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Open Access Original Article

Crescent Journal of Medical and Biological Sciences
Vol. 8, No. 1, January 2021, 35–41
eISSN 2148-9696

Design and Validation of a Diagnostic Tool for Distinguishing Temperament of Brain (Mizaj-e Demagh) in Iranian Traditional Medicine

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Abstract

Objectives: Mizaj (temperament) refers to a concept in Persian medicine and is the basis for defining health and disease. Brain, as the most important organ of the body (*Aza-e-raeiseh*), controls vital functions. So far, no standardized questionnaire has been designed for distinguishing temperament in Persian medicine. Therefore, the aim of this study was to provide a reliable objective self-report questionnaire and a standardized diagnostic checklist for Mizaj identification via determining their reliability and validity in Persian medicine.

Materials and Methods: This was an exploratory sequential study in which we designed a 121-item questionnaire, and a 20-item checklist as an item pool using Mizaj-related indices searched in Persian medicine references. The number of items for questionnaire and checklist finally reached 35 and 12 after qualitative and quantitative assessments (e.g., content and face validities). The test-retest reliability of each question of the questionnaire and checklist and their consistency were evaluated by participation based on the weighted and Fleiss' kappa statistics, and intraclass correlation coefficient (ICC). The final version of the questionnaire and checklist were divided into two subscales (i.e., warm/cold and wet/dry), and the minimum and maximum scores were determined.

Results: Significant findings of our data showed that the weighted and Fleiss' kappa coefficients of the 35-item questionnaire (between 0.4 and 0.9) and 12-item checklist (between 0.4 and 0.8) were found in the study based on their reliability. The degree of reliability in the self-report questionnaire was assessed using weighted kappa (WK), where 6 items of the questionnaire were omitted due to a WK less than 0.6 and the number of items reached 35. While 2 items of the checklist with Fleiss' kappa (FK) <0.2 were omitted and the number of items reached 12 items. WK coefficients of the 35-item questionnaire (between 0.4 and 0.9) and 12-item checklist (between 0.4 and 0.8) were found in the study, suggesting their reliability. The highest WK was found to be linked to sleep, and psychic and physical functions, suggesting the appropriateness of questions/items and design. The calculated ICC of the two stages for the warm/cold and wet/dry subscales of 35-item questionnaire was determined as 0.92 and 0.91, respectively, showing the stability of total score. ICC of the final score for the warm/cold subscale of the 35-item questionnaire was 0.88 (0.86 to 0.96), while this value was 0.91 for the wet/dry subscale (0.83 to 0.95).

Conclusions: The present questionnaire and checklist were validated in terms of the design, reliability, and validity of a standard Mizaj determination questionnaire and checklist. The final questionnaire and checklist may be capable of distinguishing Mizaj of brain at the clinical and research levels for Persian medicine practitioners.

Keywords: Persian medicine, Iranian traditional medicine, Mizaj, Brain, Temperament, Questionnaire

Introduction

Mizaj (temperament) is one of the most important and fundamental principles in the diagnosis and treatment of diseases, not only in Persian medicine, but also in traditional Chinese medicine, and other medical schools of ancient civilizations. Many medical schools have paid special attention to personal differences in health and illness, and have largely adjusted their health care prescriptions according to these personal differences (1).

Nowadays, modern medicine focuses on individual differences in pathogenesis, disease progression, and treatment response based on personalized medicine using nutrigenomics, metabonomics, pharmacogenomics, and so on. (2,3), which is more or less similar to the model adopted by Persian medicine in terms of concept of Mizaj. Mizaj is originally created by the reaction of various elements in the human body and the effect of their qualities on each other, leading to the influence of the physical and emotional characteristics, as well as physiological functions of the body. In this way, each person is classified according to his or her physical, functional, and psychological characteristics (1,4). In Persian medicine, different types of Mizaj are categorized into nine general groups based on a mixture of warmness, coldness, wetness, dryness, and temperance (5,6).

Therefore, reliable tools and measurement scales are needed to determine the Mizaj, both for research and clinical practice. The self-report questionnaires

Received 3 June 2020, **Accepted** 19 September 2020, **Available online** 8 November 2020

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or standardized diagnostic checklists can be used as diagnostic tools in the first step. Brain, as the most important organ of the body (*Aza-e-raeiseh*), controls vital functions. So far, no standardized questionnaire has been developed to distinguish the temperament of brain in Persian medicine. Thus, the aim of this study was to design a self-report questionnaire and a standardized diagnostic checklist for distinguishing Mizaj of brain and to evaluate their reliability and validity.

Materials and Methods

This study was a combination of two-stage exploratory sequential design. In order to know the phenomenon, the study was performed to produce items with a qualitative approach for obtaining qualitative data in the first stage and then the next stage (the quantitative stage) was implemented in accordance with the research goal for assessing the questionnaire.

Explaining the Concept by a Qualitative Methodology

Item Generation

In the theoretical phase, the main goal of this stage was defining an appropriate concept of Mizaj of brain to the participants (warm, cold, dry, and wet) in Persian medicine based on the Schwartz-Barcott and Kim's hybrid model. This hybrid model is based on the development of the concept through qualitative studies of the phenomenon in the same place where the phenomenon occurs. In this hybrid model, theoretical and experimental studies are combined to evolve the concept.

After selecting the researchers' favorite concept, in order to identify the dimensions and characteristics of Mizaj, reputable English-language search engines such as PubMed, Scopus, ScienceDirect, and Google Scholar, and Persian-language databases such as Magiran, Irandoc, IranMedex, and SID were searched for keywords such as Mizaj, brain, warm and wet, warm and dry, cold and wet, and cold and dry.

The criteria for distinguishing Mizaj were extracted from ten books on Persian medicine, including the perfect book of the Art of Medicine/The Royal Book (*Kamil al-Sinaa al Tibbiya al-Maliki*), Canon of Medicine (*Al-Qanun fi al-Tibb*), Great Elixir (*Exir Azam*), Liber al-Mansuri (*Al-Mansuri-fi-Teb*), Treasure of the Khwarazm Shah (*Zakhireye Khwarazmshahi*), *Tebb-e-Akbari*, *Tohfe*-ye-*Saadieh*, Sharh-e Gilani, Sharh-e Amoli, and Sharh-e Gharshi. Articles published by the researchers focused on Persian medicine in recent years were also extracted to enter the fieldwork phase.

In the fieldwork phase, empirical data from qualitative studies were used to reinforce and refine the elementary definition of the concept formed in the first phase. This phase also included three steps: setting stage, negotiating entry, and selecting participants. In the setting stage, after obtaining permission from the Ethics Committee of the university and receiving the letter of introduction, the necessary talks and coordination were held with the participants and officials of the place where we conducted the research.

In this study, the participants were selected by purposive sampling technique, which is a good method for qualitative research. Participants included 14 subjects referred to the Health Center of Persian Medicine, and experts with minimum 5 years of work experience (11 Persian medicine specialists). Efforts were made to ensure that participants were more diverse in terms of age, gender, specialization, marital status, background, and place of work and life. Furthermore, the demographic characteristics of the participants and the field under study were described in detail. The inclusion criteria were the personal satisfaction, the absence of advanced uncontrolled diseases, the lack of clear symptoms of distemperament, and not being medically known to have neurological or psychiatric disorders. In addition, those who were reluctant to participate, were excluded from the study.

Item Pool Generation

Interview questions were designed based on a review of the texts. Moreover, during the interview, the questions were reviewed based on the opinions of experts, and the necessary corrections were made. During interviews, the concepts and characteristics of warm, cold, wet, and dry temperaments were explained in an understandable way, using the common dialect of the society. At this stage, after obtaining the explicit consent, the face-to-face interviews were conducted in a relaxed and stress-free environment with the experts, as well as the participants. Each interview lasted 30 to 120 minutes in one or two sessions, and the main criteria were the tolerance, the amount of information, and the agreement of the participants. The interviews were recorded using pro voice recorder software. The researcher also ensured that the names of the participants remained confidential.

Examples of open-ended questions asked from Persian medicine specialists:

- What is the meaning of warm, cold, wet, and dry temperament?
- What are the symptoms of warm, cold, wet, and dry temperament?
- Explain how do you distinguish the warm, cold, wet, and dry temperaments?
- What symptoms are most important to you in distinguishing any Mizaj of brain?

Examples of interview questions asked from participants:

- What do you mean by warm, cold, wet, and dry temperament?
- Please explain your emotional state?
- Please explain about your sleep?
- Talk about your daily activities and how to do things?

Finally, meaning units were defined based on the concepts derived from the interviews, and then coding

and categorization was performed at this phase. The MAXQDA12 software was used for coding. Content analysis was used to analyze the data derived from the interviews.

In this study, several methods were used to design the bases of coldness/warmness or wetness/dryness and indices of distinguishing Mizaj, including:

- Determining the dimensions and scale of the tool based on the results of the qualitative stage
- Extrapolation
- Expert opinions

After this step, the initial version of the measurement tool was developed. Given the nature of the concept being assessed, the primary tool was designed in two formats: self-report questionnaire and specialist checklist. To prepare both templates, several items were designed for each of the signs mentioned in the texts and expressed in the interviews. For the self-report questionnaire, 121 items were designed. While the initial checklist consisted of 20 items.

Qualitative Face Validity

To establish a qualitative face validity, Persian medicine specialists and 94 subjects at different age groups (35-55 years old) were asked to comment on semantic understanding, irrelevancy, and clarity of the items provided in initially designed questionnaire, as well as the questions of the checklist. After establishing the necessary corrections based on the presented opinions, in the next step, to reduce and correct the items which were disproportionate and to determine the importance of each item, the quantitative method of the Clinical Impact Score was used. Therefore, a five-point Likert-type scale was considered for each of the indices:

- Completely important (score 5)
- Significant (score 4)
- Moderately important (score 3)
- Slightly important (score 2)
- It does not matter at all (score 1)

Then, 10 Persian medicine specialists and experts were asked to examine each of the indices (items) and to select an option. The researcher then calculated the scoring effect of each item separately based on the following formula:

Clinical Impact Score = Frequency (%) × Importance

Content Validity

Two indicators, namely, content validity ratio (CVR) and content validity index (CVI) were used to quantitatively evaluate the content validity. To this end, 26 Persian medicine specialists with more than five years experience collaborated in evaluating the validity of the questionnaire and checklist for each item and set-up of the CRV based on the following three-part spectrum: "necessary, useful but not necessary, and not necessary.

As a matter of course, quantitative methods were used to assess the content validity as a complementary method after obtaining qualitative feedback from experts and subsequent necessary corrections. In the first phase, the following formula was applied to calculate the value of CVR:

$$CVR = \frac{NE - N/2}{N/2}$$

Where, *NE* is the number of specialists, who had selected the "necessary", and *N* is the total number of specialists.

The questionnaire and checklist extracted from the above-mentioned phase was scored by experts based on the points 'completely relevant, relevant, relatively relevant, and not relevant' via email (7). The responses were summarized through Excel tables and the CVI was determined for each item. Accordingly, Item-level Content Validity Index (I-CVI) was calculated according to the following formula, proposed by Waltz and Bausell (8):

$$CVI = \frac{\text{The number of experts giving a rating of } relevant\ to\ each\ item\ *}{Total\ number\ of\ raters}$$

*rank three or four for each item

A cut-off point of 0.8 was considered for the total score (9). The following formula was first used to compute the probability of chance agreement:

$$P_c = \left[\frac{N!}{A!\,(N-A)!}\right] \times 0.5^N$$

Where N is the number of specialists, and A is the number of agreements on good relevance. Then, K^* was calculated using the proportion of agreements on relevance or I-CVI and the probability of a chance agreement:

$$K^* = \frac{I_{CVI} - P_c}{1 - P_c}$$

Reliability Assessment

The reliability of the questionnaire and that of checklist were measured by test-retest. In other words, the test questions were given to a single group twice under the same conditions, and the correlation coefficient between the two tests was measured. Therefore, this method was repeated for the self-report questionnaire by 40 participants with an interval of 10 days. Due to the interference of memory effect, fatigue and real changes, this coefficient changes. Therefore, the time interval between the two tests is very important. The best statistical test for determining reliability is the intraclass correlation coefficient (ICC > 0.8) (10). Weighted kappa (WK) statistics (WK > 0.4) was applied for each item.

Results

Item Generation

By reviewing 10 reference books and interviews, 7 criteria

for distinguishing Mizaj were extracted as follows:

Hair growth and advantages and disadvantages of hot and cold weather, foods and smells, sleep and wakefulness, human head model and its components, nasal drops, brain functions (emotional state and behavior [mood], physical activity, movements, psychic function, sensory-motor function, and sensory perception), and speech and voice of the individual.

Therefore, the main items and their subcategories and the symptoms related to each were classified. Overall, 7 main criteria, 23 categories, and 59 subcategories were extracted (Table 1). For each criterion which was described in the texts and interviews, one to three, and in one case, 9 basic items were designed as the item pool. Finally, the initial self-report questionnaire with 121 items and the primary checklist with 20 items were developed using questionnaires in the fields of psychology, psychiatry, lifestyle, and sleep, as well as books.

Primary Validity Assessment

At this stage, 13 items without adequate clarity and fluency were removed from the 121 items of initial questionnaire and 2 items were also removed from the checklist based on the opinions of specialists and other participants. Furthermore, some items were modified accordingly.

Table 1. The Relative and Absolute Frequencies of Participants in Terms of Demographic Characteristics

	Number	%
Sex		
Women	21	52.5
Men	19	47.5
Total	40	100
Marital status		
Married	32	80
Single	8	20
Total	40	100
Education		
Without high school diploma	2	5
Diploma and post-diploma	12	30
Bachelor's and Master's degrees	22	55
PhD and above	4	10
Total	40	100
Job		
Unemployed or housewife	4	10
Retired	1	2.52.5
Freelance	8	20
Employee	15	37.5
Physician or other medical professions	2	5
Student	5	12.5
Faculty or university lecturer	5	12.5
Total	40	100
Age (y)		
20 to 25	4	10
26 to 30	8	20
31 to 35	11	27.5
36 to 40	10	25
41 and more	7	17.5

A 108-item self-report questionnaire and an 18-item checklist were entered the next step.

Face Validity

The108-item questionnaire was given to 25 participants of both sexes with different levels of education (from less educated to PhD graduate). At this stage, 41 items, mostly either duplicate or ambiguous, or poorly identifiable ones were removed, and a 67-item questionnaire was provided to the same volunteers for the second time. This time, another 12 items were removed based on the opinions of most participants and a 55-item questionnaire was given to 66 participants for the third time, but all the 55 items remained unchanged this time. The self-report questionnaire, therefore, entered the content validity stage with 55 items. Regarding the checklist and its face validity, the 18-item checklist was given to 16 Persian medicine experts and they gave their opinions about the face validity of the checklist; at last the 18 items remained unchanged.

Content Validity Findings

The 55-item self-report questionnaire and the 18-item checklist were emailed to 40 Persian medicine experts and asked to comment on the grammar of the items, the use of appropriate words, and the clarity and fluency of the items. Twenty-six specialists responded to the emails, and after reviewing their opinions and correcting the necessary issues, the questionnaire was sent to 16 Persian medicine specialists for determining the CVR of each item. Finally, items with a minimum score of above 0.49 were recognized as valid according to the Lawshe table. At this stage, 5 and 3 items or questions were removed from the questionnaire and checklist, respectively, due to the lack of this minimum level and the two items were merged into one item (Table 2).

In this study, CVI determination was performed in two stages. In the first stage, the questionnaire and checklist were emailed to 10 Persian medicine specialists. After collecting their comments and reviewing the answers and making the necessary corrections, the questionnaire and checklist were again emailed to 15 Persian medicine specialists, and, the CVI was re-measured. Finally, 5 and 1 items with I-CVI of less than 0.7 were omitted from the questionnaire and checklist, respectively. A 44-item self-report questionnaire and 14-item checklist were finally prepared for the reliability phase (Tables 3 and 4).

Reliability Findings

Forty participants completed the self-report questionnaire twice (test and retest stages) with a 10-day interval and 28 of them were visited by three specialists in determining their temperament. The relative and absolute frequencies of participants in terms of demographic characteristics have been summarized in Table 1.

The degree of reliability in the self-report questionnaire was assessed using WK, where 6 items of the questionnaire

Table 2. Self-report Questionnaire Items at Different Stages

Stage	No. of Items	The Items Removed	The Remaining Items
Primary tool design	121	13	108
Face validity			
First stage	108	41	67
Second stage	67	12	55
Third stage	55	0	55
Content validity			
CVR	55	6	49
CVI	49	5	44
Final	44	9	35

Table 3. The Checklist Items at Different Stages

Stage	No. of Items	The Items Removed	The Remaining Items
Primary tool design	20	2	18
Face validity	18	0	18
Content validity			
CVR	18	3	15
CVI	15	1	14
Final	14	2	12

Table 4. ICC for the 35-Item Questionnaire

Questionnaire Subscales	ICC	95%CI	
		Lower Limit	Upper Limit
Cold/warm	0.926	0.860	0.961
Wet/dry	0.910	0.831	0.953

were omitted due to WK less than 0.6 and the number of items reached 35. While 2 items of checklist with Fleiss' kappa (FK) <0.2 were omitted and the number of items reached 12 items (10). The items of self-report questionnaire at different stages have been summarized in Tables 2 and 3. Regarding all indices of distinguishing Mizaj, the questions with the highest kappa were associated with sleep, and psychic and physical functions. It should be taken into consideration that a considerable portion of the items/questions in the questionnaire and checklist covered physical function.

The calculated ICC of the two stages for the warm/cold and wet/dry subscales of 35-item questionnaire is indicated in Table 4. The correlation of cold/warm subscale score in the questionnaire with that in the checklist and final diagnosis score were evaluated in the current study (Tables 5-8), where no significant correlation was found.

Scoring

First, the minimum and maximum scores of each tool were calculated based on the questions of each temperament. The score was then divided by 3 (three types of temperaments). This score was considered the between-class distance. The score for the 23-item cold/warm subscale in the questionnaire was determined to be 23 to 115, while this score was 12 to 36 for the 12-item wet/dry subscale. On the other hand, the score for the 10-item cold/warm subscale in the checklist was determined to be 10 to 50, while this score was 2 to 10 for the 2-item wet/dry subscale.

Table 5. Correlation of Cold/Warm Subscale Score in the Questionnaire With That of Checklist Per Expert

Expert	Correlation	95%CI	
		Lower Limit	Upper Limit
1	0.529	0.234	0.715
2	0.4910.491	0.116	0.744
3	0.582	0.185	0.818
Mean	0.620	0.303	0.792

Table 6. Correlation of Cold/Warm Subscale Score in the Questionnaire With a Final Diagnosis Score in Cold/Warm Subscale Per Expert

Expert	Correlation	95%CI	
		Lower Limit	Upper Limit
1	0.612	0.342	0.780
2	0.360	-0.108	0.699
3	0.521	0.195	0.784
Mean	0.576	0.231	0.798

Table 7. Correlation of Wet/Dry Subscale Score in the Questionnaire With That of Checklist Per Expert

Expert	Correlation	95%CI	
		Lower Limit	Upper Limit
1	-0.454	-0.735	-0.071
2	-0.024	0.407	0.405
3	-0.056	-0.469	0.373
Mean	-0.192	-0.575	-0.206

Table 8. Correlation of Wet/Dry Subscale Score in the Questionnaire With a Final Diagnosis Score in Wet//Dry Subscale Per Expert

Expert	Correlation	95%CI	
		Lower Limit	Upper Limit
1	-0.059	-0.452	0.361
2	-0.117	-0.490	0.291
3	0.058	-0.365	0.499
Mean	-0.117	-0.486	0.286

Discussion

This study was conducted to design and validate a standard tool for distinguishing Mizaj of brain based on a simple Mizaj (i.e., warm, cold, wet, and dry). In the present study, an attempt was made to design a reliable objective self-report questionnaire and a standardized diagnostic

checklist for distinguishing Mizaj. Reliability and validity of the designed items were evaluated by professional and trained experts in Persian medicine through the statistical and epidemiological methods. In recent studies, tools that have undergone reliability and validity assessment (12-15), are mostly in the field of general Mizaj. A number of these studies have been performed qualitatively. However, there are limited studies on the diagnostic tools used for different parts of the body or a specific disease in Persian medicine, where distinguishing Mizaj is not sufficiently validated.

In the current study, 10 comprehensible books of Persian medicine were first explored for indices of distinguishing Mizaj, then empirical data from qualitative studies were applied to reinforce and refine the elementary definition of the concept formed in the first phase. In the first step, we designed a 121-item questionnaire, and a 20-item checklist as the item pool. Afterward, a 108-item self-report questionnaire and an 18-item checklist were developed in primary validity assessment. In the face validity stage, a 55-item self-report questionnaire and an 18-item checklist were developed while a 44-item self-report questionnaire and a 14-item checklist were finally prepared for the reliability phase after the content validity assessment.

In the study of Mojahedi et al, a questionnaire with 52 items was initially provided based on Mizaj-associated indices, that was then reduced to 47 items via content validity analysis (1), whereas our items were higher than that in their study. Salmannezhad et al conducted a study to develop a Mizaj identification standard tool by providing a 119-item questionnaire in the first step, the extracted indices of which were reduced to 60 questions after the primary validation phase (15). Roshandel et al developed a questionnaire for distinguishing Mizaj with a relatively good level of reliability and validity, however content validity and reliability were not adequately addressed (12). We applied WK to determine the reliability of the self-report questionnaire and checklist, where the number of items for questionnaire and checklist reached 35 and 12, respectively. In this stage, the highest WK was found to be linked to sleep, and psychic and physical functions, suggesting the appropriateness of questions/items and design. These findings are more or less in agreement with those of Salmannezhad et al, who showed that sleep, and psychic and physical functions-related items exhibited acceptable kappa (15). The ICC of the two stages for the warm/cold and wet/dry subscales of 35-item questionnaire was calculated as 0.92 and 0.91 in the current study, respectively, indicating the stability of total score. ICC of the final score for the warm/cold subscale of the 35-item questionnaire was 0.88 (0.86 to 0.96), while this value was 0.91 for wet/dry subscale (0.83 to 0.95). Theas results corroborate those of Salmannezhad et al, where the ICC of the total scores of the two stages was reported 0.901 (0.841 to 0.938).

The 23-item cold/warm subscale score in the questionnaire was determined to be 23 to 115, while this was 12 to 36 for the 12-item wet/dry subscale. Furthermore, our findings revealed that the score for the 10-item cold/warm subscale in the checklist was between 10 to 50, while this was 2 to 10 for the 2-item wet/dry subscale (Table 9).

The large number of participants with considerable practitioner agreement about sentences of the questions led to the clarity of the sentences, which should be considered great strength. Additionally, an adequate number of participants in the temperate volunteers of the warm/cold and wet/dry subscales were evaluated in the present study for determining cut-off points. The equilibrium group was excluded by Mojahedi et al due to the small sample size, leading to a decreased validity (1), while the sensitivity and specificity of temperance cut-off points were determined as previously reported by Salmannezhad et al (15). In addition, Salmannezhad et al reported that Mizaj of brain is one of the main indices of general Mizaj (16).

Temperament or Mizaj-e demagh is used in many studies in the humanities, including psychology, management, and economics. Since there is no standard questionnaire on temperament, interdisciplinary studies in the above-mentioned fields have always been difficult. This questionnaire can be used as the first standard questionnaire to distinguish the type of temperament in interdisciplinary studies. Moreover, considering the brain as the most important organ of the human body, correctly

Table 9. Scores of Cold/Warm and Wet/Dry Subscales of Mizaj in Questionnaire and Checklist

	Scope Range	Class Distance	Diagnosis (Wetness/Coldness)	Diagnosis (Temperance)	Diagnosis (Dryness/Warmness)
Questionnaire					
Warm/cold	23 to 115 (23-115 =92)	31	23 to 54	55 to 85	86 to 115
Wet/dry	12 to 36 (36-12 = 24)	8	12 to 20	21 to 28	29 to 36
Checklist					
Cold/warm	10 to 50 (50-10 = 40)	13	10 to 23	24 to 37	38 to 50
Wet/dry	2 to 10 (10-2 = 8)	2	2 to 4	5 to 7	8 to 10

distinguishing the temperament can be a great help in maintaining human health.

It is recommended that additional research should be conducted in this area. The construct validity and criteria of the present questionnaire and checklist could also be further studied, as well as other studies on further numbers of questionnaires.

Limitations

Our study should be taken into consideration in the light of some limitations. First, a number of indices on distinguishing Mizaj were omitted form final questionnaire and checklist during the various stages of validation due to lack of appropriate efficiency (e.g., primary validity assessment, and content validity). Second, the indices were not divided into minor and major criteria; and third, criterion validity and construct validity were not performed in this study.

Conclusions

The present questionnaire and checklist were validated for the design, reliability, and validity of a standard Mizaj determination questionnaire. The final questionnaire and checklist could be capable of distinguishing Mizaj of brain at the clinical and research levels for Persian medicine practitioners. Further investigations based on such questions, samples, and multivariate statistics may provide additional clues about these tools, their repeatability, and their association with Mizaj status.

Conflict of Interests

Authors have no conflict of interests.

Ethical Issues

The Ethics Committee of Shahid Beheshti University of Medical Sciences approved the study under the code of IR.SBMURETECH.REC.1395.1023 and all participants provided informed written consent.

Financial Support

This study was financially supported by Shahid Beheshti University of Medical Sciences.

Acknowledgments

This article was derived from the Ph.D. thesis of Seyed Mahmood Fattahi Masoom conducted at Faculty of Iranian Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran (Project Number: 191). We like to express our gratitude to the School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran, for the financial support, as well as the participants and Persian Medicine experts who cooperated in this research.

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