Running title: Risk factors for couples' discontinuation

Couples' discontinuation of fertility treatments:
A longitudinal study on demographic, biomedical and psychosocial risk factors

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Declaration of interest statement
The authors report no conflicts of interest.

Conflict of interest statement
The authors declare that they have no conflict of interest.

Informed consent: "Informed consent was obtained from all individual participants included in the study.

Abstract

Purpose: To explore the role of infertility-psychosocial variables on treatment discontinuation after controlling for demographic and biomedical variables in couples seeking reimbursed fertility treatment.

Methods: A prospective study was conducted in 139 couples seeking fertility treatment. Between February 2010 and March 2011, participants completed measures of anxiety (STAI-State), depression (BDI-II), infertility-stress (FPI) and infertility coping strategies (COMPI-CSS). Medical data related to diagnosis, treatment and discontinuation were collected in December 2013. A multiple logistic regression was performed to identify the predictors of discontinuation.

Results: The discontinuation rate was 29.5%. Female education level, engagement in ART procedures and female causation decreased the likelihood of treatment discontinuation, whereas female age and depression increased the likelihood of discontinuation. Female depression was the strongest predictor in this model. The model correctly identified 75.5% of cases.

Conclusions: Female age and female depression are associated with a higher likelihood of treatment discontinuation in couples seeking treatment. Reproductive health professionals should therefore inform couples about the link between the fertility treatment discontinuation and both female age and female depression. Couples in which female partners present clinically relevant depression should be referred to a mental health professional to prevent premature abandonment of fertility treatments and thus increase success rates.

Capsule

Among demographic, biomedical and psychosocial variables analyzed as predictors of couples'
discontinuation of reimbursed fertility treatment, female depression and age predicted
discontinuation, and female causation, ART and female education predicted compliance.

Introduction

Infertility is a medical condition affecting nearly one in every ten couples [1] unable to achieve a clinical pregnancy after 12 months of regular unprotected sexual intercourse [2]. Within developed countries, more than half of these couples seek medical help [1] and pursue fertility treatment [3,4]. However, a significant portion decides to discontinue fertility care.

Discontinuation of fertility treatment diminishes the probability of successful pregnancy, whereas compliance with treatment increases the probability of treatment success[5–8]. The WHO defines compliance or adherence as 'the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider'[8, p. 3]. In the context of fertility treatments, '…compliance would refer to the uptake of the ART cycles recommended by the doctor until pregnancy is achieved or until there is a recommendation to end treatment…'[6, p. 125].

The high prevalence of discontinuation, an estimated 30% of couples [3,5], is thus surprising. Discontinuation rates nevertheless vary across studies (e.g., 5.6% [9], 70% [10]) because of the use of different conceptualizations of discontinuation. For example, patients to whom treatment is denied because of a poor prognosis ("actively censored patients"[11]) are inconsistently considered discontinuers.

Several investigations have attempted to understand why patients discontinue fertility treatment. According to these studies, a psychological burden is the most commonly cited reason by patients for discontinuation [3,5,10,12–14]. Psychological variables have also been found to predict discontinuation [9,15], and associations between discontinuation and marital and personal problems [13,16,17], perceived poor diagnosis [5,13], female age [15,18,19] and parity [20] have also been reported. Although these studies have helped elucidate the discontinuation phenomenon, gaps in the literature remain (for a review, see Gameiro *et al*., [21]). First, the lack of consensus regarding the definition of discontinuation engenders inconsistent results across studies. Different reasons have been reported, such as emotional stress [12]but also successful pregnancy [10]. Second, most studies ask participants to select the main reason for discontinuation from a preexisting list of possible reasons [12,13,22] (see

[16,20,23] for exceptions). However, discontinuation may be based on multiple reasons, including non-listed reasons or aspects patients are unable to self-report owing to lack of self-awareness. Furthermore, patients' responses may be sensitive to recall bias when studies are not prospective. Third, most studies have focused on the individual, particularly females [3,12,23] ([16,24]for exceptions), yet the decision to discontinue treatment is likely made by both members of the couple, as are previous reproductive choices such as the decision to stop contraception or pursue treatment [25,26]. Fourth, researchers have generally used either demographic and biomedical variables [17,20,27] or psychosocial variables [3,12] as independent variables. Recently, a study has investigated demographic, medical and psychosocial predictors [24]. However, the analysis of psychosocial variables was made separately for women and men. Moreover, studies indicating that psychological adjustment influences couples' decision to discontinue treatment use generalized measures, such as anxiety and depression [9,15,16] (exception for [24]), that do not capture the specific distress associated with the infertility experience or treatments [28]. Infertility-specific variables, such as active-avoidance coping, are known to be associated with higher infertility distress [29–31], and they may thus be expected to influence the decision to discontinue fertility treatment.

To bridge these gaps, this study aims to contribute to a deeper understanding of the discontinuation of fertility treatment by testing a model that includes relevant information from both members of the couple in a prospective design. For this purpose, demographic characteristics, biomedical information, general psychological adjustment, and infertility-specific adjustment were simultaneously analyzed as predictors of discontinuation of fertility treatment. Specifically, based on previous evidence within the discontinuation and compliance literatures, predictors to include in the model were female age [15,18,19], education, and home-to-hospital distance [8], type of treatment [21,32], previous pregnancies (whether the patient had been pregnant at least once, as a positive beta HCG examination [19]) and type of diagnosis [16]. Finally, anxiety, depression, and infertility-specific psychosocial adjustment measures were also included. Discontinuation

is conceptualized here as the decision to discontinue fertility treatment before live birth is achieved for reasons other than medical advice or treatment costs [33].

Methods

Setting

The Portuguese public health-care system is tax financed and provides partial reimbursement for infertility medication (69% of total costs) and well as three ART cycles for married/cohabiting couples within a pre-established female age range (18-42 years for first-line treatments; 18-40 for second-line).

Ethical approval was obtained from the Portuguese Data Protection Authority and the Hospital Ethics Committee.

Sample and recruitment

Between February 2010 and March 2011 (T1), 411 individual patients (216 women, 195 men) attending the public fertility center at [removed for blind review] agreed to participate in the study (detailed information elsewhere [removed for blind review]). After signing the consent form, participants completed the study questionnaires. The exclusion criteria were as follows: a) a participant had not completed the questionnaires or left > 50% of the items of a given measure unanswered (n = 35); b) the couple had children together (n = 16); and c) a previously diagnosed sexually transmitted disease or unfavorable genetic diagnosis (n = 5). Criteria b) and c) were adopted to prevent bias considering previous evidence of an association with discontinuation [5,20]. Because a parental project starts with a decision shared by both members of the couple [25], we hypothesize that couples having previous children in common have a higher likelihood of discontinuing. Medical records were then analyzed retrospectively in December 2013 (T2) to collect information on the treatments, number of cycles, diagnosis and discontinuation. The final sample comprised 139 couples (278 patients). . Members of couples

were paired anonymously by asking each participant for their own and their partners' name initials and date of birth.

Measures

Sociodemographic variables, including patients' age, education level, residence, length of cohabitation and number of children, were obtained at baseline (T1) through a specifically designed questionnaire. Information about treatments, diagnosis and discontinuation was collected from medical records at T2.

The Fertility Problem Inventory [FPI; 34,Portuguese version; 35] has 46 items scored on a 6-point agreement scale and assesses perceived infertility-related stress across five different domains (social concern, sexual concern, relationship concern, need for parenthood and rejection of a child-free lifestyle). Good reliability was obtained in every subscale (α ranging from .72 to .84).

The Copenhagen Multi-center Psychosocial Infertility Coping Strategy Scales [COMPI-CSS; 29,Portuguese version; 30] assesses four infertility-specific coping strategies: active-avoidance; active-confronting; passive-avoidance; and meaning-based. The items are scored from 1 (not used) to 6 (used a great deal). Reliability for this sample was acceptable (α ranging between .51 and .80).

The State-Trait Anxiety Inventory Form Y [STAI-Y; 36,Portuguese version; 37] comprises 40 items scored from 1 to 4, with high scores indicating higher anxiety. Subscales showed good reliability (α between .91 and .93).

The Beck Depression Inventory-II [BDI-II; 38,Portuguese version; 39] has 21 items representing depressive symptoms. For each item, respondents choose one among four statements reflecting the intensity of that symptom, with higher scores indicating substantial depressive symptomatology. Cronbach's alpha was .93 for men and .90 for women.

Data analysis

Data were organized with each row including data from one couple, with the couple being the unit of analysis [40]. Couples were categorized as either compliers or discontinuers. Discontinuers were patients who missed one appointment at the fertility center and did not

return or ask for a new consultation before December 2013. Patients who reached the maximum age limit and/or completed the limit of three financed ART cycles were assumed to be compliers.

Home-to-hospital distance was dichotomized into long distance (farther than average) and short distance (average and closer than average). Because there is mixed evidence regarding the causation (which member was diagnosed with infertility) and its relationship with psychological adjustment [see 41], and discontinuation of treatment [21], two dummy variables were created to explore if female or male causation have different contributions to the decision of discontinuing treatments (presence of female causation vs others and presence of male causation vs. others).

Confirmatory factor and internal consistency analyses were performed for FPI and COMPI-CSS and the results confirmed the original structure (for details please see Online Resource 1). Depression was classified into a dichotomous variable by using Beck's [38] cutoff criteria of > 13 for clinical depression. Anxiety was also dichotomized to distinguish patients with higher levels of anxiety from patients with medium or lower levels of anxiety [42].

A hierarchical multiple logistic regression with discontinuation as a dependent variable was then performed. Variables of different nature, i.e., 1) demographic (age, education, home-to-hospital distance), 2) biomedical (type of treatment, infertility factor, previous pregnancies), 3) general psychological adjustment (anxiety, depression) and 4) infertility-related psychosocial variables (infertility-related stress and coping strategies), were entered into the regression in a four-step procedure following the guidelines of Cohen and colleagues [43]. *A priori* multivariate outliers were not found. All correlations between factors were below 0.6, suggesting lack of multicollinearity [44]. Analyses were performed in SPSS v.21.

Results

Descriptive analyses

Table 1 presents descriptive statistics for the psychological and infertility-related psychosocial variables. Couples were in their early thirties (men $M = 33.56$, $SD = 5.61$ and

women $M = 31.76$, $SD = 4.73$), had been living together for an average of 5.84 years ($SD = 3.30$), and resided approximately 50 kilometers ($M = 56.54$, $SD = 85.54$) from the fertility center. Most participants had completed 12 years (36.0%) or more (40.4%) of education.

On average, couples waited more than two years ($M = 27.88$ months, $SD = 24.78$) between the first attempt to conceive and the first fertility consultation. At T2, 16.5% of couples were not yet diagnosed. Of those with a diagnosis, 37.9% had male causation, 31% had female causation, 25.9% had mixed causation, and 5.2% had idiopathic infertility. Only 10% of couples had undergone previous ART treatments at baseline, and 56.8% engaged in ART between T1 and T2. At T2, the prevalence of discontinuation in this sample was 29.5%. Among compliers, 59.2% achieved clinical pregnancy (heartbeat confirmed by ultrasound at 6 weeks), 8.2% stopped treatment based on medical advice, 18.3% remained in treatment, and 14.3% reached the maximum limit of three cycles ($n = 11$) or 40/42 years of age ($n = 3$) set by Portuguese law.

Predictors of the discontinuation of fertility treatment

Table 2 presents the regression coefficients, odds ratio (OR) and 95% confidence intervals (CI) for discontinuation at T2 by demographic, biomedical, psychological adjustment, and adjustment to infertility variables at T1. The model containing all variables (step 4) was statistically significant ($X^2_{(22)} = 38.85$; $p = 0.015$), and it explained between 24.4% (Cox and Snell R^2) and 34.7% (Nagelkerke R^2) of the variance of discontinuation and correctly identified 75.5% of the cases. The Hosmer–Lemshow goodness-of-fit test was nonsignificant ($X^2 = 8.937$, $p = 0.348$), indicating model's good fit [45].

Female age and education level were the only demographic characteristics significantly associated with treatment discontinuation. This indicated that with each additional year of a woman's age, the risk of the couple discontinuing fertility treatment increased by a factor of 1.13 (95% CI 1.01-1.26). Moreover, every additional year of a woman's education decreased the likelihood of discontinuation [OR 0.40 (95% CI 0.22-0.72)]. The male partner' education and the home-to-hospital distance did not significantly predict discontinuation.

Whereas previous pregnancies were not associated with treatment discontinuation, the use of ART between T1 and T2 was a significant predictor. Couples who had had IVF, ICSI or

TESE were less likely to discontinue treatment [OR 0.32 (95% CI 0.11-0.94)] than those who had been prescribed medication or had undergone IUI only. Additionally, while male causation was not a significant predictor of discontinuation, female causation was a predictor of compliance, as it decreased the likelihood of discontinuation by a factor of 0.28 (95% CI 0.09-0.87).

Male depression and both male and female anxiety were not significantly associated with discontinuation. However, female depression was the strongest predictor in the model. Couples with clinically depressed (BDI > 13) female partners were 4.98 times more likely to discontinue treatment (95% CI 1.02-24.43) than couples with female partners who did not report clinically significant depressive symptomatology. None of the infertility-specific adjustment variables was significantly associated with discontinuation.

Discussion

This study aimed to identify risk factors for the discontinuation of fertility treatments by simultaneously controlling for a pool of demographic, biomedical, psychological and infertility-related psychosocial variables. A couples' perspective was adopted based on the assumption that the decision to discontinue treatment involves both members of the couple.

The discontinuation rate in this study was 29.5%. Other studies have reported similar rates, with percentages varying between 23% and 35% for reimbursed treatments when pregnancies and active censoring are excluded [3–5,10,20]. These results suggest that fertility centers could be wasting financial, logistic and human resources with about one-third of couples who arrive to the clinic but do not comply with treatment, particularly since treatment is free in some states or countries and medication is highly reimbursed.

Our findings showed that five variables significantly predicted couples' discontinuation of fertility treatment: female age, female education level, ART procedures, female causation for the fertility difficulties, and female depression.

The findings concerning demographic characteristics are consistent with previous research showing that older [15,18,19] and less educated women [15] were more likely to discontinue treatment. Because female age is one of the most important factors for treatment success [46,47], older women have a higher probability of receiving physician advise not to pursue treatment [9]. Although active censoring was not considered discontinuation in this study, couples with advanced female age may decide not to pursue fertility treatment after having been informed of the low chances of pregnancy associated with advanced female age. Consistent with others [15], female education was found to be a protective factor of treatment discontinuation, suggesting that women with a higher education are more informed about the importance of compliance with fertility treatments to increase the chance of pregnancy. Recent evidence suggests that even when males and females share a high education level, women seek more health information than men [48], which may explain why male education was not a significant predictor in our study. Although the residence-to-hospital distance has been associated with discontinuation in other health conditions [8] and although the high number of appointments required for fertility treatment can disrupt the daily routine [19,32], home-to-hospital distance did not predict discontinuation. However, in this study, couples lived an average distance of 50 km from the center and we choose to dichotomize the distance in the analysis; other studies might find effects for patients who do not live close to the fertility center and or using distance as continuous variable.

Regarding biomedical variables, the association between ART procedures and compliance was unexpected. Because IVF, ICSI and TESE are more intrusive procedures than IUI, we were expecting that patients undergoing more invasive treatments would be more likely to discontinue them. However, evidence suggests that couples receiving ART treatments are usually more involved and satisfied with medical care than other patients [23,49,50]. Given that positive experiences with fertility care are related to higher intentions to comply with treatment [51], the physical burden associated with treatments might not be as relevant as previous assumed. Medical staff may be more careful when talking to patients undergoing this type of treatment, making them feel more engaged with the process, and couples may have more hope

in the effectiveness of these procedures [52,53]. Interestingly, couples with female causation for the fertility difficulties were more likely to comply with treatment. Although the presence of male causation was not a significant predictor of treatment discontinuation, our results indicate that women's feelings of self-blame and difficulty in accepting biological childlessness motivate the continuation of treatments when the diagnosis of fertility difficulties results from the female partner [54]. Previous pregnancies did not predict discontinuation; however, this variable includes both couples with female partner with children and couples who achieved pregnancy but who did not achieved live birth, and this latter group may experience pregnancy loss in different ways. Some couples may feel frustrated by nearly achieving the final goal of having a child but ultimately failing and may fear repeating such a difficult experience. Alternatively, as we know that having previous pregnancies increases the likelihood of conception [19], couples may feel more motivated when they realize they are capable of achieving a pregnancy, and they may thus be willing to comply with further treatment. Further studies should access perceptions regarding pregnancy losses both before and during treatment to assess the influence on discontinuation.

Regarding psychosocial variables, female depression was the only and the strongest psychosocial predictor of treatment discontinuation in our model. Previous studies are not consistent. One of them has identified female depression as an important predictor of discontinuation [15]. Another found that female depression is not a predictor of discontinuation [24]. However, this latter study has a reduced number of discontinuers comparing with continuers, which can create a bias in the predicting power of the analysis. Although infertility is also burdensome for men [55–57], men tend to suppress their emotions about infertility more than women [58–60] and tend to assume the main role in supporting their wives during the infertility process [58]. Clinically depressed women, by definition, may not have the emotional strength to pursue treatment, and their partners may encourage them to forgo their infertility process-related burden, leading to discontinuation. Even if these women showed depressive symptomatology before the treatment, the near fivefold increase in the likelihood of discontinuation demonstrates the value of the psychological evaluation of women and

subsequent referral to a mental healthcare professional or fertility counsellor. Our findings suggest that reducing the female partner's depression symptomatology can reduce the likelihood of discontinuing treatment . In contrast, infertility-specific psychosocial variables (infertility stress and infertility coping) did not predict discontinuation. Although other predictors, such as female depression and age, may be more important, we must consider that infertility-specific distress can be generated with new treatments and failures, not necessarily at first appointments [61]. Because infertility distress was assessed at an initial stage of fertility care, couples could have reported corresponding low levels.

This study presents some limitations. First, all participants were observed at the same fertility center. Potentially stressful or buffering characteristics related to the fertility center or its functioning were thus not controlled for. Some of the couples who discontinued treatment in this public fertility center may have eventually decided to pursue treatment in private clinics for reasons we ignored. Second, couples in our sample who discontinued fertility care were at different stages of treatment, and each stage may be differentially linked to different predictors of discontinuation. Finally, although we controlled for active censoring by excluding couples whose discontinuation was medically advised, we did not control for the couples' exposure to passive censoring that might influence the effects of variables such as female age. Ways of measuring or controlling for passive censoring should be explored further to address the role of this variable in couples' motivation/distress and consequent compliance. Although the small sample size, the model's good fit and the verification of assumptions could assure the reliability of results. Further studies analyzing discontinuation in large samples and discriminating between fertility-treatment stages and types of treatment are needed. Given that couples who underwent ART procedures were less likely to discontinue treatment, emotional experiences with fertility care may be more relevant to discontinuation than the physical burden associated with ART procedures. Hence, further research should analyze medical staff-related variables (e.g., information provision, motivation, involvement) in groups of ART and non-ART patients and test the interaction between type of treatment and physician-related variables on couples' decision to discontinue treatment.

There are important strengths that should be highlighted. First, using the couple as the unit of analysis enables the research to account for the non-independence of the data and mutual influence of each member of couples [40]. Second, this study adds to our understanding of how fertility centers and medical staff can be more sensitive to aspects that can undermine fertility care continuity, suggesting that couples should be screened for psychopathology at the beginning of treatment [15,24]. Couples with an older or clinically depressed female partner should be specifically targeted for counselling concerning the importance of compliance within MAR treatments. Future investigation should also assess whether interventions aimed at reducing depressive symptomatology can decrease discontinuation rates. Recently [62] an intervention involving reappraisal coping and relaxation showed that patients starting IVF discontinued 3 times less than those with no intervention; however, this result was not statistically significant. Another study found efficacy of a mind-body study in decrease depression [63]. Techniques aiming to reduce depression (e.g., cognitive behavioral therapy), have demonstrated efficacy in reducing depression in both infertile patients [64] and other populations (e.g., cancer patients[65]); however, evidence based on discontinuation rates as an outcome is lacking. In addition to clinically depressed women, women with depressive symptomatology should be referred to a mental health professional to prevent not only discontinuation but also other consequences of psychosocial adjustment after ART, including lower self-esteem, low maternal self-efficacy [66] and postpartum depression [67]. Preventing discontinuation in fertility treatment may not only increase success rates [5–8] and improve the efficacy and cost effectiveness of MAR treatment but also decrease the eventual psychological effects of discontinuation after unsuccessful treatment [61].

This study furthers knowledge on risk and protective factors regarding the discontinuation of fertility treatment. Female depression and female age were identified as factors that predict couples' discontinuation of fertility treatment, whereas female education, female causation for the fertility difficulties, and ART procedures were identified as predictors of compliance. Reproductive health professionals should inform couples about these findings to increase awareness of the importance of compliance. In this way, adequate support during fertility

treatments might prevent the premature abandonment of fertility treatments and ultimately increase MAR success rates.

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Table 1. Descriptive statistics for psychological and infertility-specific psychosocial variables at T1   (*n* = 139 couples).

	Mean	*SD*	**Min-Max**
Anxiety (STAI)			
STAI (F)	82.17	21.25	40-138
STAI (M)	65.24	17.84	28-130
Depressive symptoms (BDI)			
BDI (F)	8.80	9.76	0-50
BDI (M)	4.6	5.98	0-38
Fertility problem stress (FPI)			
FPI (F)	105.50	24.52	59-185
FPI (M)	98.41	22.30	46-166
Coping strategies (COMPI-CSS)			
Active avoidance (F)	2.30	1.21	1-6
Active avoidance (M)	1.99	1.05	1-6
Active confronting (F)	3.61	1.22	1-6
Active confronting (M)	3.05	1.21	1-6
Passive avoidance (F)	3.72	1.31	1-6
Passive avoidance (M)	3.22	1.29	1-6
Meaning-based coping (F)	3.82	1.23	1-6
Meaning-based coping (M)	3.76	1.28	1-6

Note: SD (standard deviation); Min, minimum; Max, maximum.

Table 2. Hierarchical multiple logistic regression predicting discontinuation at T2 from demographic, biomedical, psychological and infertility-specific psychosocial variables (n=139).

Predictor	B	SE	Wald X^2	df	P-value	Odds ratio	95% C.I. Odds ratio
Step 1							
Female age	**0.12**	**0.06**	**4.46**	**1**	**0.035**	**1.13**	**1.01 – 1.26**
Education level (F)	**-0.92**	**0.30**	**9.45**	**1**	**0.002**	**0.40**	**0.22 – 0.72**
Education level (M)	0.49	0.28	3.05	1	0.081	1.64	0.94 – 2.85
Distance	-0.75	0.56	1.78	1	0.182	0.48	0.16 – 1.42
Step 2							
IVF/ICSI/TESE	-1.15	0.56	4.27	1	0.039	0.32	0.11 – 0.94
Previous pregnancy(ies)	-0.29	0.61	0.22	1	0.637	0.75	0.23 – 2.48
Female causation	**-1.26**	**0.57**	**4.86**	**1**	**0.027**	**0.28**	**0.09 – 0.87**
Male causation	-0.58	0.51	1.29	1	0.256	0.56	0.21 – 1.52
Step 3							
Anxiety (F)	-0.65	0.66	0.98	1	0.322	0.52	0.14 – 1.90
Anxiety (M)	-0.20	0.66	0.09	1	0.763	1.22	0.34 – 4.44
Depressive symptoms (F)	**1.61**	**0.81**	**9.92**	**1**	**0.048**	**4.98**	**1.02 – 24.43**
Depressive symptoms (M)	0.15	1.02	0.02	1	0.880	1.17	0.16 – 8.59
Step 4							
Fertility stress (F)	0.01	0.01	0.30	1	0.585	1.01	0.98 – 1.03
Fertility stress (M)	-0.01	0.01	0.38	1	0.534	0.99	0.97 – 1.02
Active avoidance (F)	-0.40	0.24	2.93	1	0.087	0.67	0.42 – 1.06
Active avoidance (M)	-0.05	0.27	0.03	1	0.860	0.95	0.57 – 1.60
Active confronting (F)	0.17	0.21	0.61	1	0.434	1.18	0.78 – 1.79
Active confronting (M)	0.09	0.23	0.15	1	0.695	1.10	0.70 – 1.72
Passive avoidance (F)	-0.27	0.21	1.54	1	0.215	0.77	0.51 – 1.17
Passive avoidance (M)	-0.19	0.23	0.05	1	0.830	0.95	0.61 – 1.49
Meaning-based coping (F)	0.32	0.20	0.95	1	0.330	0.83	0.56 – 1.21
Meaning-based coping (F)	-0.44	0.21	2.38	1	0.123	1.38	0.92 – 2.07

Note: F, female; M, male.