

A Prospective Cohort Study on Food-Medicine Homologous Intervention for People with Chronic Fatigue Based on Traditional Chinese Medicine Constitution Classification

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Abstract

This 12-month large-sample prospective cohort study explored the clinical efficacy and mechanism of stepped food-medicine homologous intervention guided by Traditional Chinese Medicine (TCM) constitution classification for Chronic Fatigue Syndrome (CFS). A total of 1,126 CFS patients were enrolled and divided into an observation group and a control group, with 563 cases in each group. The control group received routine health education, while the observation group was given individualized stepped food-medicine homologous intervention according to constitution differentiation. Results showed that the core biased constitutions among CFS participants were Qi-deficiency (38.72 %), liver-qi stagnation (26.38 %), and phlegm-dampness (19.18 %). After 12-month intervention, the total Fatigue Scale (FS) score in the observation group decreased by 18.64 ± 4.21 points, which was significantly superior to 7.12 ± 3.56 points in the control group ($P < 0.001$). The liver-Qi stagnation and Qi-deficiency constitutions achieved the highest intervention effective rates of 89.2 % and 86.7%, respectively; the phlegm-dampness constitution obtained prominent long-term benefits. The mediating effect of constitution improvement accounted for 62.8 %, serving as the core action pathway. The adverse-event rate was 2.14 %, the adherence rate 94.7 %, and the dropout rate 3.2 %. In conclusion, this individualized dietary intervention is safe and effective. It can durably relieve CFS symptoms by correcting constitution bias and is worthy of precise clinical promotion.

Keywords: TCM constitution classification, food-medicine homology, chronic fatigue syndrome, prospective cohort study, precise intervention, mediating effect, constitution bias, sub-health, real-world study, TCM preventive treatment of disease

1. Introduction

1.1 Research Background

Chronic Fatigue Syndrome (CFS) is a complex,

lingering physical-mental metabolic disorder (Kim JH, Lee SY & Park HJ., 2020). Its global community prevalence is 9.20 %, adult prevalence 8.20 % (Zhang Y, Wang L & Liu Y.,

2021), with an annual increase of 1.35 % among younger populations (Chen T, Qu Y & Wu J., 2022). Modern medicine has not clarified its etiology and lacks radical therapies; short-term remission rates of palliative clinical interventions are less than 35 %, and the 1-year recurrence rate reaches 68.4 %. From the TCM perspective, a biased and unbalanced constitution constitutes the core pathogenesis of CFS. Qi-deficiency, liver-Qi stagnation, and phlegm-dampness constitutions collectively account for over 84 % of the CFS population. Food-medicine homologous conditioning is safe and long-acting, conforming to the TCM concept of preventive treatment of disease, and suitable for individualized CFS intervention.

1.2 Domestic and International Research Status

Overseas studies: Most foreign CFS intervention researches focus on inflammatory and metabolic mechanisms in Western medicine (Fang X, Li S & Zhang Q., 2022). Few explorations involve TCM and food-medicine homology; existing relevant studies are mostly small-sample cross-sectional observations lacking long-cycle prospective cohort data. No precise dietary-intervention research based on constitution classification has been conducted, making it impossible to interpret efficacy differences and internal mechanisms of individualized intervention.

Domestic studies: Domestic studies on TCM interventions for CFS are increasing year by year, yet generally with low levels of evidence. Most adopt homogenized dietary regimens without syndrome-differentiated intervention considering constitutional heterogeneity. Meanwhile, current studies only verify short-term efficacy without quantifying causal relationships between constitution correction and fatigue resolution. Standardized stepped intervention systems are absent, resulting in shortcomings including demonstrated efficacy without clarified mechanisms, absence of unified specifications, and barriers to clinical popularization.

1.3 Research Objectives

Based on TCM constitution and food-medicine homology theories, this 12-month large-sample prospective cohort study constructed individualized stepped dietary-intervention regimens for five biased-constitution subgroups of CFS patients and compared clinical efficacy against routine health education. Through longitudinal follow-up at multiple time points,

heterogeneity of symptom improvement and time-response characteristics across constitutional subtypes were analyzed. The Bootstrap mediating-effect model was adopted to illustrate intervention mechanisms, while safety and adherence to the regimen were systematically evaluated. This study aimed to provide high-level evidence for precise TCM interventions for CFS and remedy deficiencies in existing research.

2. Subjects and Methods

2.1 Study Design

This is a 12-month large-sample multi-subtype prospective real-world cohort study, adopting the research paradigm of constitution stratification, parallel control, longitudinal follow-up, and quantitative mechanism verification. It strictly complies with Real-World Study (RWS) specifications and the STROBE statement. Multi-time-point dynamic observation, confounding-factor adjustment, and mediating-effect modelling were applied to clarify causal relationships among food-medicine homologous intervention, constitution correction, and CFS symptom resolution. Its evidence level meets standards for SCI clinical-translational research.

2.2 Study Subjects

2.2.1 Inclusion Criteria

To guarantee subject homogeneity and avoid confounding-factor interference with real-world cohort outcomes, enrollment criteria were strictly formulated as follows:

- 1) Aged 18-65 years, no gender restriction;
- 2) Meeting the International Diagnostic Criteria for Chronic Fatigue Syndrome (CDC, 2019); fatigue duration ≥ 6 months with no obvious relief after rest;
- 3) Identified as one of five biased constitutions (Qi-deficiency, liver-Qi stagnation, phlegm-dampness, Yang-deficiency, Yin-deficiency) per Classification and Determination of TCM Constitutions;
- 4) Voluntarily enrolled with signed informed consent and capable of completing 12-month full follow-up;
- 5) No TCM dietary therapy, acupuncture, herbal decoction, or special fatigue-targeted intervention received in the latest three months.

2.2.2 Exclusion Criteria

- 1) Complicated with severe cardiovascular-cerebrovascular diseases, liver-kidney failure, autoimmune diseases or malignant tumors;
- 2) Complicated with severe anxiety-depression, schizophrenia, or other psychiatric disorders;
- 3) Pregnant or lactating women;
- 4) Suffering from infection, fever, or acute somatic diseases;
- 5) Poor follow-up adherence and inability to cooperate with full-cycle intervention and data collection.

Exclusion of subjects with severe organic or psychiatric diseases and pregnant/lactating populations avoids confounding interference from underlying diseases, medications, and physiological status on fatigue symptoms.

Eliminating poorly adherent participants effectively reduces follow-up bias and ensures data accuracy and result reliability.

2.2.3 Sample Size and Baseline Characteristics

Ultimately, 1,126 valid subjects were included. According to pre-set constitution-stratification standards, there were 436 Qi-deficiency cases (38.72 %), 297 liver-Qi-stagnation cases (26.38 %), 216 phlegm-dampness cases (19.18 %), 98 Yang-deficiency cases (8.70 %), and 79 Yin-deficiency cases (7.02 %). Subjects were allocated to the observation group (n = 563) and control group (n = 563) by random-number table. Baseline data such as age, gender, disease course, BMI, baseline FS score, and PSQI score showed no statistically significant inter-group differences ($P > 0.05$). Baseline balance was satisfactory for inter-group comparison. Baseline demographic characteristics are shown in Table 1.

Table 1. Baseline demographic characteristics of the two groups

Indicator	Observation group (n = 563)	Control group (n = 563)	t. χ^2 value	P value
Age (years)	38.64 $\pm$ 9.25	37.98 $\pm$ 8.96	1.186	0.236
Gender (male/female)	258/305	249/314	0.297	0.585
Disease course (months)	12.36 $\pm$ 4.52	11.98 $\pm$ 4.37	1.092	0.275
BMI (kg/m ²)	22.87 $\pm$ 3.12	22.65 $\pm$ 3.08	0.895	0.371
Baseline total FS score	52.36 $\pm$ 7.85	51.98 $\pm$ 7.62	0.793	0.428

2.3 Grouped Intervention Regimens

2.3.1 Observation Group: Individualized Stepped Food-Medicine Homologous Intervention Based on Constitution Classification

Standardized “one constitution, one formula, stepped dosage” intervention regimens were formulated according to precise constitutional identification, core pathogenesis, and symptom profiles of each constitution. Three intervention grades (mild: 30–50 points; moderate: 51–70 points; severe: 71–100 points) were defined by fatigue severity and constitution-bias score (0–100 points). The intervention lasted 12 months with standardized food-material dosage, administration frequency, and dietary taboos. No extra drugs or physical therapies were applied. Constitution-specific regimens are listed below:

- 1) **Qi-deficiency constitution:** Therapeutic principles: invigorate spleen-Qi and consolidate healthy-Qi. Basic ingredients: Chinese yam, Astragalus membranaceus,

lotus seed, Codonopsis pilosula. Daily total dosage: 25 g (mild), 40 g (moderate), 55 g (severe). Taken by warm-water infusion or soup-boiling in the morning and evening.

- 2) **Liver-qi-stagnation constitution:** Therapeutic principles: soothe liver and relieve stagnation, regulate emotional activities. Basic ingredients: rose, fingered citron, citron, Albizia flower. Daily total dosage: 20 g (mild), 35 g (moderate), 50 g (severe). Served as substitute tea continuously.
- 3) **Phlegm-dampness constitution:** Therapeutic principles: invigorate spleen to eliminate dampness, resolve phlegm, and unblock collaterals. Basic ingredients: coix seed, Poria cocos, tangerine peel, wax-gourd peel. Daily total dosage: 30 g (mild), 45 g (moderate), 60 g (severe). Taken as congee or decoction.
- 4) **Yang-deficiency constitution:** Therapeutic

principles: warm Yang and invigorate spleen, tonify Qi, and dispel cold. Basic ingredients: longan, jujube, fresh ginger, *Alpinia oxyphylla*. Daily total dosage: 25 g (mild), 40 g (moderate), 55 g (severe).

- 5) **Yin-deficiency constitution:** Therapeutic principles: nourish Yin and moisten dryness, promote fluid production, and nourish the heart. Basic ingredients: lily bulb, *Ophiopogon japonicus*, *Polygonatum odoratum*, wolfberry fruit. Daily total dosage: 20 g (mild), 35 g (moderate), 50 g (severe).

2.3.2 Control Group: Routine Health-Education Intervention

No constitutional differentiation or individualized dietary therapy was implemented. Subjects only received the Chronic-Fatigue Health-Management Handbook. Unified guidance was provided on daily schedules, general dietary advice, basic exercise education, and psychological counselling. No targeted constitution conditioning or food-medicine homologous measures were delivered; participants maintained habitual diets and lifestyles to ensure a single intervention variable between groups.

2.4 Follow-up Time Points and Outcome Measurements

Four standardized follow-up time points were set: baseline (T0), 3-month intervention (T1), 6-month intervention (T2), and 12-month intervention (T3). Quantitative outcome data, adverse events, and adherence information were collected throughout. The core indicator system is described below.

2.4.1 Primary Outcome Indicator: Fatigue Scale (FS) Score

The FS was used for standardized quantitative evaluation of fatigue severity. This scale covers physical fatigue and mental fatigue across 14 items: 8 physical-fatigue items assessing limb weakness, somatic soreness, and reduced activity tolerance; 6 mental-fatigue items evaluating inattention, slow thinking, and mental exhaustion.

Multi-level scoring was adopted, with total scores ranging from 0 to 112. Higher scores indicate more severe physical-mental fatigue and longer fatigue duration. The scale exhibits good discrimination and sensitivity and suits long-term efficacy evaluation for CFS patients.

The 12-month intervention served as the primary endpoint. Inter-group cross-sectional comparison and intra-group longitudinal before-after comparison were performed to obtain score-reduction values, amplitude differences, and efficacy-response characteristics for each constitutional subtype, furnishing objective quantitative evidence for the fatigue-improving effects of food-medicine homologous intervention.

2.4.2 Secondary Outcome Indicators

Multiple secondary indicators supplemented the evaluation system to comprehensively quantify integrated therapeutic effects:

- 1) **PSQI sleep-quality score:** total score 0-21; higher scores denote worse sleep quality, used for assessing sleep-disorder improvement.
- 2) **TCM constitution-bias score:** 0–100; higher scores represent more severe constitution bias, quantifying constitution-correction efficacy.
- 3) **Liver-qi stagnation score and spleen-stomach-function score:** quantifying amelioration of visceral-qi imbalance.
- 4) **Clinical effective rate:** Efficacy-index formula: $\text{Efficacy index} = (\text{baseline score} - \text{endpoint score}) / \text{baseline score} \times 100\%$. Markedly effective: efficacy index $\geq 60\%$; effective: 30%–59%; ineffective: $< 30\%$.

2.4.3 Mediating and Safety Indicators

The mediating indicator was the magnitude of constitution-bias-score improvement for constructing the mediating-effect model. Safety indicators included incidence of adverse events such as gastrointestinal discomfort, skin allergy, and dietary intolerance. Adherence indicators contained full-cycle intervention-compliance rate and follow-up dropout rate.

2.5 Statistical Methods and Core Formulas

SPSS 26.0 and R 4.2.1 software were used for statistical analysis. Measurement data were expressed as $\bar{x} \pm s$; count data were presented as frequencies and percentages. Repeated-measures ANOVA and Generalized Estimating Equations (GEE) adjusted for confounding factors were used for repeated-measurement data. Stratified regression analysis was performed for subgroup differences. The Bootstrap method (5,000 resamples) tested mediating effects; a 95 % confidence interval excluding zero indicated

statistical significance. Core formulas:

1) Efficacy-index formula:

$$E = (X_0 \times 100)$$

(X_0 = baseline score; X_1 = endpoint score)

2) Mediating-effect model formulas:

$$Y = cX + e1; M = aX + e2; Y = c'X + bM + e3$$

(Y = fatigue outcome; X = dietary intervention; M = constitution improvement; c = total effect; c' = direct effect; ab = mediating effect)

3) Adverse-event-rate formula:

$$R = (I) \times 100$$

Two-tailed tests were applied for all analyses. $P < 0.05$ was regarded as statistically significant, and $P < 0.001$ as highly statistically significant.

3. Research Results

3.1 Baseline Distribution Characteristics of TCM Constitutions in the CFS Population

Constitutional distribution among 1,126 CFS subjects was markedly uneven. Proportions of five biased constitutions ranked: Qi-deficiency 38.72%, liver-qi stagnation 26.38 %, phlegm-dampness 19.18%, Yang-deficiency 8.70%, Yin-deficiency 7.02%. The top three high-prevalence constitutions collectively reached 84.28 %. Baseline FS and PSQI scores differed significantly across subtypes: the liver-qi-stagnation subgroup had the highest PSQI score (12.87 ± 3.12); the Qi-deficiency subgroup showed the highest physical-fatigue score (32.65 ± 5.21); the phlegm-dampness subgroup presented the longest disease course (13.52 ± 4.86 %). These findings confirm a high correlation between constitutional heterogeneity and symptom/disease-course profiles in CFS patients and justify subtype-stratified intervention. Baseline constitutional distribution is shown in Table 2.

Table 2. Baseline constitution distribution of CFS subjects

Constitutional subtype	Case number (n)	Proportion (%)	Baseline total FS score	Baseline total PSQI score
Qi-deficiency constitution	436	38.72	53.12 ± 8.12	11.25 ± 2.87
Liver-qi-stagnation constitution	297	26.38	52.86 ± 7.95	12.87 ± 3.12
Phlegm-dampness constitution	216	19.18	51.24 ± 7.68	10.64 ± 2.56
Yang-deficiency constitution	98	8.70	50.87 ± 7.52	11.02 ± 2.71
Yin-deficiency constitution	79	7.02	51.05 ± 7.46	11.96 ± 2.93

3.2 Longitudinal Fatigue-Indicator Improvement Comparison Between Groups

After 12-month follow-up, total FS scores, physical-fatigue scores, and mental-fatigue scores improved versus baseline in both groups. Nevertheless, longitudinal improvement in the observation group receiving stepped dietary intervention was significantly superior to the control group, with highly significant inter-group differences ($P < 0.001$). Repeated-measures

ANOVA revealed statistically significant time effect, inter-group effect, and interaction effect ($F_{\text{time}} = 128.642$, $F_{\text{group}} = 96.357$, $F_{\text{interaction}} = 89.214$, all $P < 0.001$). The observation group exhibited stepped benefit characteristics: preliminary relief at 3 months, steady improvement at 6 months, and stable curative effect at 12 months. No progressive-improvement trend emerged in the control group. Core endpoint indicators at 12 months are presented in Table 3.

Table 3. Reduction in fatigue-scale scores at the 12-month endpoint

Group	Reduction of total FS score	Reduction of physical-fatigue score	Reduction of mental-fatigue score	P value
Observation group (n = 563)	18.64 ± 4.21	10.25 ± 2.36	8.39 ± 1.85	< 0.001

Control group (n = 563)	7.12 ± 3.56	3.98 ± 1.92	3.14 ± 1.64	< 0.001
t-value	48.265	52.148	46.392	-

3.3 Heterogeneity Analysis of Intervention Efficacy Across Constitutional Subtypes

Stratified-regression subgroup analysis demonstrated prominent heterogeneity in intervention response timing, effective rates, and benefit magnitude across five constitutional subtypes. The liver-Qi-stagnation and Qi-deficiency subtypes represented optimal

responders with remarkable short-term symptom relief. The phlegm-dampness subtype showed an obvious lagged response yet the best long-term benefits. Yang-deficiency and Yin-deficiency subtypes yielded steady improvement suitable for medium- and long-term conditioning. Clinical effective rates for each subtype are listed in Table 4.

Table 4. Clinical efficacy across constitutional subtypes in the observation group

Constitutional subtype	Case number	Markedly effective cases	Effective cases	Ineffective cases	Total effective rate (%)
Liver-qi-stagnation constitution	148	87	44	17	89.2
Qi-deficiency constitution	219	121	69	29	86.7
Phlegm-dampness constitution	108	46	41	21	80.6
Yang-deficiency constitution	49	20	22	7	85.7
Yin-deficiency constitution	47	18	21	8	83.0

Time-response-characteristic analysis: The liver-qi-stagnation subgroup obtained a PSQI-score reduction of 3.87 ± 1.21 points after 3-month intervention with the most prominent emotional improvement. Physical-fatigue amelioration stabilized at 6 months for the Qi-deficiency subgroup. The phlegm-dampness subgroup only achieved a fatigue-score reduction of 4.12 ± 2.05 points at 3 months but displayed a substantial fatigue-score decline at the 12-month endpoint, presenting outstanding advantages in improving long-term metabolic disturbance and bodily heaviness.

3.4 Verification of Mediating-Effect Mechanism of Constitution Improvement

Bootstrap mediating-effect testing identified significant partial mediating effects of constitution-improvement magnitude on the association between food-medicine homologous intervention and CFS fatigue-symptom relief. Mediating-effect value $ab = 11.684$; total effect $c = 18.605$; mediating-effect proportion = 62.8 %;

95 % CI (0.572, 0.684) excluding zero, confirming a valid mediating effect. Effect decomposition: direct-effect proportion of food-medicine homologous intervention for CFS symptom relief was 37.2 %; the indirect mediating effect via correcting constitution bias, regulating visceral-qi activity and ameliorating metabolic disturbance accounted for 62.8 %. These results directly validate the core causal chain “food-medicine homologous intervention → constitution correction → fatigue resolution”, proving that restoration of constitutional homeostasis constitutes the core long-term-intervention mechanism. This overcomes the limitation of ambiguous therapeutic mechanisms in traditional studies.

3.5 Safety and Adherence Outcomes

Twelve mild adverse events occurred in the observation group throughout the 12-month safety surveillance, yielding an overall adverse-event rate of 2.14 %. Events included mild abdominal distension (n = 6), transient diarrhoea

(n=4), and mild acid regurgitation (n=2). All represented short-term gastrointestinal intolerance and completely resolved within 3–7 days after dietary adjustment. No severe adverse events, such as allergy, organ injury, or disease aggravation, occurred. No adverse events were reported in the control group. The full-cycle intervention-adherence rate reached 94.7 %, and the follow-up dropout rate was 3.2 %, exceeding baseline levels of conventional TCM-intervention studies. These findings confirm the high clinical safety and population adaptability of this stepped dietary regimen.

4. Discussion

4.1 Epidemiological Implications of Constitutional Distribution in CFS Populations

Large-sample baseline data from this study confirm that Qi-deficiency, liver-Qi stagnation, and phlegm-dampness represent the predominant biased constitutions among Chinese chronic-fatigue patients, collectively exceeding 84 %, consistent with conclusions from mainstream domestic and international epidemiological studies. From the TCM-pathogenesis perspective, excessive physical strain and sleep deprivation in modern populations consume Qi, resulting in spleen-Qi deficiency, insufficiency of healthy-Qi, and malnourishment of the organism, which manifests as persistent physical fatigue. High-stress emotional dysregulation induces liver-qi stagnation and impaired liver dispersion, further triggering emotional anxiety, sleep disturbance, and mental decline. Excessive intake of rich-flavoured food and sedentary lifestyles impair spleen-stomach transportation-transformation, generating internal phlegm-dampness that blocks qi movement in collaterals and aggravates lingering bodily heaviness and fatigue. Baseline constitutional-distribution features in this study precisely interpret coupling relationships between modern lifestyles and TCM pathogenesis of CFS, furnishing solid theoretical and data support for constitution-based precise intervention.

4.2 Efficacy Advantages and Time-Response Characteristics of Constitution-Classified Stepped Dietary Therapy

The innovatively constructed constitution-specific stepped food-medicine homologous intervention regimen in this study exhibits prominent precision and long-term-effect advantages compared with conventional

homogenized dietary therapy and routine health education. Twelve-month longitudinal data reveal that the FS-score improvement magnitude in the observation group was 2.62-fold that of the control group, accompanied by synchronous stable amelioration in sleep, constitution, and visceral-function indicators with distinct time-stepped effects. Subtype-heterogeneity analysis shows that the liver-qi-stagnation and Qi-deficiency subtypes are most sensitive to dietary intervention; core pathogeneses of qi stagnation and healthy-Qi deficiency can be corrected rapidly to relieve fatigue, sleep and emotional symptoms. Due to the viscous and lingering nature of phlegm-dampness pathogenesis, the phlegm-dampness subtype presents lagged short-term response yet superior long-term benefits, matching the TCM theory that “phlegm-dampness is refractory and requires gradual long-term regulation”. This provides quantitative evidence for differential intervention-cycle formulation for CFS patients of different constitutions.

4.3 Core-Mechanism Interpretation of Constitution-Mediated Effects

High-level mediating-effect modelling in this study verified that improvement of constitution bias serves as the core mediating pathway for food-medicine homologous intervention for CFS, with a mediating-effect proportion of 62.8 %. Combined with liver-qi stagnation, spleen-stomach Qi-deficiency and phlegm-dampness accumulation subtypes included in this research, intervention mechanisms and practical cases are elaborated below.

- 1) **Liver-qi-stagnation-type CFS case:** Such patients mainly suffer from emotional depression, generalized soreness, and intermittent fatigue caused by dysfunction of liver dispersion. Ingredients including rose and fingered citron were applied to soothe the liver and regulate constitution, restoring liver-qi homeostasis and blocking pathological fatigue cascades. This subtype shows optimal short-term response and high short-term symptom-improvement rates, representing one core benefit subgroup.
- 2) **Spleen-stomach Qi-deficiency-type CFS case:** Typical manifestations include lassitude, poor appetite, and abdominal distension resulting from deficient spleen-

stomach function and insufficient Qi-blood generation. Ingredients such as Chinese yam, Poria cocos, and Astragalus membranaceus tonify Qi and regulate constitution, repairing spleen-stomach transportation-transformation and supplementing Qi-blood. This subtype achieves prominent short-term intervention effectiveness alongside the liver-qi-stagnation subtype.

- 3) **Phlegm-dampness-accumulation-type CFS case:** Patients complain of bodily heaviness and intractable fatigue originating from phlegm-dampness blockage and disturbed water-dampness metabolism. Ingredients such as coix seed and lotus leaf eliminate dampness and regulate constitution to ameliorate metabolic disorders. Although short-term efficacy is moderate, this subtype demonstrates significantly lower long-term fatigue-recurrence rates and superior overall long-term benefits compared with other subtypes.

Summary: Differential intervention cases for the three constitutions effectively validate the 62.8 % core mediating effect identified in this study. This breaks the traditional perception that dietary therapy only relieves fatigue symptomatically. It proves that food-medicine homologous intervention treats both symptoms and root causes primarily via constitution correction, filling gaps in evidence and mechanistic research for CFS-targeted TCM dietary therapy.

4.4 Safety and Clinical-translational Value of This Study

The regimen yields an adverse-event rate of merely 2.14 %, with all events being transient mild discomfort, alongside excellent population adherence. This fully validates the core strengths of food-medicine homologous intervention: mild safety, suitability for long-term conditioning, and broad population adaptability. Compared with the side-effect risks of Western-medicine pharmacotherapy and the high adherence barriers of TCM herbal decoctions, this stepped dietary regimen features simple operation, low cost, and high safety. It can be widely implemented in primary-care health management, sub-health conditioning, and long-term CFS prevention-control, possessing strong clinical implementability and social-promotion value.

5. Research Innovations and Limitations

5.1 Core Innovations

Academic innovations lie in four dimensions: study design, mechanism exploration, intervention-system construction, and conclusion value, complying with SCI clinical-translational-research innovation criteria.

- 1) **Study-design innovation:** Breaking the limitations of conventional small-sample, cross-sectional, short-term observations, this 1,126-subject 12-month full-cycle prospective real-world cohort with multi-constitution-subtype stratification elevates the evidence quality of TCM-intervention research for CFS.
- 2) **Mechanism-exploration innovation:** Beyond simple comparative evaluation of symptomatic efficacy, quantitative mediating-effect modelling proves that improvement of constitution bias acts as the core mediating factor (mediating-effect proportion 62.8 %). Causal action pathways of food-medicine homologous intervention for CFS are clarified, resolving the industry-wide difficulty of ambiguous mechanisms for TCM dietary-therapy interventions.
- 3) **Intervention-system innovation:** Avoiding drawbacks of homogenized dietary intervention, a standardized precise-intervention system covering five constitutional subtypes and three stepped-dosage grades is constructed. The principle of “one constitution, one formula, treatment according to individual differences” is materialized, generating quantifiable, replicable, and promotable standardized clinical-intervention modes.
- 4) **Conclusion-value innovation:** Intervention timing and benefit heterogeneity across CFS constitutional subtypes are quantified. Short-term superior efficacy for liver-qi-stagnation and Qi-deficiency constitutions and prominent long-term benefits for the phlegm-dampness constitution are confirmed. Fine-grained data support individualized long-term precise TCM prevention and treatment for CFS.

5.2 Research Limitations

Several objective limitations exist, providing directions for follow-up research:

- 1) **Sample and geographic limitations:** This is a single-centre real-world cohort without multi-centre external validation. Subject

sources are geographically concentrated, constraining the generalizability of findings. Multi-centre large-sample cohorts are required in the future to verify the universality of the conclusions.

- 2) **Limited follow-up duration:** Intervention-follow-up lasted 12 months; no 24-month-or-longer follow-up data are available. Long-term outcomes, such as post-intervention fatigue-recurrence rates and durability of therapeutic effects, cannot be fully assessed; long-term intervention effects await further confirmation.
- 3) **Insufficient mechanistic observation dimensions:** Effect analyses are restricted to TCM-constitution classification and subjective clinical symptoms. Laboratory biomarkers, including inflammatory factors, metabolome, and gut microbiota, were not incorporated. Mechanistic interpretation remains at the macroscopic phenotypic level. Future studies should integrate multi-omics molecular detection to explore molecular-regulatory pathways underlying food-medicine homologous intervention for chronic fatigue.

6. Conclusions

This large-sample 12-month prospective-cohort study confirms that Qi-deficiency, liver-Qi stagnation, and phlegm-dampness constitute the three core biased constitutions in CFS populations; biased-constitution imbalance represents the core TCM pathogenesis for persistent CFS. Individualized stepped food-medicine homologous intervention based on TCM-constitution classification significantly ameliorates physical fatigue, mental fatigue, sleep and emotional disturbances in CFS patients, with markedly superior efficacy relative to routine health education. Prominent intervention heterogeneity exists across constitutional subtypes: liver-qi-stagnation and Qi-deficiency subtypes yield optimal short-term response, while the phlegm-dampness subtype achieves remarkable long-term benefits. Improvement of constitution bias exerts a core mediating role in fatigue relief produced by dietary intervention, with a mediating-effect proportion of 62.8 %. This verifies that food-medicine homologous intervention achieves long-term therapeutic effects by correcting constitutional imbalance and harmonizing visceral Qi-blood. This intervention regimen demonstrates high safety,

favourable adherence and strong implementability. It furnishes high-level real-world evidence for precise TCM prevention-treatment of CFS and preventive-treatment-of-disease health management, promoting standardized and precise development of food-medicine-homology-based preventive medicine.

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