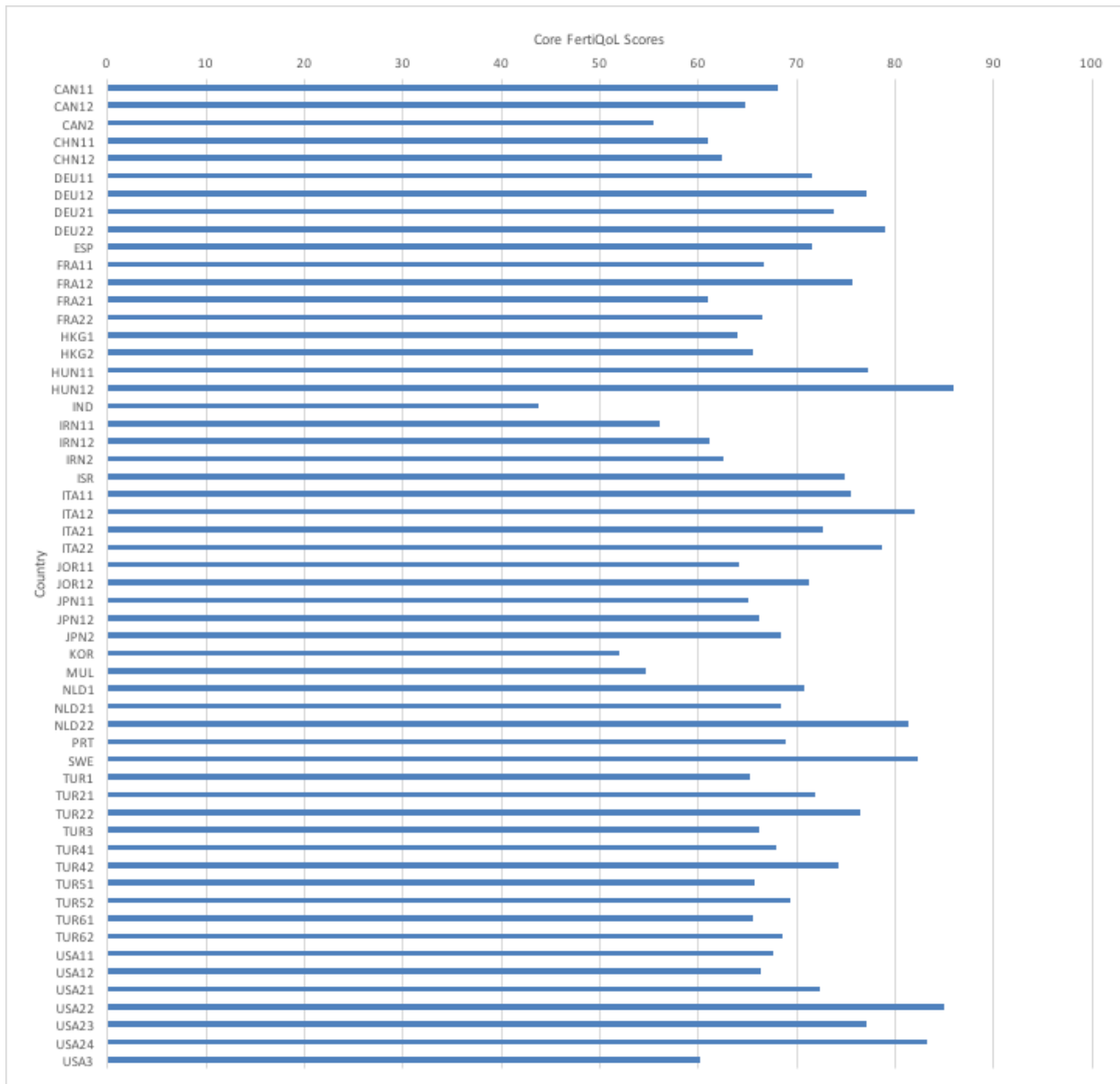
738 N=31 only independent samples included; mean scores from all studies ranged from 42.1 – 91.7, medians  
739 for each subscale ranged from 59.80 - 75.42.

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

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



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746 **Note.** Three-letter country abbreviations used. First number after abbreviation is used when multiple  
 747 studies for a country (studies numbered alphabetically) and second number is used when multiple  
 748 independent groups within a study.

749 N=31 only independent samples included.

750 CAN=Canada, CNH=China, DEU=Germany, ESP=Spain, FRA=France, HKG=Hong Kong,  
 751 HUN=Hungary, IND=India, IRN=Iran, ISR=Israel, ITA=Italy, JOR=Jordan, JPN=Japan, KOR=Korea,  
 752 MUL=Multiple countries combined, NLD=Netherlands, PRT=Portugal, SWE=Sweden, TUR=Turkey,  
 753 USA=United States.

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

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