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Review Article

Cloninger's personality model in fibromyalgia syndrome: A systematic review and meta-analyses

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Abstract

Introduction: Fibromyalgia Syndrome (FMS) is a widespread chronic musculoskeletal pain disorder. Although many treatments are available for fibromyalgia, management remains a challenge. Recent evidence suggests that personality traits may influence fibromyalgia.

Materials and Methods: According to PRISMA guidelines, this systematic review and meta-analysis explored harm avoidance and self-directedness in fibromyalgia patients using Cloninger's personality model. The meta-analysis included 14 studies evaluating harm avoidance and 11 studies evaluating self-directedness in patients with fibromyalgia compared with healthy individuals. Reported data from primary studies were pooled in a random-effects model using the Hedges' g approach.

Results: Fibromyalgia patients demonstrated high harm avoidance (Hedges' g= 1.31; 95% CI: 0.97 to 1.65) and low self-directedness (Hedges' g= -0.71; 95% CI: -1.00 to -0.42) comparing to healthy individuals. Additionally, the results showed that high harm avoidance was significantly related to an increased risk of FMS, although high self-directedness played a protective role against it.

Conclusion: The results demonstrated that high harm avoidance and low self-directedness are distinct personality traits in patients with fibromyalgia. Early identification and evaluation of a profile of high harm avoidance and low self-directedness may help conceptualize the underlying complex mechanisms of fibromyalgia. Additionally, it could identify patients who are more prone to entering a vicious cycle of disability and pain. Further research is required to understand the role of personality characteristics better.

Keywords: Fibromyalgia, Personality, Temperament

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Introduction

Fibromyalgia Syndrome (FMS) is a widespread chronic pain condition throughout the body characterized by subjective complaints with no objective diagnostic criteria. However, the pathogenesis and diagnosis of FMS need to be better understood (1,2).

This condition is classified as central sensitization syndrome, whose cardinal manifestation is chronic, non-inflammatory, and diffuse musculoskeletal pain (3,4). The diagnosis of FMS is usually based on medical history and physical examination to rule out other biomedical causes (5-7). Due to its

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unknown etiology and unpredictable remitting/relapsing cycles, FMS is often called a "mysterious disease." Therefore, FMS diagnosis and management have become challenging for clinicians (8,9). The prevalence of FMS is estimated to be around 3-6%, of which more than 90% of patients are female (10,11). The onset of FMS typically occurs between 45 and 60 years of age (12). Widespread pain and a general reduction in the pain threshold may lead to diminished quality of life (13). In addition to personal discomfort, FMS may cause an economic downturn for the family and, owing to its costs is associated with a high burden on society (14-16). Many researchers have addressed neurochemical imbalances in the central nervous system of patients with FMS. These imbalances may manifest as generalized somatic pain and hypersensitivity with anatomically spread hyperalgesia (17,18). In addition to pain, this condition is associated with debilitating fatigue, sleep disruption, morning stiffness, paresthesia, and neurocognitive deficits (19,20). Several studies have listed numerous complex etiological routes into FMS, such as genetics, personality traits, sensitization, the hypothalamus-pituitary-adrenal axis, and stressors (21). Hence, FMS can result from an interaction between biological, psychological, and social factors (21-23). Extensive research on FMS psychological aspects has confirmed that personality traits and individual characteristics may act as differential variables to determine how pain is experienced. Thus, it has been speculated that psychological factors, such as personality traits, play an essential role in the development and maintenance of FMS and the severity of reported symptoms and complaints (24,25). For this reason, in the last decade, research has increasingly focused on the role of personality traits in FMS patients.

Personality traits are enduring styles of action, thought, and feeling that determine how individuals react to external stimuli and cope with stressful situations (26-28). Recent research suggests that pain may be ameliorated or exacerbated by personality traits, such as harm avoidance and neuroticism, which substantially affect how pain is experienced (25,29).

Furthermore, personality traits determine patient medication adherence and the utilization of medical services (30,31). Assessment of personality traits in FMS patients is important because of its contribution to a deeper understanding of patients and their management (32). Due to the challenges in measuring personality traits, the role of personality traits in FMS remains to be seen. Some of the reported results are contradictory, as some studies have claimed that certain personality traits might be more evident in FMS patients (33-36), whereas others have found no defined profiles (37-39). Findings are still inconsistent.

Cloninger's personality model assumes that the personality causal structure is based on the underlying biogenetic mechanisms and environmental influences (40). Cloninger's model consists of four temperament dimensions and three character dimensions. These dimensions are viewed as the result of continuous interactions over a person's lifetime (41). Temperament refers to the emotional core of personality and is based on genetics. However, character refers to the cognitive core of personality, which is influenced by experience and cultural learning (42,43). The four dimensions of temperament that are moderately heritable and stable throughout life include harm avoidance, reward dependence, novelty seeking, and persistence (42,44). Self-directedness, cooperativeness, and self-transcendence are character dimensions that reflect individual differences in goals, values, and self-conscious emotions (45).

According to Cloninger's model, some studies suggest that chronic pain conditions are characterized by higher harm avoidance and lower self-directedness (40,42,44-47). Naylor et al., in their critical review, used Cloninger's model and highlighted that individuals with different chronic pain types exhibit a profile of significantly higher harm avoidance and lower self-directedness compared to healthy subjects (44). A recent systematic review of personality traits in FMS patients also confirmed that harm avoidance and self-directedness were distinguishing traits among patients with fibromyalgia (46).

This paper solely focused on harm avoidance and self-directedness of Cloninger's model, and other features were not considered. Although several studies have reported high harm avoidance and low self-directedness in FMS patients (e.g., 47-51), no meta-analysis has been conducted to summarize these studies. Therefore, this paper examined the hypothesis of a high level of harm avoidance and a low level of self-directedness in FMS patients and overviewed the role of these personality traits in developing and maintaining fibromyalgia. To

accomplish this, two separate meta-analyses investigated harm avoidance and self-directedness in patients with FMS.

Materials and Methods

This article summarized and synthesized harm avoidance and self-directedness as personality traits in FMS patients by systematically searching publications in the electronic database for all articles published up to August 31, 2022. No time barriers were placed on the search. The following MeSH terms were used for electronic searches with Boolean operators: "Personality", "Temperament", "Character", "Personality Profiles", "Individual Differences", "Fibromyalgia," and "Fibrositis." The search terms were intentionally broad to maximize the identification of relevant papers based on background reading. Therefore, these terms were also searched: "Harm Avoidance", "Self-directedness", "The Temperament and Character Inventory", "Cloninger's Model", "Widespread Chronic Pain," and "Chronic Diffuse Pain".

The databases used were PubMed, EMBASE, PsychINFO, Social Sciences Citation Index (SSCI), Science Direct, and Scopus. Additionally, the references listed in the retrieved articles were manually reviewed to identify additional pertinent publications.

This review was carried out by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure.1) (52).

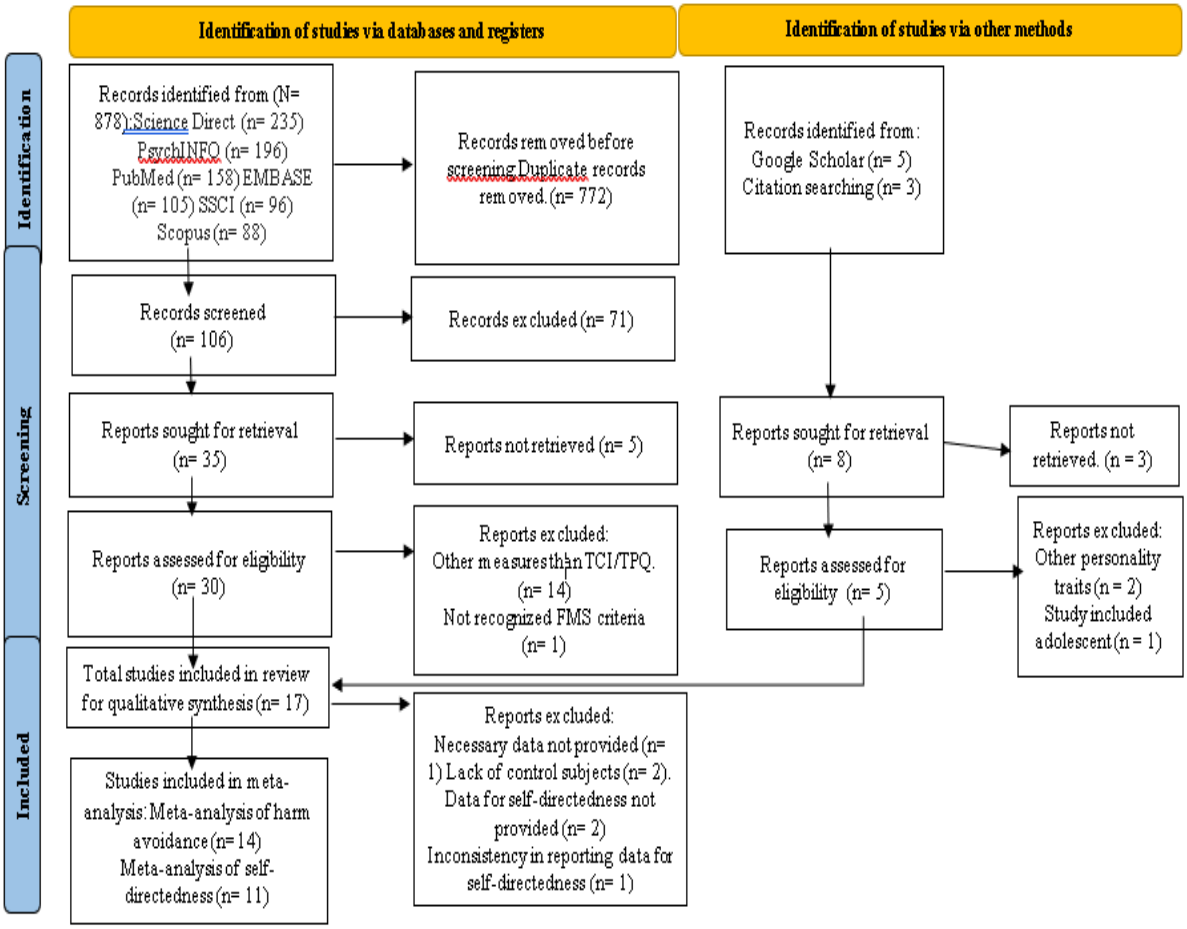

Figure 1. Flow chart of the report selection process (PRISMA-guided process)

In this review, the inclusion criteria were comprised of studies with adult patients, age range between 18 to 65, diagnosis of FMS, and using the Temperament and Character Inventory (TCI) or the Tridimensional Personality Questionnaire (TPQ) (53). The definite diagnostic criteria were in line with FMS diagnostic criteria established by the American College of Rheumatology (ACR) (54). Therefore, only studies with a clear definition of FMS and time criteria for diagnosis were selected. Two authors independently screened all potentially eligible studies to exclude irrelevant papers.

Consequently, full-text versions of relevant papers were retrieved and reviewed regarding the criteria.

Additionally, one study (48) was included after personal communication with the authors provided the standard deviation of harm avoidance and self-directedness for patients and healthy controls. Titles, abstracts, and full texts were excluded from the systematic review based on primary exclusion criteria. Secondary exclusion criteria determined the meta-analyses sample (Box 1).

Box 1. Primary and secondary study exclusion criteria

Primary study exclusion criteria — systematic review
- Other disease than fibromyalgia
- Included elderly adults (age≥ 65) or adolescents (≤ 18 years)
- Not used Cloninger's model of personality
- No raw data on TPQ/TCI dimensions (harm avoidance and self-directedness)
- Not reported basic sample information (number of participants, gender structure)
- No definite diagnostic fibromyalgia criteria
Secondary study exclusion criteria — meta-analysis
- No comparison between patients and healthy subjects
- Not reported standard error/standard deviation and variance
- Without reporting data separately for patients and healthy subjects

Each title and abstract were read and judged based on the inclusion/exclusion criteria at the initial screening stage. According to those criteria, at the final stage, authors independently evaluated full papers for further scrutiny of relevant studies. Any differences in verdict were followed by a discussion to reach a consensus. The remaining studies met the inclusion criteria. Figure 1 depicts the stages at which studies were identified and the number of studies excluded.

The required information was summarized and organized by an Excel and Mendeley software extraction table. Meta-analysis was conducted using the second version of the comprehensive meta-analysis (CMA.2) software package. Effect sizes (Hedges' g) were calculated and pooled with a random-effects model. The effect sizes in a pooled forest plot were calculated with 95% confidence intervals (95% CIs), and a $P< 0.05$ was considered significant. Heterogeneity across studies was evaluated by Cochran's Q test and I2 statistics index (55). Publication bias was investigated by funnel plot and Egger's test (56).

A total of 878 records were identified through electronic databases. One hundred and six articles were identified after duplicates were removed. After including other exclusion criteria, 30 articles were assessed for eligibility. Further to this, 15 articles were removed at the eligibility stage. Additionally, a manual search of the reference lists of the remaining studies was conducted to find further relevant studies. Two studies were found by hand search. Overall, 17 full-text articles were systematically reviewed in this study. Figure 1 summarizes the screening procedure based on PRISMA guidelines. Two features were analyzed in the meta-analysis stage: harm avoidance and self-directedness. For harm avoidance, 14 studies were found, two of which compared two distinct, non-overlapping groups of FMS patients with healthy controls (49,50). As a result, they were included separately in the meta-analysis; therefore, 16 groups were extracted for harm avoidance. For self-directedness, 11 studies met meta-analysis criteria. Similarly, two studies (49,50) that compared two groups of FMS patients with healthy controls were included separately in the meta-analysis; as a result, 13 groups were included in the meta-analysis for this feature.

Studies were conducted in 7 different countries: Spain (n=3), Italy (n=3), Sweden (n=2), Brazil (n=2), Turkey (n=2), Israel (n=1), and Korea (n=1). All the cases and controls were women, except in two studies (57,58),

including male participants (35 males enrolled). The meta-analysis included 1,029 FMS cases and 1,428 control subjects (total N= 2,457).

For each study, the effect size was computed from the data reported in the articles (e.g., means, standard deviations, sample size) using Hedges' g unbiased approach. Table 1 summarizes the findings and details of all primary studies.

Data extraction and coding of the primary articles included: 1- characteristics of the publication (e.g., authors, year of publication, country); 2- characteristics of the sample (e.g., total sample size, mean age, gender was coded as the frequency of women in a sample); 3- criteria used to diagnose fibromyalgia syndrome; 4- tools used to explore personality traits (Box 1).

According to Cloninger's personality model, human personality is formed by temperament (mainly genetically determined and relatively stable over a lifetime) and character (predominantly developmentally) (59,60).

The studies reviewed in this paper included the TCI (11 articles), TCI-Revised (TCI-R) (5 articles), and TPQ (1 article). The remainder of this subsection provides more details on these questionnaires.

The TPQ included only three higher-order personality dimensions of temperament: harm avoidance, novelty seeking, and reward dependence, as measured by the 100-item self-reported true/false questionnaire. Based on the TPQ, the TCI, a 240-item true/false questionnaire, was developed by Robert Cloninger to assess the seven factors of the psychobiological model of personality: four temperament dimensions (novelty seeking, harm avoidance, reward dependence, and persistence) and three character dimensions (self-directedness, cooperativeness, and self-transcendence). Subsequently, in 1999, Cloninger developed a revised version of the TCI (TCI-R), consisting of 240 items on a 5-point Likert scale ranging from 1 (definitely false) to 5 (definitely true) (53,61,62). The differences between TPQ and TCI are small, and high correlations have been reported between scores on the TPQ and TCI dimensions (63). Among the articles reviewed systematically in this study, 12 articles applied the ACR 1990 criteria, three articles used the 2010 ACR diagnostic criteria, and one study used the 2016 revision criteria. One study should have reported a specific version of the criteria. ACR criteria are introduced in this subsection. The 1990 ACR official diagnostic criteria for FMS required tenderness in at least 11 of 18 tender point sites on the body when a pressure of 4 kg/cm was applied for at least three months and the presence of extended widespread pain for diagnosis (64,65). To simplify the diagnostic process, the ACR 2010/2011 criteria abandoned the tender point count as a requirement for diagnosis. They emphasized patient symptoms, including non-painful and cognitive disorders (8,66). Based on the 2016 revision criteria: [1] Generalized pain (pain in four out of five regions) for at least three months, [2] Widespread Pain Index (WPI)≥ 7, Symptom Severity Scale (SSS) score≥ 5, or WPI of 4-6, and SSS score ≥ 9, [3] a diagnosis of fibromyalgia does not exclude other medical illnesses; fibromyalgia may be diagnosed in adults when all these criteria are met (54).

Two meta-analyses were performed separately to calculate the effect sizes of the TCI subscales (harm avoidance and self-directedness) between FMS patients and healthy subjects. Furthermore, negative Hedges' g was taken here to indicate healthy controls scored higher on a dimension. In contrast, positive Hedges' g indicated FMS patients scored higher. Figure 2 presents the effect size of harm avoidance dimension between patients and controls. As seen, there is a significant difference between patients and controls in harm avoidance (Hedge's g= 1.31; SE= 0.17; 95% CI= 0.97 to 1.64; *P*< 0.001, N= 2,457). Moreover, significant heterogeneity exists across effect sizes (Q= 163.75; *P*< 0.001). The I2 statistic is 91.75%, and the Tau Squared ($\tau 2$) is 0.42 (Table 1).

Table 1. Summary of included studies

Author	Year/ country	Sample size	Sample characteristics	Scale	FMS criteria	Findings	Mean scores and standard deviations	
							FMS patients	Healthy controls
Anderberg et al. (112)	1999 Sweden	76 (FMS patients and healthy control)	Mean age= 48.6 %100 female	TCI	ACR 1990 criteria	The FMS patients scored significantly higher than the HCs in HA, regardless of concomitant psychiatric disorder. High HA is suggested to be strongly associated to anxiety and depression.	HA: 19.9±6.2 SD: 31.8±7.1	HA: 14.70±5 SD: 33.8±5.8

Kim et al. (113)	2007 Korea	80 (FMS patients and healthy control)	Mean age= 39.7 %100 female	TCI	ACR 1990 criteria	FMS patients scored significantly higher in HA and SD scale than healthy control.	HA: 23.2±6.0 SD: 22.6±5.4	HA: 19.0±6.3 SD: 27.3±12.4
Verdejo-Garcı´a et al. (114)	2009 Spain	72 (FMS patients and healthy control)	Mean age= 45.8 %100 female	TCI-R	ACR 1990 criteria	FMS patients got significantly higher scores in HA scale than control group.	HA: 101.17±20.8 SD not measured.	HA: 88.86±18.42 SD not measured.
Lundburg et al. (115)	2009 Sweden	843 (FMS patients and healthy control)	Mean age= 41.2 %100 female	TCI	ACR 1990 criteria	FMS was associated with high HA and low SD.	HA: 21.4±6.8 SD: 26.2±7.3	HA: 14.7±6.1 SD: 32.6±6.1
Mazza et al. (57)	2009 Italy	140 (FMS patients and healthy control)	Mean age= 36.3 %59 female	TCI-R	ACR 1990 criteria	FMS patients were found to have higher HA and lower SD scores than healthy controls in the pretreatment and post treatment period with SSRIs.	HA: 109.5±18.8 Inconsistency in reporting data for SD.	HA: 102.6±18.7 Inconsistency in reporting data for SD
Glazer et al. (116)	2010 Israel	159 (FMS patients and their first-degree relatives without FMS)	Mean age= 45.1 %100 female	TPQ	ACR 1990 criteria	FMS patients and their relatives had higher scores on HA than relatives without FMS. Personality traits similarities between FMS patients their relatives, especially in HA.	HA: 17.4±6.8 SD not measured.	HA: 12.6±6.3 SD not measured.
Altunoren et al. (117)	2011 Turkey	102 (FMS patients and healthy control)	Mean age= 35.2 %100 female	TCI	ACR criteria	FMS patients had higher harm avoidance scores and lower self-directedness scores than healthy controls.	HA: 21.8±6.6 SD: 25. 1±7.1	HA: 17.4±4.8 SD: 30.1±5.7
Santos et al. (33)	2011 Brazil	69 (FMS patients)	Mean age= 46.3 %100 female	TCI	ACR 1990 criteria	FMS patients with current major depressive episode reported higher levels of HA and lower levels of SD compared with non-depressed patients.	MDE*absent (a) HA: 18.37±6.85 SD: 31.34±6.86 MDE*present (b) HA: 23.79±6.90 SD: 25.39±7.21	Lack of controls. Two groups of patients were compared.
Gencay-Can et al. (118)	2012 Turkey	90 (FMS patients and healthy control)	Mean age= 35.3 %100 female	TCI	ACR 1990 criteria	FMS patients had significantly higher HA scores and lower SD scores. High HA scores were associated with impaired functioning, depression, and anxiety symptoms.	Necessary data not provided.	
Garcia-Fontanals et al. (119)	2016 Spain	80 (FMS patients and healthy control)	Mean age= 47.1 %100 female	TCI-R	ACR 1990 criteria	FMS patients exhibited greater levels of HA and lower SD. Higher HA was associated with higher perceived pain intensity and emotional distress.	HA: 120.81±14.32 SD: 120.81±14.32	HA: 94.0±16.88 SD: 158.03±15.10
Ablin et al. (58)	2016 Israel	204 (FMS and Chronic Fatigue Syndrome patients)	Mean age= 41.7 %89/9 female	TCI-R (140 items)	ACR 2010 criteria	Cluster 1 associated with higher levels of HA and lower levels of SD and showed a poor adaptive pattern.	Cluster 1 HA: 73.76±9.69 SD: 57.59±9.09 Cluster 2 HA: 59.73±11.07 SD: 73.79±7.54	Lack of controls. Two groups of patients were compared.
Leombruni et al. (22)	2016 Italy	170 (FMS patients and healthy control)	Mean age= 52.04 %100 female	TCI	ACR 2010 criteria	FMS patients scored significantly different from healthy controls on the HA and SD. Cluster 1 patients had higher scores on HA and lower scores on SD and reported more serious symptoms and more severe anxious–depressive symptomatology.	HA: 21.87±6.39 SD: 28.25±6.36	HA: 14.87±5.70 SD: 33.52±6.16
Garcia-Fontanals et al. (49)	2017 Spain	80 (FMS patients and healthy control)	Mean age= 47.1 %100 female	TCI-R	ACR 1990 criteria	Patients with FMS showed higher HA than the control group. The presence of a CPS increased HA scores. FMS patients with CPS had low SD.	with CPS* (a) HA: 124.88± 15.73 SD: 139.62±14.92 without CPS* (b) HA: 113.93± 8.76 SD: 162.47±16.12	HA: 98.08±16.61 SD: 158.08±16.08
Santos et al. (51)	2017 Brazil	156 (FMS patients and healthy control)	Mean age= 46.4 %100 female	TCI	ACR 1990 criteria	FMS patients showed increased levels of HA and decreased levels of SD compared to a control group.	HA: 20.77±7.02 SD: 28.85±7.37	HA: 15.67±4.87 SD: 33.04±6.26
Balbaloglu et.al. (50)	2018 Turkey	154 (FMS patients and healthy control)	Mean age= 40.6 %100 female	TCI	ACR 1990 criteria	Both fibromyalgia groups had significantly higher scores in HA and lower scores in SD.	with paresthesia (a) HA: 26.39±2.56 SD: 16.51±3.16 without paresthesia (b) HA: 22.31±2.83 SD: 20.23±3.81	HA: 15.02±2.49 SD: 24.09±3.59
Dogru et al. (120)	2018 Turkey	155 (FMS patients and healthy control)	Mean age= 41.2 %100 female	TCI	ACR 2010 criteria	FMS patients scored significantly different from healthy controls on the HA. SD scores were not statistically significant.	HA: 20.48±6.81 SD: 26.05±7.66	HA: 16.63±5.81 SD: 25.20±6.86
Romeo et al. (48)	2022 Italy	108 (FMS patients and healthy control)	Mean age= 50. 7 %100 female	TCI	ACR 2016 criteria	FM patients showed higher alexithymia, higher harm avoidance and lower self-directedness compared with the HC.	HA: 115.9±13.4 SD: 127.9±24.5	HA: 90.8±15.9 SD: 140. 0±15.8

HA= Harm Avoidance; SD= Self-directedness; TCI= Temperament and Character Inventory; TPQ= Tridimensional Personality Questionnaire.
*CPS= Clinical Psychopathological Syndromes

These suggested that the observed heterogeneity was due to actual study differences rather than random error. This necessitates moderator analyses when heterogeneity tests or Q statistics are significant. However, the authors could not perform moderator analyses because of the limited information in the published studies. This was to determine whether current depression and anxiety symptoms impact FMS personality traits. Therefore, further studies are necessary to examine the impact of depressive and anxiety disorders on FMS personality profiles.

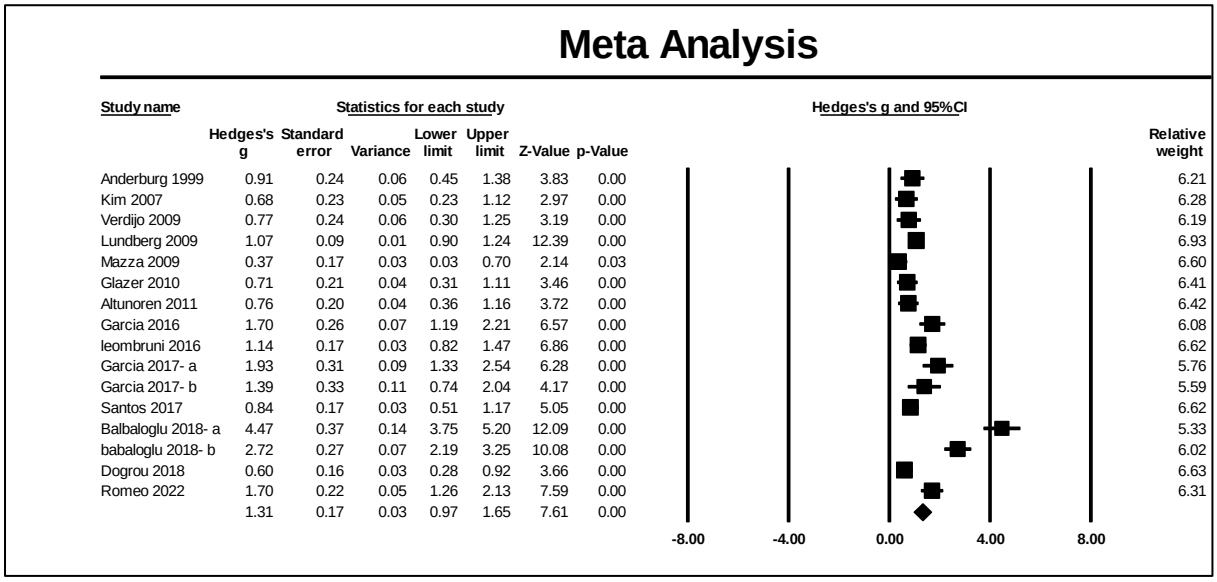

Figure 2. Random-effects meta-analysis forest plot for harm avoidance: Comparison between FMS patients and healthy controls. CI: Confidence Intervals.

A funnel plot (Figure 3) was produced using CMA to demonstrate the distribution of effect sizes by study weight. Because the funnel plot symmetry interpretation was subjective, the tandem method was used to test publication bias (67). First, a fail-safe N was calculated (z= 23.51, *P*< 0.000). Egger's regression, which yielded a non-significant bias intercept, was computed (β= 3.95, t= 1.84, *P*= 0.08). As a whole, these analyses yielded no evidence of substantial publication bias. When data were pooled in a meta-analysis, high harm avoidance was significantly related to an increased risk of FMS (odds ratio= 10.99, 95% CI= 5.93 to 20.38, z= 7.61, *P*< 0.000).

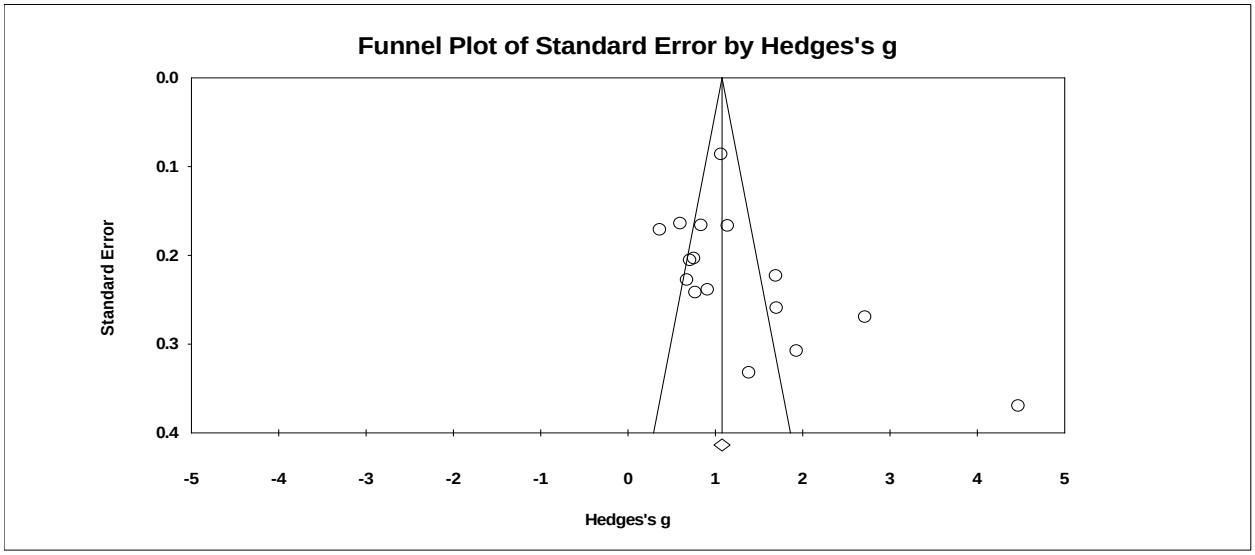

Figure 3. Funnel plot for harm avoidance meta-analysis. The circles represent included studies; the vertical line indicates the estimated mean effect size.

Figure 4 presents the effect size between patients and controls in the self-directedness dimension. There was a significant difference between patients and healthy individuals in self-directedness (Hedge's g= -0.71; SE= 0.25; 95% CI= -1.00 to -0.42; *P*< 0.001, N= 2,086). Moreover, significant heterogeneity exists across effect sizes (Q= 96.30; *P*< 0.001). The I2 statistic is 87.54%, and the Tau Squared (τ2) is 0.23 (Table 2). These suggested that the observed heterogeneity was due to actual differences among studies rather than random error. The researchers were required to perform moderator analyses when the heterogeneity test or Q statistics were significant. However, the authors could not perform moderator analyses because of the limited information in the published studies.

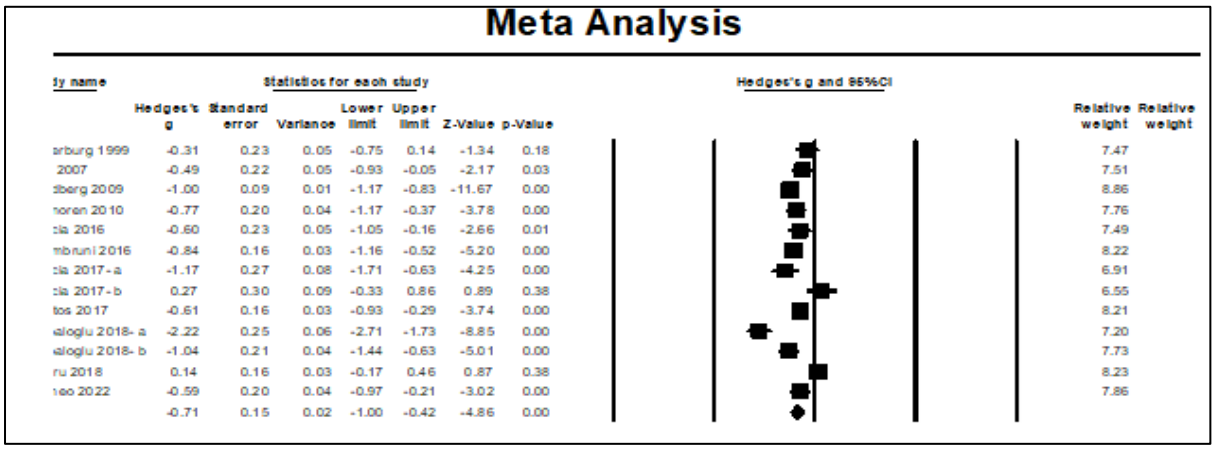

Figure 4. Random-effects meta-analysis forest plot for self-directedness: Comparison between FMS patients with fibromyalgia and healthy controls. CI: Confidence Intervals

A funnel plot (Figure 5) was produced using CMA to demonstrate the distribution of effect sizes by study weight. The tandem method was used to test publication bias since the funnel plot symmetry interpretation was subjective (67). First, a fail-safe N was calculated (z= -13.85, *P*< 0.001). Egger's regression, which yielded a non-significant bias intercept, was computed (β= 1.40, t= 0.62, *P*= 0.54). Combined, these analyses yielded no evidence of publication bias. In addition, the pooling of data produced an odds ratio of 0.27 (95% CI= 0.16 to 0.46, z= -4.87, *P*< 0.001) per unit decrease in self-directedness score on FMS risk. Studies showed that high self-directedness played a protective role against FMS.

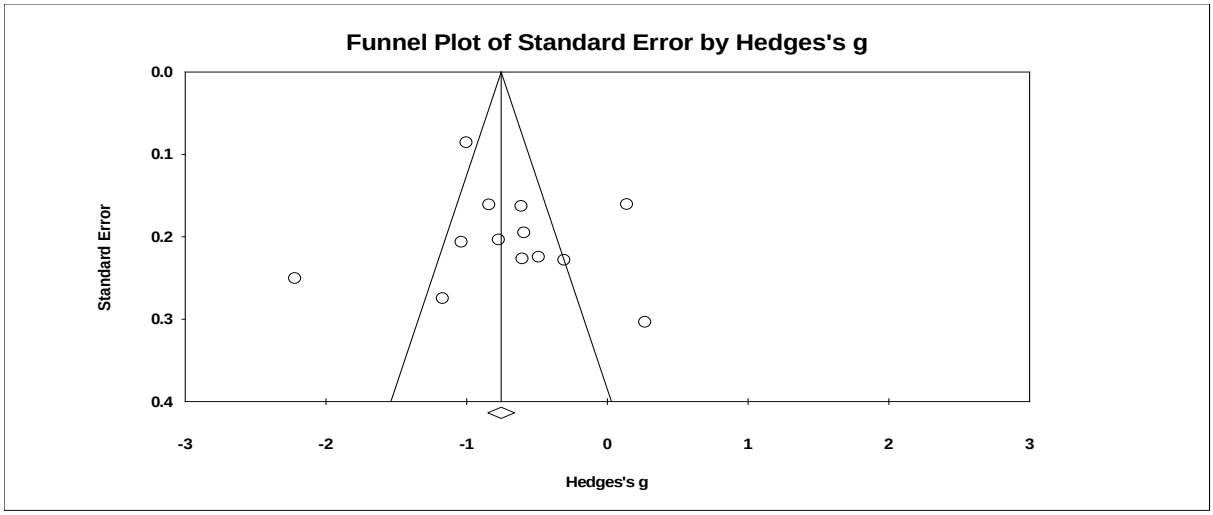

Figure 5. Funnel plot for self-directedness meta-analysis. The circles represent included studies; the vertical line indicates the estimated mean effect size.

Table 2 represents the magnitudes and directions of effect sizes for harm avoidance and self-directedness included in the meta-analysis.

Table 2. Summary of meta-analytic results of the following personality domains: Harm avoidance and Self-directedness

Domain	K	N	FMS	HS	Pooled effect size Hedge's g (P)	95 % CI		Homogeneity statistics			Egger's *t*-test for publication bias	Trim and fill
						LL	UL	Q (df)	P	I^2		
Harm avoidance	16	2457	1029	1428	1.31 (0.000)	0.97	1.65	163.75 (14)	0.000	91.75	1.49 (P= 0.16)	0
Self-directedness	13	2086	804	1282	-0.71 (0.000)	-1.00	-0.42	96.30 (12)	0.000	87.54	0.62 (P= 0.54)	0

K= number of studies; N= total number of participants; FMS= fibromyalgia patients; HS= healthy subjects; LL= lower limit; UL= Upper Limit; Q and I^2= indicate heterogeneity statistics; df= degrees of freedom.
Statistically significant values are reported in bold.

Discussion

This study provided a systematic review and meta-analysis of studies that examined two personality traits between FMS patients and healthy controls. The results suggested that FMS patients would likely display higher harm avoidance and lower self-directedness than healthy subjects. This finding is consistent with studies that reported patients with psychosomatic and other chronic pain disorders, such as temporomandibular disorder (47), tension-type headaches (68), migraines (69,70), and nonspecific musculoskeletal disorders (71). Consistent with the current results, previous review articles have indicated higher harm avoidance and lower self-directedness in chronic disorders, such as migraines (72), Parkinson's disease (73), burning mouth syndrome (74), and somatoform disorder (75). Harm avoidance is "a heritable tendency to inhibit or avoid responses to aversive cues" (76). There is some support for a link between harm avoidance and serotonergic activity, as well as the dopamine system (76,77).

People with high harm avoidance are perceived as being excessively worried, fearful, doubtful, easily fatigued, and sensitive to criticism and punishment. Hence, they require more reassurance and encouragement than others (44,47,59). Self-directedness refers to the degree to which something is meaningful and purposeful. Self-directed people trust their abilities and handle difficult situations efficiently (78).

Individuals with low self-directedness are often blaming, destructive, fragile, immature, irresponsible, and lacking an internal locus of control. They also tend to have low self-efficacy, preventing them from successfully showing problem-solving behavior in a given situation; hence, it is difficult to cope with stress (44,59). Self-directed people trust their abilities and handle difficult situations efficiently (78).

The fear-avoidance model and FMS personality profile

It is widely acknowledged that pain is a crucial component of classical conditioning and an influential element in initiating early defensive responses to avoid or minimize the impact of aversive stimuli (79-81). Strategies intended to reduce genuine bodily threats can paradoxically increase suffering and disability when the pain becomes chronic and persists. This might also lead to protective responses that share features with conditioned stimuli and generalize to novel situations (79,82).

A key component of harm avoidance is coping with potentially harmful life events such as ongoing pain (47). Individuals high in harm avoidance are susceptible to pain-related fear because they can easily acquire conditioned avoidant responses to aversive stimuli. As a result, they tend to respond strongly to previously established signals of noxious stimuli and learn to avoid punishment and novelty passively (44,60,83). Additionally, harm avoidance may predispose some patients to fear avoidance behavior, which would further worsen their disability and increase pain (60,84).

According to the fear-avoidance model, high-harm avoidance is crucial in anticipating pain, ruminating, and worrying. These negative appraisals may lead to pain-related fear and avoidance of events or activities, resulting in greater disability and depression. Subsequently, an endless loop of fear and avoidance is initiated by the interaction between fear-avoidance beliefs, behavioral performance, and disability. In addition, patients' inability to handle events efficiently and set meaningful

life goals increases their vulnerability to pain. For this reason, FMS sufferers scoring low in self-directedness may find it difficult to control and positively influence an aversive situation, stop ruminating, overcome obstacles, and engage in more active coping behaviors according to their objectives and values (22,44,59,60) (Figure 6). Consequently, being high in harm avoidance and low in self-directedness leaves patients vulnerable and unable to deal with stressful situations, such as fibromyalgia (22).

The impact of harm avoidance and self-directedness on pain perception

Pain perception is influenced by harm avoidance, which is associated with serotonin (85). The higher the harm avoidance score, the greater the perceived pain intensity (83). Evidence shows that higher harm avoidance scores are associated with increased pain ratings and reduced pain tolerance in healthy individuals (86). Studies have shown that serotonin is a key neuromodulator of pain transmission in descending nociceptive modulatory pathways associated with FMS (44). One major hypothesis regarding fibromyalgia is serotonergic dysfunction, supported by low serotonin levels (87,88). Moreover, evidence shows the efficacy of Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) in FMS management (89). A reduction in harm avoidance scores was found in studies of patients with depression and generalized anxiety disorders who were taking Tricyclic Antidepressants (TCA) or SSRIs (86). Furthermore, harm-avoidant personalities are predisposed to react intensely to signals of aversive stimuli, associated with decreased endogenous analgesia. Several brain imaging studies have demonstrated that activating specific brain structures during harm avoidance behavior also affects endogenous analgesia (90). Furthermore, one study found that participants with high harm avoidance reported enhanced pain perception, whereas those with high self-directedness reported less severe pain. According to this study, self-directedness was argued to be a protective factor against chronic pain. This means that patients with a higher internal locus of control, which involves a higher level of self-efficacy, are less likely to experience significant pain (91).

In summary, regarding pain stimulus intensity, harm avoidance may influence an individual's perception of pain intensity within which pain is perceived as threatening. However, self-directedness may play the opposite role: the higher the self-directedness score, the lower the perceived intensity of pain experienced by the patient. Thus, patients with a personality characterized by high harm avoidance and low self-directedness may find it difficult to deal with chronic pain (92). Although complex human experiences, such as pain, require a multidimensional perspective, further studies are necessary.

Mood and FMS personality profile

Regarding the high comorbidity of depressive and anxiety disorders with fibromyalgia (93,94), several studies have shown that low self-directedness and high harm avoidance are also associated with mood disorders (95,96). Additionally, there was an association between higher harm avoidance scores and an increased risk of suicidal ideation and attempts (97).

Anxiety is related to pain catastrophizing, fear of movement, and avoidant behavior (98). Depressive symptoms may promote pain sensation and functional disability (99) in patients with fibromyalgia. Furthermore, a vicious cycle may be established following the repeated occurrence of pain sensation, depression, and anxiety, which may prompt greater pain sensitivity (65).

An explanation for the association between personality traits and mood could be the gray matter volume of the medial PreFrontal Cortex (mPFC), which has been linked to anxiety and depression symptoms. Additionally, the higher the trait of harm avoidance, the lower the level of mPFC metabolic activity. In particular, the mPFC plays a crucial role in fear conditioning as patients with chronic pain perceive pain as a threat. Glutamate mediates conditioned fear responses, leading to maladaptive behaviors such as fatigue, mood disorders, and anxiety. Chronic pain is associated with reduced glutamate content in the mPFC.

This, in turn, is significantly correlated with harm avoidance symptoms, such as excessive fear and worry, pessimistic thinking, fatigue-proneness, and sensitivity to punishment and criticism (100). Sleep disturbances are the second pathway through which personality may be associated with mood disorders and fibromyalgia. Studies have shown that

participants with insomnia reported significantly greater harm avoidance and lower self-directedness than good sleepers. Sleep and circadian dysregulation appear to be related to harm avoidance and self-directedness, which are considered precursors to mood disorders (101). A patient's mood during testing notably affects personality traits measurement (60). Owing to the high prevalence of mood disorders in patients with FMS (93,98), measurement bias for personality traits may occur, necessitating the control of concomitant depression and anxiety disorders in future studies (60).

As noted by Conversano et al., because of the high prevalence of Axis I psychopathologies in FMS patients, the use of a comprehensive personality model and the control of depression and anxiety seems to be very relevant for a better understanding of the "FMS personality profile" (102). Further studies are needed to determine whether the control of mood disturbances affects personality domain assessment in patients with FMS.

Gender and FMS personality profile

Many studies have compared men and women based on Cloninger's temperament and character dimensions (103,104) that found significant effects of gender on personality dimensions (104). In their meta-analysis, Miettunen et al. (105) reported that women scored consistently higher in harm avoidance than men. Furthermore, personality studies have reported high harm avoidance in somatic disorders (106,107), which were shown to be more prevalent in females (reported at least 50% more than in men) and associated with a higher somatic symptom burden (108,109).

Although evidence indicates that fibromyalgia is more prevalent in women (almost 90%), Wolf et al. argued that there was a gender bias in diagnosing and evaluating FMS. Two large population studies have indicated that 60.8% and 60.5% of patients with fibromyalgia are women (110).

However, FMS occurrence in males has rarely been investigated, so there is still limited empirical evidence on the psychological characteristics of men with FMS (111). Notably, in this meta-analysis, almost 2% (20 patients) of FMS patients were men. Thus, the observed difference in effect sizes between FMS patients and healthy participants might not reflect male FMS patients' personality characteristics. Generalizing the current findings to male FMS patients warrants further research.

Although the present study provided an overview of the literature, several limitations should be mentioned. First, the personality assessments (TCI and TPQ) were self-reported. Second, the choice of scientific databases and the inclusion criteria could lead to excluding some important studies in this field.

Third, most of the studies included female participants, and thus gender differences were left partially uncontrolled.

Fourth, this paper focused on the harm avoidance and self-directedness of Cloninger's model and did not review other features; this is among the study limitations-finally, not all studies controlled for current depression and anxiety. Despite the limitations outlined, further controlled studies with larger samples are needed before a substantial conclusion is drawn.

Conclusion

This study provides a comprehensive overview of the current literature on the role of harm avoidance and self-directedness as personality dimensions in FMS. Assessment of personality also facilitates awareness of the patient's strengths, weaknesses, and goals, contributing to optimizing non-pharmacological therapies. Considering the findings, early identification and evaluation of a profile with higher harm avoidance and lower self-directedness may contribute to conceptualizing the underlying complex mechanisms of FMS and improving current treatments and management planning.

Timely personality assessments may identify patients more prone to developing psychiatric illnesses and help those more resistant to treatment and more vulnerable to entering the vicious cycle of pain and disability.

However, much more research is needed to define better the role of personality characteristics in FMS pathogenesis and symptoms. In addition, it is imperative to establish useful models for studying and treating fibromyalgia.

Finally, in the clinical evaluation of FMS patients, we should not only examine the pain and the number of tender points. It should also be combined with a careful personality assessment and diagnosing and treating comorbid psychological disorders.

Ethical considerations

The authors have no conflicts of interest to declare. All analyses were secondary, and the primary data were anonymized. For this type of study, formal consent is not required. The study was performed with the approval of the ethics committee of the Isfahan University of Medical Sciences (IR.MUI.REC.1395.1.149) and the Research Ethics Committees of the University of Isfahan (IR.UI.REC.1400.001).

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