

# Male psychological adaptation to unsuccessful medically assisted reproduction treatments: a systematic review

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**BACKGROUND:** Similarly to women, men suffer from engaging in fertility treatments, both physically and psychologically. Although there is a vast body of evidence on the emotional adjustment of women to infertility, there are no systematic reviews focusing on men's psychological adaptation to infertility and related treatments.

**OBJECTIVE AND RATIONALE:** The main research questions addressed in this review were 'Does male psychological adaptation to unsuccessful medically assisted reproduction (MAR) treatment vary over time?' and 'Which psychosocial variables act as protective or risk factors for psychological maladaptation?'

**SEARCH METHODS:** A literature search was conducted from inception to September 2015 on five databases using combinations of MeSH terms and keywords. Eligible studies had to present quantitative prospective designs and samples including men who did not achieve pregnancy or parenthood at follow-up. A narrative synthesis approach was used to conduct the review.

**OUTCOMES:** Twelve studies from three continents were eligible from 2534 records identified in the search. The results revealed that psychological symptoms of maladjustment significantly increased in men 1 year after the first fertility evaluation. No significant differences were found two or more years after the initial consultation. Evidence was found for anxiety, depression, active-avoidance coping, catastrophizing, difficulties in partner communication and the use of avoidance or religious coping from the wife as risk factors for psychological maladjustment. Protective factors were related to the use of coping strategies that involve seeking information and attribution of a positive meaning to infertility, having the support of others and of one's spouse, and engaging in open communication about the infertility problem.

**WIDER IMPLICATIONS:** Our findings recommend an active involvement of men during the treatment process by health care professionals, and the inclusion of coping skills training and couple communication enhancement interventions in counselling. Further prospective large studies with high-quality design and power are warranted.

**Key words:** infertility / men / systematic review / adaptation / psychological / protective and risk factors / stress / depression / marital relationship / coping behaviour

## Introduction

A Google search for 'infertility in women' retrieves ~24 million hits and 'infertility in men' ~20 million hits, with a difference of 17% in the number of hits presented. This difference increases to 44% when performing a search using the same terms in PubMed (~18 000 against 10 000 hits) and to 72% in a PsycInfo search (~43 000 against 12 000). These numbers reflect the way men have been underrepresented within the infertility literature by clinicians and researchers, especially concerning psychiatric and psychological research.

There are both historical and cultural reasons for this disproportion. While infertility was already established as a subspecialty in the first half of the twentieth century, the term andrology emerged for the first time in 1951 to draw attention to the equal importance of females and males in reproduction (Schirren, 1985). Until the 1980s, medical doctors and mental health professionals believed that idiopathic infertility psychologically affected women exclusively, with personalities characterized by unconscious conflict and traits such as neuroticism (see Stanton *et al.*, 2002; Van Balen, 2002; Wischmann, 2003). The introduction of intracytoplasmic sperm injection (ICSI) in the early 90s (Palermo *et al.*, 1992) allowed men with very low sperm counts to achieve parenthood. Despite being the most relevant therapeutic advance in male fertility treatment, this technique was announced as 'a promising assisted-fertilization technique that may benefit women who have not become pregnant by *in vitro* fertilization (IVF)' (Palermo *et al.*, 1992, p. 17).

As this and other sophisticated ART procedures evolved alongside diagnoses, the percentage of causation attributed to the male partner increased, while unexplained infertility decreased. It is now known that male factor contributes to infertility in 30–40% of diagnoses and is the sole cause in a further 20% of cases (Adamson and Baker, 2003). Although more than half of infertility cases have male causation, 18–27% of couples still do not undergo male evaluation (Eisenberg *et al.*, 2013). Additionally, growing evidence indicates that men also have biological clocks and that advanced male age increases the time to pregnancy and decreases the likelihood of conception (Hassan and Killick, 2003; Dunson *et al.*, 2004; Louis *et al.*, 2013).

In a parallel manner, the field of reproductive health psychology has increasingly moved away from a belief that infertility stress primarily affects women towards a belief that infertility is a stressor shared by the couple, even when causation is attributed to only one of its members (Peterson *et al.*, 2008; Johnson and Johnson, 2009; Greil and McQuillan, 2010). It is also now recognized that the way that men and women experience

medical and psychological circumstances related to infertility can vary based on biological, cultural, and social factors (Nakamura *et al.*, 2008; Deka and Sarma, 2010). Hence, several articles are currently being published with the specific purpose of calling for greater recognition of and focus on the male experience of infertility (Inhorn and Patrizio, 2015; Joja *et al.*, 2015; Petok, 2015). Although there has been an increase in recent studies focusing on men, the predominance of female samples in research continues under the argument that women suffer more than men with treatment and its failures, both physically and psychologically (Greil, 1997; Jordan and Revenson, 1999; Newton *et al.*, 1999). However, there is evidence that (i) men are also subjected to embarrassing and painful procedures inherent to medically assisted reproduction (MAR) namely, the pressure to ejaculate through masturbation on demand and the pain that follows the use of testicular sperm extraction techniques (Inhorn, 2013), and (ii) the assumption that infertility causes more distress to women is based on outdated gender stereotyping, as all women report more distress in general psychological adjustment and health-related adjustment measures (Edelmann and Connolly, 2000). Infertility has even been shown to cause more detrimental psychological effects for men than for women. For example, Fairweather-Schmidt *et al.* (2014) observed that infertility independently predicted depressive symptomatology in men but not in women. Additionally, Huijts *et al.* (2013) analysed more than 20 000 subjects aged  $\geq 40$  and found an association between childlessness and poorer psychological well-being for men but not for women.

It is clear that men are emotionally affected by infertility (Culley *et al.*, 2013). Although there is a vast body of evidence on the emotional adjustment of women to infertility (Verhaak *et al.*, 2007a; Gourounti *et al.*, 2010; Rockliff *et al.*, 2014), there are no systematic reviews focusing on the male psychological adaptation to infertility.

## Purpose of this review

This study reviews empirical research on male psychological adaptation to unsuccessful fertility treatment. Psychological adaptation refers both to the processes and to the outcomes of attempting to respond efficiently to variations in the individual's environment, which here concerns the experience of fertility treatment. These adaptation processes include changes in behaviour in order to adjust to the environment effectively (e.g. coping) and the ability to relate to others and engage in social interactions and relationships (American Psychological Association, 2015). This review attempts to answer two questions: (i) Does male psychological adaptation to unsuccessful fertility treatment vary over time? and (ii) Which psychosocial variables can act as protective or risk factors for psychological maladaptation?

## Method

### Search strategy

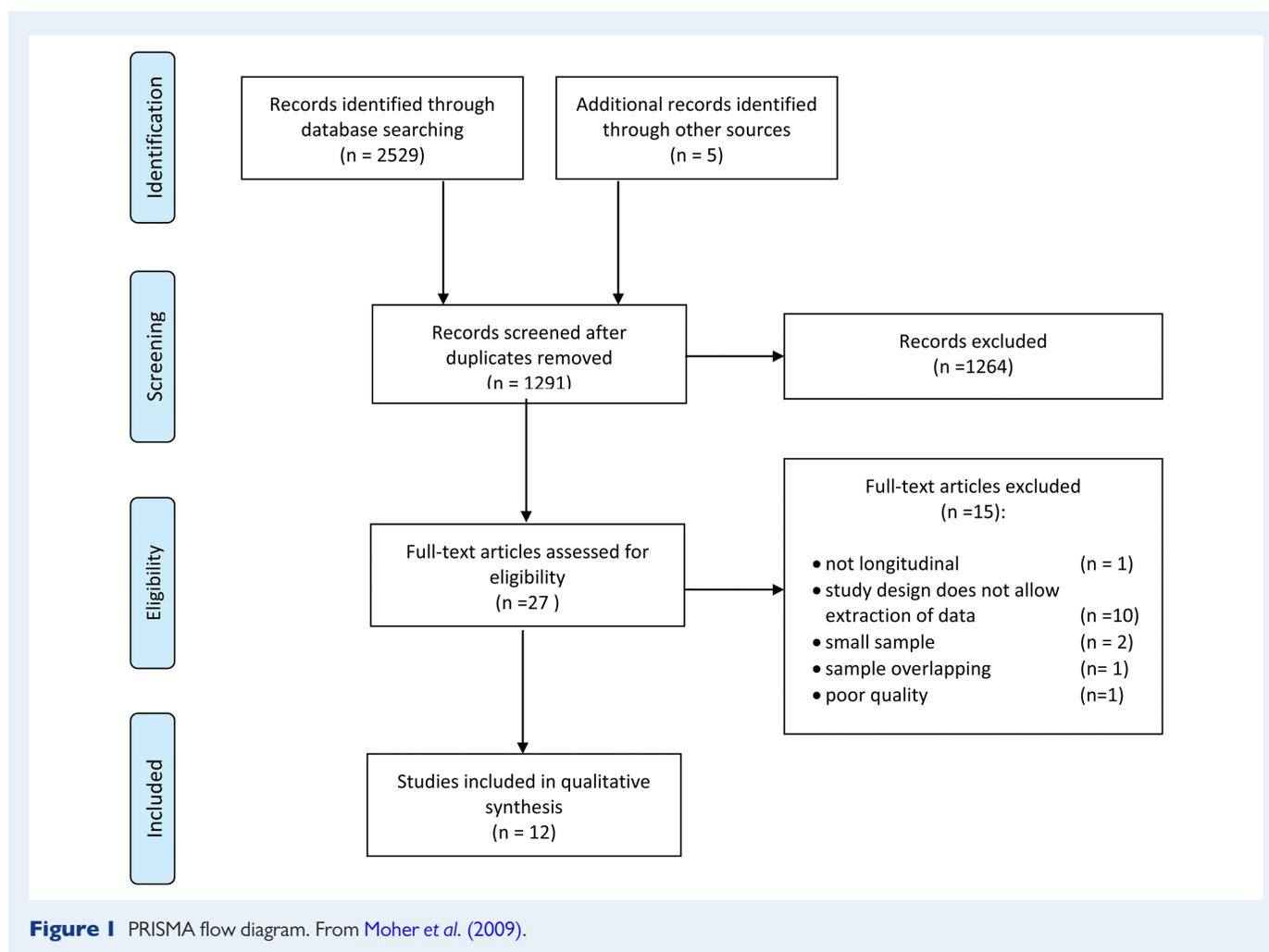
A literature search was performed independently by two researchers (J.P. and M.B.-P.) using the ISI Web of Science, Medline, PsycArticles, Scielo and Scopus electronic databases. There were no restrictions for the time of publication (from inception to September 2015). The following combinations of MeSH terms were used in the search strategy: [(‘male, infertility’) OR (‘infertility’ AND ‘male’)] AND (‘adaptation’ OR ‘stress’ OR ‘depression’ OR ‘anxiety’ OR ‘quality of life’ OR ‘adjustment’ OR ‘psycho\*’ OR ‘distress’ OR ‘coping’ OR ‘mental health’ OR ‘well-being’ OR ‘emotional adjustment’ OR ‘social support’). Additional studies were sought through snowball sampling. To be considered in this review, studies had to be published in English, Spanish, French or Portuguese.

### Study selection

Data were analysed in accordance with the PRISMA checklist and the PRISMA flowchart (Fig. 1). The search strategy yielded 2534 potentially relevant abstracts. After being transferred and stored, the reference database programme Endnote X6 identified 1243 duplicates, leaving 1291 for a more rigorous assessment. Manual inspection of the titles and abstracts left 208 studies. Studies were further excluded if they did not meet the following criteria: (i) a quantitative longitudinal design and (ii) a measure of psychological adaptation as a dependent variable. Disagreements were discussed

and resolved by consensus among three reviewers (M.V.M., M.B.-P., and J.P.). Next, 27 full texts were examined independently by these three researchers.

One study was excluded because baseline and follow-up data were collected simultaneously using a retrospective design (Wischmann et al., 2014). Ten studies were excluded for not allowing extraction of data pertaining exclusively to men who did not conceive or had not become parents at follow-up. In five of them, it was not possible to differentiate men who did not conceive from those who did conceive at the follow-up measurement (Benazon et al., 1992; Anderson et al., 2003; Sydsjö et al., 2011; Sydsjö et al., 2014a, b), and in one it was not possible to differentiate male from female scores (Najafi et al., 2015). In the other four studies (Sydsjö et al., 2005; Peterson et al., 2009, 2011; Martins et al., 2014b), the outcome assessed accounted for several moments in time, and thus, conclusions regarding differences between baseline and follow-up could be biased compared with other studies. This decision was reinforced by the fact that the change measured in three of these studies (Peterson et al., 2009, 2011; Martins et al., 2014b) included a 1-year follow-up in regression analyses that overlapped with a previous study included in this review (Schmidt et al., 2005a). Additionally, two studies were excluded because of the small sample size (<30) of men facing infertility at follow-up (Verhaak et al., 2005b; Fairweather-Schmidt et al., 2014). Finally, one additional study was removed (Martins et al., 2013) because of sample overlapping in regards to the dependent variable and follow-up measurement with a previous study (Schmidt et al., 2005a).



Next, reviewers independently performed a formal assessment of quality by adapting a standardized framework for non-intervention studies (Shepherd *et al.*, 2006; Dancet *et al.*, 2010). To be included, studies had to have an explicit and clear description of at least four of the following criteria (i) a theoretical framework or an outlined rationale; (ii) aims and objectives; (iii) setting; (iv) sample; (v) methodology; and (vi) sufficient original data to mediate between data and interpretation (see Supplementary Table S1). One study (Dhaliwal *et al.*, 2004) was excluded at this stage.

Figure 1 depicts the study selection process. A narrative synthesis approach was used to conduct the review. This technique synthesizes evidence in a systematic way in order to develop an encompassing narrative (Mays *et al.*, 2005).

## Results

### Study characteristics

A total of 12 studies were included in this review. All of these studies were peer-reviewed articles published in eight different journals between 1991 and 2015. Table 1 presents the participants' characteristics. Data from these 12 studies were collected in seven countries, with the majority being from Europe ( $n = 8$ ), three from America, and one from Asia. These studies had a large number of participants responding to both the baseline and follow-up assessments but the number of men included in the group whose treatments were unsuccessful and had not achieved spontaneous pregnancy or alternative fatherhood (e.g. adoption) was significantly lower, ranging from 45 to 375. Participants were predominantly in their early thirties, and they had been trying to conceive for 3 or 4 years. The study of Kraaij *et al.* (2008) was an exception, given that the sample consisted of men for whom the infertility was definite (had started trying to conceive 12 years on average before being recruited) and who had an unfulfilled child wish. Half of the selected studies evaluated participants at baseline before entering a new cycle of fertility treatment, and follow-ups ranged from 4 weeks to 5 years. With the exception of one study based on a structured interview (Holley *et al.*, 2015), all variables related to psychological adaptation in the selected articles were based on self-report measures. The most studied psychological adaptation variables were depression (Möller and Fällström, 1991; Berghuis and Stanton, 2002; Kraaij *et al.*, 2008; Bak *et al.*, 2012; Holley *et al.*, 2015) and coping strategies using both general population self-report scales (Berghuis and Stanton, 2002; Kraaij *et al.*, 2008) and a scale specifically designed to assess specific coping strategies in an infertility context (Schmidt *et al.*, 2005a; Peronace *et al.*, 2007). Infertility-related stress was a dependent variable in four studies (Pook *et al.*, 2002; Schmidt *et al.*, 2005a; Schneider and Forthofer, 2005; Peronace *et al.*, 2007), but the study of Peronace *et al.* (2007) was removed when analysing the changes of infertility stress over time because of a sample overlap with the Schmidt *et al.* (2005b) study. The quality of the marital relationship was assessed both by general population questionnaires (Möller and Fällström, 1991; Schanz *et al.*, 2013) and by an infertility-specific questionnaire (Schmidt *et al.*, 2005b) in three studies. Two studies focused on anxiety (Möller and Fällström, 1991; Bak *et al.*, 2012). Other psychological adaptation variables studied were aggression and hysteria (Möller and Fällström, 1991), mental health (Peronace *et al.*, 2007), the social environment (Peronace *et al.*, 2007), well-being (Schanz *et al.*, 2013), desire for a child (Schanz *et al.*, 2013), infertility-related communication strategies (Schmidt *et al.*, 2005a), and sexual functioning (Bayar *et al.*, 2014).

### Male psychological adaptation to unsuccessful MAR treatments over time

Eight studies were identified as repeating assessments of men's psychological adaptation to unsuccessful treatments over time (Table II). The majority of investigations set their baseline assessment before the onset of either the first cycle of fertility treatment or a subsequent cycle. Although it is the oldest study, Möller and Fällström's (1991) design was the only one assessing male patients visiting a fertility clinic for the first time before diagnosis. The chosen interval between measurements varied immensely, from 4 weeks to 5 years. Apart from the study by Berghuis and Stanton (2002), who evaluated depression 1 week after taking a pregnancy test following an assisted insemination (AI) cycle, follow-ups were based solely on the amount of time since baseline. Of the 14 instruments identified as assessing psychological adaptation over time in these studies, only seven reported psychometric properties within the corresponding samples (Berghuis and Stanton, 2002; Schmidt *et al.*, 2005b; Schneider and Forthofer, 2005; Peronace *et al.*, 2007; Kraaij *et al.*, 2008; Schanz *et al.*, 2013; Holley *et al.*, 2015).

Three studies repeated their assessment of depression over the course of fertility treatments in subsamples of men who did not succeed in achieving pregnancy or parenthood. Using the Beck Depression Inventory (BDI, Beck *et al.*, 1988b), both Bak *et al.* (2012) and Berghuis and Stanton (2002) found an increase in self-reported depression levels within a few weeks after baseline assessment (Bak *et al.*, 2012:  $W = 11.72 \pm 2.76$ ,  $P < 0.0001$ ; Berghuis and Stanton: statistics not presented). Based on a 2-year interval after the first infertility consultation, no significant differences were found in the depression index subscale of the Symptom Rating Scale developed by Möller and Fällström (1991: statistics not presented).

Anxiety was prospectively assessed by two studies. Using the Beck Anxiety Inventory (BAI, Beck *et al.*, 1988a), Bak *et al.* (2012) measured four anxiety subscales 4 weeks after a diagnosis of non-obstructive azoospermia (NOA) was given and then repeated the measure 4 weeks after the diagnosis of sertoli cell-only syndrome (SCO) or chromosomal anomalies. With the exception of panic anxiety ( $W = -0.19 \pm 1.31$ , n.s.), all other subscale levels were lower at follow-up (subjective anxiety:  $W = 3.56 \pm 2.705$ ,  $P < 0.0001$ ; neurophysical anxiety:  $W = 1.50 \pm 1.63$ ,  $P < 0.0001$ ; autonomic anxiety:  $W = 1.75 \pm 1.42$ ,  $P < 0.0001$ ). There were no significant differences in anxiety levels found 2 years after the initial measurement (Möller and Fällström, 1991; statistics not presented).

Two studies assessed changes in the use of coping strategies before and after unsuccessful fertility treatments through ANOVAs. Peronace *et al.* (2007) found an increase in the use of coping strategies in general 1 year after having started a new cycle ( $F = 57.47$ ;  $P < 0.001$ ). Pook *et al.* (2002) analysed changes in five coping strategies over time. Although no significant differences were found in depressive coping ( $F = 0.13$ ), distraction ( $F = 0.89$ ), and minimizing and wishful thinking ( $F = 0.21$ ), the use of active coping strategies ( $F = 6.16$ ;  $P = 0.017$ ) decreased and the use of religiousness and seeking meaning ( $F = 4.49$ ;  $P = 0.040$ ) increased in men 4 months after the workup compared with the levels prior to the workup. These results did not interact with a previous fertility workup ( $F = 1.13$ ;  $P = 0.37$ ).

The amount of stress specifically related to the infertility problem was longitudinally assessed by three studies, with contradictory findings. Pook *et al.* (2002) found a significant decrease in male infertility-related

**Table 1** Main characteristics of all studies included in this review.

Reference	Country where data were collected	Sample sizes	Mean male age	Infertility mean duration (years)	Moments of measurement		Longitudinal participation rate	Psychological adaptation outcome measure
					Baseline (T1)	Follow-up (T2)		
Bak et al. (2012)	Korea	N = 264 (132f, 132m) n = 72 men diagnosed with NOA	31.97		4 weeks after diagnosis	4 weeks after T1	96%	Anxiety Depression
Bayar et al. (2014)	Turkey	N = 110 (55f, 55m) n = 45 men, no pregnancy at T2	33.9	4	Before first cycle	3 months after T1	91%	Sexual functioning
Berghuis and Stanton (2002)	USA	N = 86 (43f, 43m) n = 43 men, no pregnancy at T2	34.7	2.8	1 week before AI	1 week after negative pregnancy test	85%	Depression Coping strategies
Kraaij et al. (2008)	Netherlands	N = 169 (105f, 64m) n = 20 men with definite infertility		12	Not defined	2 years after T1	89%	Depression Coping strategies
Holley et al. (2015)	USA	N = 834 (448f, 386m) n = 144 men, no pregnancy/child at T2	37.8	2.4	Before first cycle	4, 10 and 18 months after T1	59%	Major depressive disorder during treatment
Möller and Fällström (1991)	Sweden	N = 142 (71m, 71f) n = 35 men, no pregnancy/child at T2	30.6	3.3	First visit	2 years after T1	89%	Psychosomatic symptoms Marital relationship
Peronace et al. (2007)	Denmark	N = 256m n = 256 men, no pregnancy/child at T2	34	4.3	Before (new) cycle	1 year after T1	86%	Mental health Coping strategies Social environment
Pook et al. (2002)	Germany	N = 45m n = 45 men, no pregnancy/child at T2	33.4		Before (new) fertility workup	4 months after fertility workup	100%	Infertility-related stress Coping strategies
Schanz et al. (2013)	Germany	N = 275m n = 45 men, no pregnancy/child at T2	35.6	3.8	Fertility consultation	5 years after T1	37%	Well-being Desire for a child Partnership
Schmidt et al. (2005a)	Denmark	N = 816 (441f, 375m) n = 375 men, no pregnancy/child at T2			Before (new) cycle	1 year after T1	86%	Infertility-related stress Infertility-related communication strategies Infertility-related coping strategies
Schmidt et al. (2005b)	Denmark	N = 816 (441f, 375m) n = 375 men, no pregnancy/child at T2			Before (new) cycle	1 year after T1	86%	Infertility-related marital benefit
Schneider and Forthofer (2005)	USA	N = 128 (66f, 62m) n = 62 men, no pregnancy/child at T2	33	2.7	Fertility consultation	2 years after T1	82%	Infertility-related stress

N, total sample size of the study at baseline; n, number of male participants who at follow-up did not achieve pregnancy or parenthood: only statistics for these participants were included in the qualitative synthesis of results; NOA, non-obstructive azoospermia; AI, assisted insemination.

**Table II Male psychological adjustment over time to unsuccessful infertility treatments.**

Reference	Sample size	Moments of measurement		Measures	Results
		Baseline (T1)	Follow-up (T2)		
Bak <i>et al.</i> (2012), Korea	n = 72 men with non-obstructive azoospermia	4 weeks after diagnosis	4 weeks after T1	Anxiety: BAI Depression: BDI	Subjective anxiety: T1 > T2; neurophysical anxiety: T1 > T2; autonomic anxiety: T1 > T2; panic anxiety: T1 = T2; depression: T1 < T2; Wilcoxon test
Bayar <i>et al.</i> (2014), Turkey	n = 45 men, no pregnancy at T2	Before first cycle	3 months after T1	Sexual Functioning: ASEX	Drive: T1 > T2; arousal T1 > T2; erection T1 = T2; orgasm T1 > T2; satisfaction from orgasm T1 > T2; sexual functioning total score T1 > T2; Wilcoxon test
Berghuis and Stanton (2002), USA	n = 43 men, no pregnancy at T2	1 week before AI	1 week after pregnancy test	Depression: BDI	Depression: T1 < T2; ANOVA
Möller and Fällström (1991), Sweden	n = 35 men, no pregnancy/child at T2	First visit	2 years after T1	Psychosomatic symptoms: SRS Marital relationship: RRMW	Psychosomatic index: T1 = T2; anxiety index: T1 = T2; depression index: T1 = T2; aggression index: T1 = T2; hysteria index: T1 = T2; marital relationship: T1 = T2; Student's t-test
Peronace <i>et al.</i> (2007), UK	n = 256 men, no pregnancy/child at T2	Before (new) cycle	1 year after T1	Mental health: SF-36 Coping strategies: COMPI CSS Social environment: DLHBS	Mental health T1 > T2; coping effort T1 < T2; negative comments T1 < T2; understanding T1 > T2; ANOVA
Pook <i>et al.</i> (2002), Germany	n = 45 men, no pregnancy/child at T2	Before (new) fertility workup	4 months after fertility workup	Infertility-related stress: IDS Coping strategies: FQCI-SF	Infertility stress: T1 > T2; depressive coping: T1 = T2; active coping: T1 > T2; distraction: T1 = T2; religiousness and seeking meaning: T1 < T2; minimizing and wishful thinking T1 = T2; ANOVA
Schanz <i>et al.</i> (2013), Germany	n = 45 men, no pregnancy/child at T2	Fertility consultation	5 years after T1	Infertility-related quality of life: TLMK	Desire for a child: T1 > T2; partnership: T1 = T2; psychological well-being: T1 = T2; Wilcoxon test
Schmidt <i>et al.</i> (2005a), Denmark	n = 375 men, no pregnancy/child at T2	Before (new) cycle	1 year after T1	Infertility-related stress: COMPI FPSS	Personal stress: T1 > T2; marital stress: T1 > T2; social stress: T1 < T2; infertility stress: T1 < T2; Student's t-test

AI, assisted insemination; BAI, Beck Anxiety Inventory (Beck *et al.*, 1988a); BDI, Beck Depression Inventory (Beck *et al.*, 1988b); ASEX, Arizona Sex Life Inventory (McGahuey *et al.*, 2000); SRS, Symptom Rating Scale (Möller and Fällström, 1991); RRMW, Ratings of relationship between man and woman (Möller and Fällström, 1991); SF-36, Short-Form-36 Inventory (Ware *et al.*, 1993); COMPI CSS, COMPI Coping Strategy Scales (Schmidt *et al.*, 2005a, c); DLHBS, Danish Longitudinal Health Behavior Study (Due *et al.*, 1999); IDS, Infertility Distress Scale (Pook *et al.*, 1999); FQCI-SF, Freiburg Questionnaire of Coping with Illness – Short Form (Muthny, 1989); TLMK, Tubingen Quality of Life Questionnaire for men with involuntary childlessness (Schanz *et al.*, 2005); COMPI FPSS, COMPI Fertility Problem Stress Scales (Schmidt *et al.*, 2005a).

stress 4 months after the workup ( $F = 18.04$ ;  $P = 0.001$ ). Although this effect remained significant ( $F = 24.03$ ;  $P = 0.001$ ) in the subsample of men for whom this was the first fertility workup ( $n = 16$ ), there were no significant differences in infertility stress levels ( $F = 1.70$ ) for those who had undergone previous workups ( $n = 28$ ). Schmidt et al. (2005a) analysed these differences with t-tests and found that the levels of reported male infertility stress before starting a new cycle were higher 1 year later ( $P < 0.001$ ). Compared with baseline levels, these men presented higher infertility-related stress levels in the social domain subscale but indicated less stress in the marital and personal domains (all  $P < 0.001$ ), thus suggesting that the stress associated with infertility can result from social pressure and a lack of social support.

Peronace et al. (2007) also focused on changes in relation to the social environment of men being treated for infertility. Compared with the moment before starting a new cycle, men reported less support and understanding ( $F = 20.58$ ;  $P < 0.001$ ) and more negative reactions and comments ( $F = 21.53$ ;  $P < 0.001$ ) from family and friends 1 year later.

Regarding the marital relationship, despite the above-mentioned significant decrease in marital stress levels 1 year after starting a new cycle (Schmidt et al., 2005a), no significant differences were found in two studies using longer follow-ups. Specifically, Möller and Fällström (1991) found no differences in the marital relationship ratings of men between the first visit and 2 years later (statistics not presented). There were also no significant differences in the reported quality of life associated with partnership found by Schanz et al. (2013), who followed patients 5 years after a fertility consultation ( $W = -0.22 \pm 0.82$ ).

Bayar and colleagues (2014) found that men reported higher sexual functioning on the Arizona Sex Life Inventory (McGahuey et al., 2000) before entering a first treatment cycle than 3 months after ( $P < 0.001$ ). This decrease in the total score was also observed on the subscales drive ( $P < 0.001$ ), arousal ( $P = 0.005$ ), orgasm ( $P = 0.001$ ) and satisfaction from orgasm ( $P < 0.001$ ), but no significant differences were found regarding erection ( $P = 0.216$ ).

Other psychological adaptation variables related to emotional needs were independently studied. Although there was a decrease in mental health and energy vitality at a 1-year follow-up evaluation ( $F = 16.45$ ;  $P < 0.001$ ; Peronace et al., 2007), there were no significant differences in psychosomatic symptomatology, aggression or hysteria at 2-year follow-up (Möller and Fällström, 1991; statistics not presented) and no differences in psychological well-being ( $W = 0.03 \pm 0.57$ ) at a 5-year follow-up (Schanz et al., 2013).

## Protective and risk factors for male psychological maladaptation to unsuccessful MAR treatments

Table III summarizes the six studies that met this review's criteria for investigating the psychosocial determinants of psychological adjustment to infertility in men. The baseline for the analysed cohorts was stipulated as occurring at a random fertility consultation (Schneider and Forthofer, 2005), before the first cycle (Holley et al., 2015) or any cycle of treatments (Schmidt et al., 2005a, b), exactly 1 week before an assisted insemination (AI) cycle occurred (Berghuis and Stanton, 2002), or after unsuccessful treatment (Kraaij et al., 2008). Apart from the study of Berghuis and Stanton (2002), for which the outcome was measured 1 week after a pregnancy test was taken, follow-ups were conducted at 12 (Schmidt et al., 2005a, b), 18 (Holley et al., 2015), or 24 months

(Schneider and Forthofer, 2005; Kraaij et al., 2008) after baseline. All self-report scales containing continuous variables were analysed regarding internal consistency and/or factor structure, and all studies used regression techniques in their analysis.

Depression was chosen as a dependent variable by three studies, with two of them having used coping strategies as independent variables. Berghuis and Stanton (2002) analysed the effects of coping strategies on depression rated by both men and their wives 1 week before the AI and 1 week after a negative pregnancy test result following AI. These authors found that male depression symptoms can be reduced by using coping strategies that involve positive reinterpretation ( $\beta = -0.50$ ;  $P < 0.001$ ), emotional processing ( $\beta = -0.61$ ;  $P < 0.001$ ), or emotional expression ( $\beta = -0.41$ ;  $P < 0.007$ ). The only positive predictors of depression were the partners' use of avoidance and religious coping ( $\beta = 0.60$ ;  $P < 0.001$  and  $\beta = 0.71$ ;  $P < 0.001$ , respectively). Using different measures, Kraaij et al. (2008) found that catastrophizing predicted depression 2 years after treatment ( $\beta = 0.26$ ;  $P < 0.05$ ). This was the only strategy out of 11 cognitive coping strategies that had a significant effect (see Table III). While both Berghuis and Stanton (2002) and Kraaij et al. (2008) studies used self-report scales of depression, the study of Holley and colleagues (2015) used a structured interview to assess major depressive disorder (MDD). Patients were interviewed before entering the first fertility treatment cycle (baseline), and 4, 10 and 18 months afterwards. Individuals were considered depressed at follow-up if they had been diagnosed with MDD at least one time after baseline and over the course of treatment. While partner support did not significantly predict MDD (OR 0.80, 95% CI 0.51–1.25), significant contributions were found from baseline MDD (OR 10.10, 95% CI 3.21–31.74), and self-reported depression (OR 2.27, 95% CI 1.40–3.70), and anxiety (OR 2.02, 95% CI 1.23–3.31).

Three studies assessed infertility stress. In the study by Schneider and Forthofer (2005), participants rated their degree of infertility stress 2 years after a fertility consultation in which they responded to questions concerning social and spousal support, self-esteem, perceived health, the importance of having biological children, and attribution of responsibility for the fertility problem. The only variables that significantly contributed to male infertility stress were social support and spousal support (statistics not presented). Schmidt and colleagues (2005a) analysed the predictive power of infertility-related coping and communication, in men before a new cycle of treatment, in infertility stress 1 year later while controlling for age. Infertility stress was predicted by difficulties in partner communication (OR 3.69, 95% CI 2.09–6.43) and by the use of infertility-related active-avoidance coping (OR 2.41, 95% CI 1.29–4.53). These two variables were also the only predictors of infertility stress in the personal (OR 3.56, 95% CI 1.38–4.74; OR 2.12, 95% CI 1.04–4.32, respectively) and social domains (OR 2.76, 95% CI 1.55–4.91; OR 2.58, 95% CI 1.34–4.96, respectively).

Regarding the impact on the couple relationship, the authors tested the described predictors in terms of the stress (Schmidt et al., 2005a) as well as the strength and closeness (Schmidt et al., 2005b) that infertility can cause in a relationship. The results revealed that difficulties in partner communication predicted high infertility-related marital stress levels (OR 2.27, 95% CI 1.22–4.22, Schmidt et al., 2005a) and low marital benefits (OR 0.52, 95% CI 0.26–1.03, Schmidt et al., 2005b). Strategies for communicating with others did not influence the levels of marital stress (Schmidt et al., 2005a), but the use of open-minded strategies (i.e. discussing both factual and emotional issues related to infertility in both

**Table III Predictors of male psychological adjustment to unsuccessful infertility treatments.**

Reference	Sample size	Predictors [T1]	Outcomes [T2]	Results
Berghuis and Stanton (2002), USA	n = 43 men, no pregnancy at T2	Coping strategies (seek social support; problem-focused coping; avoidance; positive reinterpretation and growth; religious coping): COPE Coping strategies (emotional processing; emotional expression): EACS [1 week before AI]	Depression: BDI [1 week after pregnancy test]	Positive reinterpretation, emotional processing and emotional expression negatively predicted depression; partner avoidance and partner religious coping positively predicted depression; Hierarchical multiple regression.
Holley et al. (2015)	n = 144 men, no pregnancy/child at T2	Depression: CESD Anxiety: STAI-State Partner support: PSSSC Past major depressive disorder: CID1, depression module [before first cycle]	Major depressive disorder: CID1, depression module [4, 10 and 18 months after T1]	Depression, anxiety, and past major depressive disorder positively predicted the presence of major depressive disorder at one or more follow-up points; Hierarchical multiple logistic regression.
Kraaij et al. (2008), Netherlands	n = 20 men with definite infertility	Coping cognitive strategies (self-blame; acceptance; rumination; positive refocusing; refocus on planning; positive refocusing; refocus on planning; positive reappraisal; putting into perspective; catastrophizing; other-blame): CERQ [undefined]	Depressive symptoms: SCL-90 [2 years after T1]	Catastrophizing positively predicted depressive symptoms; Hierarchical multiple regression
Schmidt et al. (2005a), Denmark	n = 375 men, no pregnancy or child at T2	Infertility-related communication strategies (open-minded; formal; secrecy): COMPI ICS Infertility-related coping strategies (active-avoidance; active-confronting; passive-avoidance; meaning-based): COMPI CSS Difficulties in partner communication [Before (new) cycle]	Infertility-related stress (personal domain; marital domain; social domain): COMPI FPSS [1 year after T1]	Difficulties in partner communication positively predicted personal stress, marital stress, social stress, and total infertility stress; active-avoidance coping positively predicted personal stress, social stress, and total infertility stress; active-confronting coping negatively predicted marital stress; Odds ratio
Schmidt et al. (2005b), Denmark	n = 375 men, no pregnancy or child at T2	Infertility-related communication strategies (open-minded; formal; secrecy): COMPI ICS Infertility-related coping strategies (active-avoidance; active-confronting; passive-avoidance; meaning-based): COMPI CSS Difficulties in partner communication [Before (new) cycle]	Infertility-related marital benefit: COMPI MS [1 year after T1]	Medium and high use of meaning-based coping strategies, medium use of active-confronting coping, low use of active-avoidance coping, use of open-minded communication strategies and no difficulties in partner communication predicted high marital benefit; Odds ratio
Schneider and Forthofer (2005), USA	n = 62 men, no pregnancy or child at T2	Social support: SSQ Spousal support: SS Self-esteem: RSES Perceived health: HSCL Importance of biological children: ICS Attribution of responsibility for the fertility problem [Fertility consultation]	Infertility-related stress: FPS [2 years after T1]	Social support and spousal support negatively predicted infertility-related stress Hierarchical multiple regression

COPE, Coping Orientations to Problems Experienced (Carver et al., 1989); EACS, Emotional Approach Coping scales (Stanton et al., 2000); AI, assisted insemination; BDI, Beck Depression Inventory (Beck et al., 1988b); CESD, Center for Epidemiologic Study of Depression scale (Radloff, 1977); STAI-State, State-Trait Anxiety Inventory, State anxiety subscale (Spielberger et al., 1983); PSSSC, perceived social support and social conflict scale (Abbey et al., 1985); CID1, Composite International Diagnostic Interview (Kessler and Ustun, 2004); CERQ, Cognitive Emotion Regulation Questionnaire (Garmefski et al., 2001); SCL-90, Symptom Check List (Derogatis, 1977); COMPI CSS, COMPI Coping Strategy scales (Schmidt et al., 2005a, c); COMPI FPSS, COMPI Fertility Problem Stress scales (Schmidt et al., 2005a); COMPI MS, COMPI Marital benefit (Schmidt, 1996; Schmidt et al., 2005b); COMPI ICS, COMPI infertility-related communication strategies (Schmidt et al., 2005a); SSQ, Social Support questionnaire (Sarason et al., 1987); SS, Spousal Support (Schneider and Forthofer, 2005); RSES, Rosenberg Self-Esteem Scale (Rosenberg, 1965); HSCL, The Hopkins Symptom Checklist (Derogatis et al., 1974); ICS, Importance of Biological Children (Abbey et al., 1992); Attribution of responsibility for the fertility problem (Schneider and Forthofer, 2005); FPS, Fertility Problem Stress (Abbey et al., 1992).

close and distant relationships) can bring marital benefit (Schmidt et al., 2005b) when compared with the use of secrecy strategies (OR .35, 95% CI 0.14–0.86) but not with the use of formal strategies (i.e. discussing factual and no or only few emotional issues related to infertility in both close and distant relationships). In the study investigating marital benefit (Schmidt et al., 2005b), coping strategies subscales were trichotomized into low, medium, and high use. While active-avoidance coping was found to be a significant risk factor (medium versus low OR 0.56, 95% CI 0.30–1.05; high versus low OR 0.48, 95% CI 0.24–0.96), meaning-based coping was a protective factor for marital benefit (medium versus low OR 2.21, 95% CI 1.06–4.66; high versus low OR 6.31, 95% CI 2.93–13.57). Only the moderate use of active-confronting coping predicted marital benefit compared with low use (medium versus low OR 1.66, 95% CI 0.91–3.03; high versus low n.s.), and high levels of active-confronting coping were associated with greater marital stress (OR 0.53, 95% CI 0.28–1.00, Schmidt et al., 2005a).

Table IV encapsulates the findings and shows which factors can benefit or pose risks to men's mental health when facing failed fertility treatments.

## Discussion

This is the first systematic review to summarize the best available evidence analysing the psychological symptoms associated with men's experience of unsuccessful fertility treatment. Following a rigorous sampling and assessment procedure, 12 studies were included for analysis in this review. Although the majority of these studies were published in the last decade, revealing the increasing interest in the male experience of infertility, evidence concerning how men psychologically

react to infertility, its treatments, and subsequent failures is far from solid.

## Summary of research synthesis

### Male psychological adaptation to unsuccessful MAR treatments over time

Although evidence is scarce, this review suggests a tendency towards poorer psychological adaptation to fertility treatments in the year following the initial evaluation. The gathered evidence suggests that infertility-related stress (Schmidt et al., 2005a) and depression increase (Berghuis and Stanton, 2002; Bak et al., 2012), and dimensions of mental health (Peronace et al., 2007) and sexual functioning (Bayar et al., 2014) show decline. Men also feel less supported and have to increase their efforts to cope with this stressor (Peronace et al., 2007), namely, by increasing seeking meaning and decreasing active coping (Pook et al., 2002).

There were two exceptions to this pattern. The first exception is the study by Bak et al. (2012), who observed a decrease in subjective, neurophysical and autonomic anxiety and found no significant differences in panic anxiety. The sample used in this study was entirely composed of men who had a diagnosis of NOA. Although treatment with ICSI is possible, only 50% of men diagnosed with NOA have a successful testicular sperm recovery (Chan and Schlegel, 2000; Ald et al., 2004). Receiving such a diagnosis means facing the much stronger risk of being unable to have biological children compared with the risk faced by other infertile men in treatment. Additionally, this group of men is more vulnerable to enduring embarrassing and painful treatment procedures (Inhorn, 2013). This tendency might explain the high anxiety levels in the first month after receiving the diagnosis and the finding that depression

**Table IV Protective and risk factors of male psychological adjustment to unsuccessful infertility treatments.**

Predictors	Moments of measure		Outcomes		
	Baseline	Follow-up	1. Depression	2. Stress	3. Marital adjustment*
Emotional processing <sup>1</sup>	1 week before AI	1 week after negative pregnancy test	(-)		
Emotional expression <sup>1</sup>			(-)		
Positive reinterpretation <sup>1</sup>			(-)		
Partner religious coping <sup>1</sup>			(+)		
Partner avoidance coping <sup>1</sup>			(+)		
Difficulties in partner communication <sup>2,3</sup>	Before (new) cycle	1 year after		(+)	(-)
Active-confronting coping <sup>2,3</sup>				(-)	(+)
Active-avoidance coping <sup>2,3</sup>				(+)	(-)
Open-minded communication strategies (versus secrecy) <sup>3</sup>					(+)
Meaning-based coping <sup>3</sup>					(+)
Anxiety <sup>4</sup>	Before first cycle	18 months after	(+)		
Depression <sup>4</sup>			(+)		
Social support <sup>5</sup>	In treatment	2 years after		(-)	
Spousal support <sup>5</sup>				(-)	
Catastrophizing <sup>6</sup>	Undefined		(+)		

<sup>1</sup>Berghuis and Stanton (2002); <sup>2</sup>Schmidt et al. (2005a); <sup>3</sup>Schmidt et al. (2005b); <sup>4</sup>Holley et al. (2015); <sup>5</sup>Schneider and Forthofer (2005); <sup>6</sup>Kraaij et al. (2008); AI, assisted insemination; (-), negative predictors; (+), positive predictors; green symbols represent protective factors, and red symbols represent risk factors.

\*Includes the outcomes marital benefit and marital stress.

increased while anxiety decreased. The second exception was in the study by Pook *et al.* (2002), in which male infertility stress decreased 4 months after treatment. However, this decrease remained significant only for those who had never seen a fertility specialist, not for those who had already undergone fertility treatment before T1. Although conclusions from this study are limited by sample size restrictions, these findings suggest that men might suffer from anticipatory stress before the first consultation.

Men's long-term psychological adaptation to failed fertility treatments does not seem to be affected, as shown by longitudinal evidence with follow-ups at two (Möller and Fällström, 1991) and 5 years (Schanz *et al.*, 2013). These studies point towards stability regarding psychosomatic symptomatology (Möller and Fällström, 1991), well-being (Schanz *et al.*, 2013), and partnership quality (Möller and Fällström, 1991; Schanz *et al.*, 2013). Moreover, men's wishes to have a child decrease 5 years after having received a diagnosis, even while they continue pursuing fertility treatment (Schanz *et al.*, 2013).

Together, findings related to male adaptation to unsuccessful treatments over time point to increased distress during the first year, followed by a return to initial psychological adjustment. The opposite pattern seems to occur with distress in the marital relationship, which decreases in the first year and returns to baseline distress levels in the following years. However, the limited number of studies increases the difficulty of making definite assumptions, particularly concerning long-term adjustment to treatments.

#### *Protective and risk factors for male psychological maladaptation to unsuccessful MAR treatments*

This review also allowed for the identification of risk and protective factors in male adjustment to MAR treatments. The few studies included in this review on the longitudinal associations found for male psychological adjustment to unsuccessful treatments covered only three main dependent variables, depression, stress, and marital adjustment, and the predictors were coping strategies, communication, and social support. The majority of protective factors consist of coping strategies related to seeking social support, emotional expression and reconstruction of life goals. Men who adopt these coping strategies are protected against depression (Berghuis and Stanton, 2002) and disruption in the marital relationship (Schmidt *et al.*, 2005a, b). The maintenance or development of good relationships within the social sphere seems to be a key protective factor. Besides seeking social support and expressing one's emotions, speaking openly about the infertility problem and feeling supported by others, particularly by one's wife, can improve marital adjustment (Schmidt *et al.*, 2005b) and decrease the distress brought by MAR treatments (Schneider and Forthofer, 2005), respectively.

Meanwhile, risk factors seem closely linked not only to feelings of isolation but also to the marital relationship. Initial anxiety and depression contribute to the onset of major depression during treatment (Holley *et al.*, 2015). Coping strategies that pose a risk to infertility adjustment might involve either cognitively emphasizing the fertility problem and its taxing nature, thus increasing depression (Kraaij *et al.*, 2008), or actively avoiding the problem, thus increasing stress and decreasing the quality of the marital relationship (Schmidt *et al.*, 2005b). Coping strategies adopted by these men's wives can also influence their adjustment to treatments. More specifically, women's use of religious or avoidance coping increases male depression after a failed cycle (Berghuis and Stanton, 2002). Adjustment to failed treatments

is also compromised when men sense barriers to marital communication regarding the infertility problem, and this perception was found to be detrimental to both infertility stress and the relationship (Schmidt *et al.*, 2005a, b).

Taken together, this review's findings help to refute the commonly held misperception that men, despite being disappointed with infertility, are not overly emotionally distressed as a result of such an experience.

### **Limitations and recommendations for future research**

The strengths of this review are its systematic review of all published studies to date from five databases, the a priori review protocol, and the fact that studies were selected both on the bases on eligibility and quality, with standard sheets used by three independent researchers. Nevertheless, there are limitations arising both from the studies and the complexity of the research questions involved. Because of the heterogeneity and introduction of bias, we made a rigorous assessment to ensure that all included subjects continued seeking treatment and had not achieved pregnancy or childbirth at follow-up. Thus, generalization to men who are not seeking treatment is not possible. Additionally, all samples included in this review were composed of heterosexual men in a relationship, and hence, conclusions on single and lesbian, gay, bisexual and transgender (LGBT) populations cannot be drawn. Finally, with the exception of one data collection from Asia, all research samples were from Europe and the United States, posing a high risk of cultural and demographic bias. Adding to this bias, the fact that treatment seekers are more frequently Caucasian, highly educated and with high family incomes (White *et al.*, 2006), another limitation of this review is that the relative contribution of demographic variables could not be considered.

Although the included research constitutes the best available evidence, a cautious approach to data interpretation is required as a result of the design of the studies. The strongest limitation is related to variations in baseline measurements and the subsequent difficulty in comparing results. Having already received a diagnosis or having experienced a previous failed cycle can represent an important bias regarding psychological adaptation over time. Of the 12 included studies, only one had a baseline measurement defined at the first consult at a fertility centre (Möller and Fällström, 1991). Interestingly, this was the only study published in the past century included in this review. Follow-up measurements also constitute a problem when reviewing the evidence. Berghuis and Stanton (2002) and Pook *et al.* (2002) were the only researchers to define a follow-up measure based on a specific moment in relation to treatment. Defining follow-ups based solely on months or years since baseline means that a subject can be reporting after only one cycle or after five cycles, either on the day of embryo transfer or when the couple has decided to take a pause from treatment even though they will continue pursuing it. These situations can be very particular in terms of anxiety, for example. We are all aware that in recent years, there have been progressively sophisticated methods of data analysis that demand increasing ratios of subjects per variable, making it difficult for research teams to spend time and resources on building a representative sample of men initiating fertility treatment. Nevertheless, research focusing on the impact of infertility at earlier stages is needed to understand how men react to the first consult or diagnosis and to test for the hypothesis of anticipatory treatment stress, in addition to research post-treatment with follow-ups based on the treatment process rather

than merely based on time. It is also relevant to include dependent variables at baseline. We recommend that a priori power analyses be performed to determine the required number of subjects necessary for a given design. The potential relationship between non-participation and abandonment of treatment is also an important problem. For example, when focusing on marital adjustment to infertility, future studies should try to control for selection bias because non-participants might be the individuals who tend to divorce or exhibit weak marital adjustment. Only then could we conclude that stress does not affect the marital relationship and that infertility can bring couples together (Martins et al., 2014b).

Another issue raised during this investigation was the lack of reporting on validation and/or adaptation procedures for instruments and scale reliability. Although all studies included in this review make at least a mention to the original validity, only 7 out of 10 studies reported validity procedures or internal consistency values regarding the actual samples (Berghuis and Stanton, 2002; Schmidt et al., 2005b; Schneider and Forthofer, 2005; Peronace et al., 2007; Kraaij et al., 2008; Schanz et al., 2013; Holley et al., 2015). The testing of psychometric properties is necessary to prove the clinical usefulness of a given measure (Streiner et al., 2014), and hence, these should be tested and reported at all times.

It should also be noted that most of the studies included in this review also included women. As far as we could ascertain, only one study treated data as non-independent (Kraaij et al., 2008), while others assumed non-independence of data by not accounting for variation in the husband's adjustment that could be explained by the wife's adjustment or predictors (Kenney et al., 2006). Future research using the dyad as a unit of analysis is needed not only to test whether effects remain after accounting for the partner's behaviour but also to differentiate genders in actor and partner effects as mentioned above.

To overcome these limitations, internal campaigns at fertility centres and associations targeting professionals and patients should be used to call attention to the lack of men in fertility research and to the need to increase knowledge on the male experience of infertility and its treatments in order to facilitate recruitment and avoid a great number of losses at follow-up. Although men have been more likely to be included in the designs of recent studies, women have been over-represented in the infertility literature because they are primarily handled as patients and participants typically selected among those attending treatment appointments. If men become more involved in treatment and participate more fully with their partners in fertility procedures, this involvement would have the added benefit of allowing researchers better opportunities to sample men and to study issues of importance related to their unique experiences regarding infertility and treatment. Only then will research within this field be able to move towards high-quality randomized controlled trials with men also participating in interventions.

## Clinical implications

The current review provides a road map for understanding men's psychological and emotional reactions to unsuccessful fertility treatments. By better understanding the unique elements of men's experiences, we can build on existing knowledge as we seek to improve the delivery of support and mental health services for men as well as to identify additional areas of needed inquiry to strengthen the existing knowledge base.

We propose that medical and mental health professionals work together to develop and implement targeted clinical interventions by

considering the unique elements of men's experience with infertility. Our first recommendation is that health care professionals work to identify ways in which men can be more directly involved in fertility treatments in all diagnostic cases. If medical providers ensure an atmosphere that helps men move from the periphery of treatment towards the centre with increased involvement, this environment could reduce feelings of marginalization. We support Malik and Coulson's (2008) recommendation to develop educational materials for men as well as to offer increased resources such as support groups or online information detailing men's emotional reactions to the infertility journey, as these strategies have been effective in ensuring greater male involvement in the process. Furthermore, the inclusion of men more directly in the treatment process is valued by fertility patients (Dancet et al., 2010) and may benefit both men and their partners by easing the solitary burdens and isolation that each partner may feel.

The majority of risk factors for male psychological maladaptation in this review were closely linked to the marital relationship, which adds validity to the existing recommendations for couples counselling (Human Fertilisation and Embryology Authority (HFEA), 2008; National Institute for Clinical Excellence (NICE), 2013). Hence, we also recommend that men be educated regarding effective communication strategies that decrease marital stress related to fertility treatment, and be informed regarding effective coping strategies that can reduce the risk factors associated with psychological distress. Coping skills training (CST) has been successfully used in other health-related low-control situations (Blumenthal et al., 2006; Whittemore et al., 2010), and men may benefit from the acquisition of coping techniques that reduce both individual and relational stress related to infertility (Peterson et al., 2009).

## Conclusion

Although studies are increasing, there is little available prospective evidence on male psychological adjustment to MAR treatments. The findings from this review indicate that psychological adjustment in men decreases in the year after the initial evaluation and that long-term adjustment is not affected. Disclosure, social support, and coping strategies related to the reconstruction of life goals and seeking support were found to be protective from male maladjustment. Coping associated with isolation, difficulties in partner communication, and partner coping can pose risks to men's adjustment to fertility treatment. The findings highlight a key role of the spouse and marital adjustment in male mental health and well-being when facing infertility. Hence, counselling should include interventions with coping skills training and couples communication enhancement strategies to deal with the challenge of infertility. Nevertheless, great efforts are needed to strengthen the methodologies of future studies to produce solid evidence on the course of male psychological adjustment not only during but also before and after fertility treatment. Further prospective large studies with high-quality design and power are warranted to perform a subsequent meta-analysis and compare results concerning diagnosis and treatment options. Education campaigns within fertility centres and public associations should be used to call attention to the importance of men's participation in reproductive health research.

## Supplementary data

Supplementary data are available at <http://humupd.oxfordjournals.org/>.

## Authors' roles

M.V.M.: protocol development, blind rating of final studies to include in review, review of literature and manuscript preparation; M.B.-P.: protocol development, literature searches, blind rating of studies to include in review and manuscript preparation; J.P.: literature searches and blind rating of studies to include in review; B.P.: supervision of research and manuscript preparation; V.A.: expertise in clinical aspects of MAR and critical revision of manuscript; L.S.: supervision of research and critical revision of manuscript; and M.E.C. supervision of research and critical revision of manuscript.

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## Conflict of interest

None declared.

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