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Modified Jade Wind-Barrier Formula (MJWB) for Preventing Common Cold in Elderly with Qi-deficiency Constitution: A Controlled Trial

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Abstract

The modified Jade Wind-Barrier formula (MJWB) may prevent the common cold in the elderly with a Qi-deficiency Constitution. Previously, no controlled trial evidence existed to illuminate the concept of "preventive treatment of disease" as outlined in the constitution theory of Traditional Chinese Medicine. This theory distinctly suggests that enhancing the Qi-deficiency Constitution and modulating its functional state can prevent the occurrence of the common cold. This controlled trial (ClinicalTrials.gov identifier NCT05640570) targeted Hong Kong elderly with Qi-deficiency Constitution with at least one common cold incidence per year. The two co-primary outcomes are the total score of the Qi-deficiency Constitution clinical features and the incidence of the common cold. Throughout the 3-month prevention study, 98 out of 109 (89.9%) participants in the MJWB arm and 100 out of 109 (91.7%) participants in the

control arm finished the trial. MJWB significantly improved the clinical features of the Qi-deficiency Constitution compared to that in the control arm (mean difference -2.9, 95% CI -4.5 to -1.3, $p < 0.001$). It particularly improved the three clinical features: "Easily get tired" (mean difference -0.6, 95% CI -0.8 to -0.3, $p < 0.001$), "Shortness of breath" (mean difference -0.2, 95% CI -0.4 to -0.1, $p = 0.012$), and "Lack of energy" (mean difference -0.3, 95% CI -0.5 to -0.0, $p = 0.021$). MJWB also significantly improved IgG ($p < 0.001$) compared with the baseline of prevention among the MJWB arm. However, the common cold incidence (odd ratio 0.9, 95% CI 0.5 to 1.6, $p = 0.756$), the number of persistent days (mean difference 0.1, 95% CI -1.4 to 1.5, $p = 0.929$), and the total Traditional Chinese Medicine syndrome score (mean difference -7.1, 95% CI -21.6 to 7.4, $p = 0.336$) showed no difference between the two arms. MJWB can significantly improve the Qi-deficiency Constitution clinical features and the IgG level, suggesting that MJWB may be helpful for participants regarding the related clinical symptoms and their potential consequences. There is no statistically significant difference in the common cold incidence, the duration of its persistence, or the common cold symptom scores when comparing the MJWB users and the non-users. A large-scale trial is worth further investigating the preventive effect of MJWB for the common cold and whether the Qi-deficiency Constitution clinical features and the IgG level improvements can help prevent the common cold in the elderly.

Keywords
Prevention; modified jade wind-barrier; qi-deficiency constitution; common cold; controlled trial

1. Introduction

Qi-deficiency Constitution is an integrated and relatively stable non-pathological state of the elderly regarding their morphological structure, physiological function, and psychological condition. The Qi-deficiency Constitution is that the elderly tend to have loose muscles, shortness of breath, lower voice frequency, excessive sweating, lassitude, easy to get tired and catch colds [1-3]. Qi-deficiency Constitution determines the susceptibility to the common cold [1, 2].

The "Nine Body Constitutions" cross-sectional study showed that 24.2% (1303/5382) of the elderly have a Qi-deficiency Constitution [4]. Item 14, "Did you easily catch the common cold?", a composed question in assessing the Qi-deficiency Constitution, revealed the susceptibility to the common cold among Hong Kong (HK) elderly with the Qi-deficiency Constitution. 1303 elderly with Qi-deficiency Constitution were prone to frequent incidences of the common cold annually: 168 had not more than 2 colds per year, 471 had 2 to 4 colds per year, 432 had 5 to 6 colds per year, 168 had 8 colds or above per year, and 64 had the common cold incidences almost every month per year [4].

Effectively targeting the Qi-deficiency Constitution may reduce the incidence of the common cold and enhance survival rates, underscoring the significance of prevention [5]. These results empowered the administration of prophylactic modified Jade Wind-Barrier formula (MJWB) on the common cold.

MJWB was formulated based on the classic formula named Jade Wind-Barrier Powder, or Yu Ping Feng San, originating in "Jiu Yuan Fang" [6]. MJWB targets HK elderly aged 65 or above with Qi-deficiency Constitution who encounter at least one common cold incidence annually. Most of the research studies targeted children or the adult population [7, 8]. However, no clinical trial has been conducted to test the "preventive effects" of targeting the common cold in the elderly with the Qi-deficiency Constitution. We hypothesize that MJWB may prevent the common cold in the elderly with a Qi-deficiency Constitution [9-11]. The controlled trial was essentially designed to compare the preventive effectiveness of MJWB intake versus no intake. The null hypothesis (H_0) was tested, which stated there was no difference between the two arms concerning their ability to improve the Qi-deficiency Constitution clinical features and reduce the common cold incidence.

2. Materials and Methods

2.1 Trial Design

This controlled clinical trial tests whether MJWB has a preventive effect on the common cold incidence among the elderly with a Qi-deficiency Constitution. The eligible participants were identified based on the inclusion and exclusion criteria. In brief, from our participants' database of the Qi-deficiency Constitution, participants who had the Qi-deficiency Constitution and sent back their signed electronic informed consent forms (ICFs) were invited to participate in the study. Blood tests were done based on the set protocol to confirm the eligible participants in the MJWB arm. Blood tests had not been done for the participants in the control arm.

The eligible participants in the MJWB arm who met the inclusion and exclusion criteria received MJWB for 3 months. Participants in the control arm who screened eligible started the trial without MJWB during the 3-month trial.

The trial was registered on ClinicalTrials.gov (ClinicalTrials.gov ID: NCT05640570). Compared with the planned methods, the trial was changed from a "pragmatic randomized controlled trial" to a "controlled trial." Also, due to the Coronavirus disease (COVID-19) pandemic in HK, the sample size was significantly reduced from the planned size.

Participants were insured (Policy Number: LFS1300135/21), effected from 30 November 2021 to 29 November 2022. The reporting of this study referred to the CONSORT Extension for Chinese Herbal Medicine Formulas 2017: Recommendations, Explanation, and Elaboration [12].

The trial was approved by the Research Ethics Committee (REC) of Hong Kong Baptist University (HKBU) (REC Reference Number: REC/21-22/0009) on 25 October 2021. The signed electronic ICFs were returned from the 303 participants from 06 December 2021 to 11 January 2022. The 152nd participant in the control arm was accepted to sign and sent back the ICF on 03 March 2022 by the cutoff date (i.e., 24 March 2022, the latest date to start the trial).

2.2 Participants

The pre-surveyed elderly with Qi-deficiency constitutions were screened based on the inclusion and exclusion criteria (Table S1). From 26 October 2021 to 20 January 2022, the research team screened the eligible participants through telephone assessment.

2.3 Interventions

MJWB, a combination of 5 raw herbs packed into a sachet, which consisted of Astragali Radix (Zhi Huangqi) (the principal medicine) 4 g, Saposhnikoviae Radix (Fangfeng) 2 g, Atractylodes macrocephala Koidz (Baizhu) 2 g, and included Nelumbinis Folium (Heye) 1 g, Chrysanthemum morifolium Ramat (Juhua) 1 g. It was prepared by Zheng Cao Tang Medicine Hong Kong Company Limited (Business Registration Certificate Number: 33422859-000-03-21-9). Quality control (quantitative and qualitative testing methods) of each ingredient was carried out based on the Pharmacopoeia of The People's Republic of China (2020 Edition).

MJWB was modified based on the classic formula, considering the individual or population differences, seasonal changes, and regional variations [6, 13]. The Nelumbinis Folium (Heye) and Chrysanthemum morifolium Ramat (Juhua) were added by the regional characteristics of HK (located in Southern China) [14].

Voucher specimens were retained and are accessible in the Digital Dry Cabinet, supplied by Che Scientific Co. (Hong Kong) Ltd., which is in AAB 105B, Hong Kong Chinese Medicine Clinical Study Centre (CMCS) of HKBU. Voucher specimens (wholly preserved 5 raw herbs used during the trial) served as an object reference documenting the identity of the herbs used in scientific publications from MJWB, from which researchers may obtain the specimen for examination in further study [15, 16].

Participants in the MJWB arm received 28 sachets of MJWB (10 g each sachet) monthly, along with the intake instruction sheets through S.F. Express, a total of 84 sachets for three months. They were instructed to take MJWB as prevention, not as treatment. The research team instructed them to follow the intake method: 1. brew one sachet in the morning and afternoon, 2. immerse and steep one MJWB sachet into 250 ml boiling water (90-100°C), 3. cover the container for 5 minutes, and then drink the prepared MJWB decoction twice daily, an hour after meal at room temperature, two hours apart from any Western Medicine. During data monitoring, the research team recorded any alterations to the MJWB intake routine made by participants in the Patient Diary- the Common Cold Incidence Record (ICCR-P).

Participants in the control arm were not given MJWB during the 3-month trial. However, from 22 July 2022 to 31 August 2022, they were given 84 sachets of MJWB (the same 3-month quantities as the MJWB arm) after finishing the observation. No data was collected for the control arm participants after the prevention trial, notwithstanding that they received MJWB.

During the trial period, participants in both arms were instructed to take prescriptions as usual if they caught a common cold or other disease(s) and take preventive measures as they normally did. The research team recorded common cold preventive measures other than the Chinese Herbal Medicine (CHM) taken in the last 4 weeks since the last phone assessment in the Research Team-the Common Cold Incidence Record (ICCR-RT). The research team responded to any inquiries regarding the intake of MJWB from participants in both arms during the trial period.

Using Research Electronic Data Capture (REDCap) software, the research team screened and assessed participants using the electronic Case Report Form (CRF), which included aspects like the Clinical Features of Qi-deficiency Constitution Questionnaire (CFQCQ). Participants recorded their common cold incidence and corresponding symptoms in the MyCap Mobile App daily using the Patient Diary, which included the ICCR-P questionnaire. Self-assessments were also accepted. During the data monitoring, each common cold episode had to be confirmed by the research team.

2.4 Outcomes

2.4.1 Co-Primary Outcomes

1. The CFQCQ total score was evaluated before and after prevention. The CFQCQ comprises 6 clinical features (CFs): "Easily get tired," "Shortness of breath," "Sweat easily," "Weak voice," "Not willing to talk," and "Lack of energy." All the CFs are calculated based on the four-point Likert scale scoring algorithm.

The scoring for "Easily get tired" and "Shortness of breath": "No = 0, Mild = 3, Moderate = 6, Severe = 9".

The scoring for "Sweat easily," "Weak voice," and "Not willing to talk" are "No = 0, Mild = 2, Moderate = 4, Severe = 6". The scoring for "Lack of energy": "No = 0, Mild = 1, Moderate = 2, Severe = 3".

The total score of the CFQCQ is the sum scores of the 6 CFs, with scores ranging from 0 (if no CFs) to 39 (if all the 6 CFs were severe) [17].

2. The common cold incidence was assessed throughout the 3-month prevention trial. The common cold incidence was evaluated in the ICCR-P if there was any common cold. The common cold's incidence (i.e., prevalence) was defined as the proportion of participants who had at least one encounter with a healthcare professional (self-reported encounters were also accepted in this trial) for a common cold during the 3-month trial period. It is calculated as the total number of participants with at least one incidence in 3 months [from 26 February 2022 (the earliest start date for the intake of MJWB) to 15 June 2022 (the latest completion date for the intake of MJWB)] divided by the total number of participants over the 3 months [18].

2.4.2 Secondary Outcomes

3. The persistence days of the common cold were assessed throughout the 84-day prevention period in the ICCR-P if there was any common cold.

4. The total symptoms score of the common cold was assessed throughout the 84-day prevention period using the Traditional Chinese Medicine Syndrome Scoring Method Questionnaire (TCMSSMQ) to determine if there was any common cold. The TCMSSMQ comprises nine symptoms: "Afraid of cold," "Sore limbs," "Lack of qi and not willing to talk," "Fever," "Stuffy nose," "Runny nose," "Dizziness," "Sweating," and "Cough." All the symptoms are calculated based on the four-point Likert scale scoring algorithm.

The scoring for "Afraid of cold," "Sore limbs," and "Lack of qi and not willing to talk" are "No = 0, Mild = 3, Moderate = 6, Severe = 9".

The scoring for "Fever," "Stuffy nose," "Runny nose," "Dizziness," "Sweating," and "Cough" is "No = 0, Mild = 1, Moderate = 2, Severe = 3".

One more choice, "Others, please specify," was added to the TCMSSMQ, thus enabling participants to fill in their symptoms of the common cold other than the nine symptoms. There is no scoring for this choice.

The total score of the TCMSSMQ is the sum of the nine symptoms, with scores ranging from 0 (if no incident symptoms) to 3780 (45 per day if all incident nine symptoms were severe, with the maximum total score of 3780 for 84 days) [19].

5. The serum IgG, IgM, and IgA were evaluated using an Enzyme-linked Immunosorbent Assay (ELISA), following the manufacturer's recommendations [20]. After allocation, the MJWB arm participants were appointed and directed to their selected Diagnostic Medical Centre LTD. laboratory centers for blood withdrawal. The laboratory centers followed the research team's Clinical Serum Sample Collection Procedure. The research team monitored the participants' diary's progress, specifically the Modified Jade Wind-Barrier Formula Intake Diary (MJWBD) and ICCR-P. The research team confirmed that participants had the intake of MJWB and assisted them in completing any missing records through phone calls, ensuring the preventive effectiveness reflected in the immunological function analysis was correlated with the intake of MJWB.

2.4.3 Other Outcomes

6. Adverse effects: Any Adverse Events and Serious Adverse Events (AEs and SAEs) were recorded. Liver and Renal Function Safety Assessment was assessed before and after prevention [21]. Blood samples were collected from the MJWB arm to evaluate the MJWB herbal safety.

2.5 Sample Size

This trial represents the initial controlled study initiated following the 'Nine Body Constitutions' cross-sectional investigation. To support the principle of "preventive treatment of disease" in Traditional Chinese Medicine's (TCM) constitution theory, we determined a sample size of 1000 participants based on our database of Qi-deficiency Constitution participants [22]. Compared with the planned methods (500 participants per arm), due to the COVID-19 pandemic in HK, the sample size was significantly reduced from the planned size. Eventually, 218 participants (i.e., 109 participants per arm) were enrolled.

2.6 Allocation

This trial targeted the elderly population with the Qi-deficiency Constitution. Participants allocated to the MJWB group were required to have normal liver and renal function. All screenings were not finished prior to the allocation: 1) initial recruitment was done before the allocation to enroll the qualified Qi-deficiency Constitution participants; 2) blood tests were then done after the allocation to confirm the eligible participants.

Specifically, in this trial, participants were chosen from the database of Qi-deficiency Constitution subjects. The elderly participants with a Qi-deficiency Constitution who sent back their signed electronic ICFs were invited to participate in the study. The participants with normal liver and renal functions were arranged to take MJWB.

2.7 Blinding (Adjudication by the Blinded Biostatistician)

In this trial, the biostatistician was blinded to the arms but not the participants and trialists. In the standard open-label approach, participants were aware of the prevention received (the 5 raw herbs could be seen through the transparent package of MJWB, dispensed in a way like routine clinical practice, with the name and dispense date on the intake instruction sheet).

However, MJWB was not freely available, which mostly removed the risk that participants allocated to the control arm could take the exact formula themselves. During the trial, the research

team was aware of the assignments but was forbidden to reveal the composition of the formula to the control arm participants.

Also, adjudication by the blinded biostatistician in the statistical analysis of outcome-based endpoints minimized the potential subjective bias.

2.8 Statistical Methods

The statistical analysis was conducted using IBM SPSS 28 for Windows [23]. Baseline demographic characteristics were presented as the mean with standard deviation (SD) for continuous variables (normally distributed data), or as the median with interquartile range [IQR] ([Q1 and Q3]) for non-normally distributed data, and as frequency and percentage (%) for categorical variables.

For the co-primary and secondary outcomes, an intention-to-treat (ITT) analysis and/or a complete case analysis were reported [24]. The statistical significance was defined as a two-sided p-value < 0.05.

Particularly, the ITT analysis (using the best-worst and worst-best sensitivity analyses) together with the complete case analysis was conducted to compare the between-group difference for the co-primary outcome (the CFQCQ total score) [24], using the analysis of covariance (ANCOVA) adjusting for baseline.

The complete case analysis was conducted to compare the between-group difference for the co-primary outcome (the common cold incidence) using the Pearson chi-square (χ^2) test.

The complete case analysis was conducted to compare the between-group differences for the secondary outcomes (the persistent days and the TCMSSMQ total score of the common cold) using the independent sample t-test and the sensitivity analysis using the Mann-Whitney U test.

The within-group difference for the secondary outcome (serum IgG, IgM, and IgA) in the MJWB arm was analyzed with the Wilcoxon signed rank test [25, 26]; the linear association of each biomarker (between before and after prevention) was analyzed by using the Spearman's rank correlation coefficient.

3. Results

3.1 Participant Flow

The invitation to participate in the trial was sent via WhatsApp Business to the senior citizens with the Qi-deficiency Constitution in our database. This trial enrolled 304 participants who remained Qi-deficiency Constitution. In the MJWB arm, 109 participants were screened as eligible to receive MJWB. In the control arm, 109 participants were screened as eligible to start the trial. This excluded 86 participants: 37 could not be reached, 1 withdrew from the screening, 46 did not meet the inclusion and exclusion criteria, and 2 withdrew after being deemed eligible.

During the trial, 10 participants in the MJWB arm discontinued the intervention by 24 March 2022 (i.e., the cutoff start date), 8 did not start taking any MJWB, and 2 withdrew without any MJWB. Moreover, during the first month, 1 withdrew due to an adverse event. Thus, 98 out of 109 (89.9%) participants in the MJWB arm completed the study. In the control arm, 9 participants either lost to follow-up or discontinued the trial: 1 could not be reached after the completion of the baseline CFQCQ assessment, and 8 completed the baseline CFQCQ assessment but withdrew during the first

month of CRF collection, 100 out of 109 (91.7%) completed the study. The drop-out rates between the MJWB arm (10.1%, 11/109) and the control arm (7.3%, 8/109) were comparable. None (0/109) of the MJWB arm participants and 0.9% (1/109) of the control arm participants were lost to follow-up of the co-primary outcomes (Figure 1).

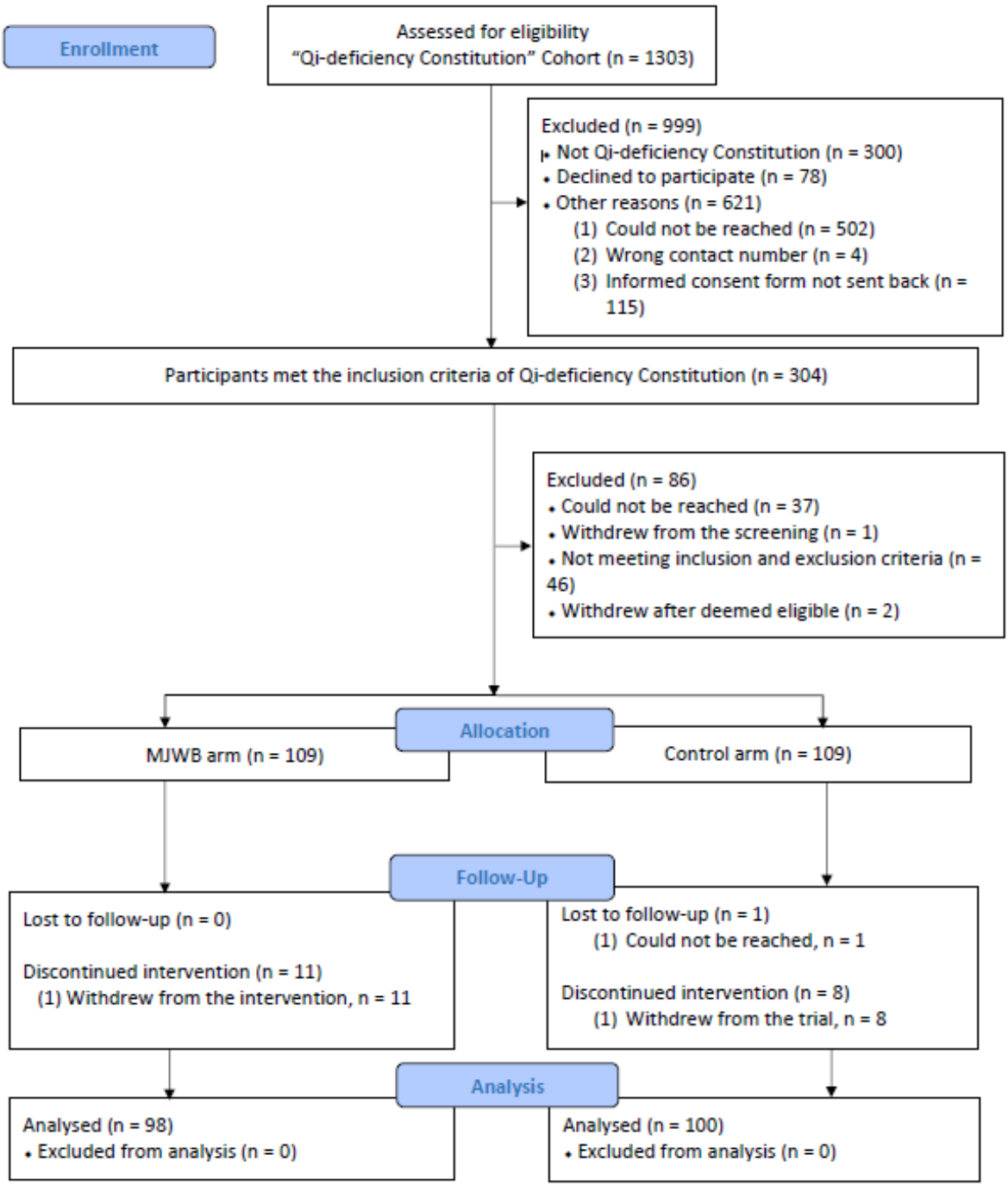

Figure 1 Study Flowchart.

Compliance with the intake of MJWB during the trial period was satisfactory, with a mean ± SD intake of 75.4 ± 13.5 sachets. Moreover, 42.8% (41/98) of the MJWB arm participants finished taking all the 84 sachets.

3.2 Baseline Data

3.2.1 Demographic Characteristics

In the MJWB arm, participants' median [IQR] age was 70.0 [68.0 and 72.0] years old. In the control arm, participants were aged 69.5 [68.0 and 73.0]. Most participants were female (72.4% in the MJWB arm and 81.0% in the control arm). During 2021-2022, participants received the COVID-19 and/or influenza vaccinations. Specifically, 91.8% (90/98) in the MJWB arm and 90.0% (90/100) in the control arm received the COVID-19 vaccination, while 58.2% (57/98) in the MJWB arm and 59.0 (59/100) in the control arm received the influenza vaccination (Table 1).

Table 1 Baseline characteristics and the vaccination.

Characteristics	MJWB arm (n = 98)	Control arm (n = 100)
Age (Year)		
65-74	83 (84.7)	88 (88.0)
75-84	15 (15.3)	11 (11.0)
≥85	0 (0.0)	1 (1.0)
Gender		
Female	71 (72.4)	81 (81.0)
Male	27 (27.6)	19 (19.0)
Vaccination (2021-2022)		
Yes	92 (93.9)	93 (93.0)
Received COVID-19 Vaccination	90 (91.8)[a]	90 (90.0)[b]
Received Influenza Vaccination	57 (58.2)[c]	59 (59.0)[d]
Received both COVID-19 and Influenza Vaccination	55 (56.1)	56 (56.0)
No	6 (6.1)	7 (7.0)

Note: Results are reported as frequency and percentage. Last injection date of COVID-19 Vaccination: [a]MJWB arm: 2021 (20 May 2021 to 24 December 2021), 2022 (3 January 2022 to 23 March 2022). [b]Control arm: 2021 (30 June 2021 to 31 December 2021), 2022 (1 January 2022 to 28 March 2022). Last Injection date of Influenza Vaccination: [c]MJWB arm: 2021 (8 October 2021 to 24 December 2021), 2022 (4 January 2022 to 25 February 2022). [d]Control arm: 2021 (28 January 2021 to 30 December 2021), 2022 (3 January 2022 to 10 February 2022).

3.2.2 Potential Key Effect Modifiers

The most prevalent comorbidities were hypertension, hyperlipidemia, rhinitis, cardiovascular diseases, and eczema. All pre-existing comorbidities (Table S2) and the potential key effect modified medications taken during the participant's medication period of MJWB (Table S3) were recorded and compared separately.

3.3 Co-primary Outcomes

3.3.1 MJWB Effects on the CFQCQ Score in Elderly

Throughout the 3-month prevention period, 98 out of 109 (89.9%) participants in the MJWB arm and 100 out of 109 (91.7%) participants in the control arm finished the trial.

The complete case analysis showed that after taking MJWB, the mean ± SD total score of the CFQCQ in the MJWB arm was 13.9 ± 5.5, compared to 16.9 ± 7.1 in the control arm. There was a statistically significant difference between the MJWB users and the non-users in the clinical features of the Qi-deficiency Constitution (mean difference -2.9, 95% CI -4.5 to -1.3, $p < 0.001$). The ITT analysis yielded consistent statistical significance in the CFQCQ total score. Specifically, there were statistically significant differences in the mean CFQCQ sub-scores for MCF1 “Easily get tired” (mean difference -0.6, 95% CI -0.8 to -0.3, $p < 0.001$), MCF2 “Shortness of breath” (mean difference -0.2, 95% CI -0.4 to -0.1, $p = 0.012$), and SCF4 “Lack of energy” (mean difference -0.3, 95% CI -0.5 to -0.0, $p = 0.021$) (Table 2).

Table 2 MJWB effects on the CFQCQ score in elderly.

Items	MJWB arm		Control arm		Mean Difference	95% CI for the mean difference	p
	Before Trial	After Trial	Before Trial	After Trial			
CFQCQ total score							
	17.2 ± 6.7[a]	14.4 ± 5.5[a]	17.1 ± 6.9[a]	17.7 ± 7.3[a]	-3.4[a]	-5.0 to -1.8[a]	<0.001[a]
	17.2 ± 6.7[b]	14.7 ± 5.8[b]	17.1 ± 6.9[b]	17.5 ± 7.1[b]	-2.9[b]	-4.4 to -1.3[b]	<0.001[b]
	16.8 ± 6.5[c]	13.9 ± 5.5[c]	17.1 ± 6.9[c]	16.9 ± 7.1[c]	-2.9[c]	-4.5 to -1.3[c]	<0.001[c]
CFQCQ sub-scores							
MCF1	2.5 ± 0.8[c]	2.3 ± 0.7[c]	2.8 ± 0.8[c]	2.9 ± 0.9[c]	-0.6[c]	-0.8 to -0.3[c]	<0.001[c]
MCF2	2.4 ± 0.7[c]	2.1 ± 0.6[c]	2.4 ± 0.8[c]	2.4 ± 0.8[c]	-0.2[c]	-0.4 to -0.1[c]	0.012[c]
SCF1	2.6 ± 1.2[c]	2.7 ± 1.0[c]	2.2 ± 1.2[c]	2.3 ± 1.2[c]	0.2[c]	-0.1 to 0.5[c]	0.157[c]
SCF2	2.1 ± 0.9[c]	1.7 ± 0.7[c]	2.2 ± 0.9[c]	1.9 ± 1.0[c]	-0.2[c]	-0.4 to 0.0[c]	0.073[c]
SCF3	1.7 ± 0.8[c]	1.5 ± 0.6[c]	1.8 ± 0.9[c]	1.7 ± 1.0[c]	-0.2[c]	-0.4 to 0.0[c]	0.063[c]
SCF4	2.2 ± 0.8[c]	1.8 ± 0.7[c]	2.4 ± 0.8[c]	2.2 ± 0.9[c]	-0.3[c]	-0.5 to -0.0[c]	0.021[c]

Note: CFQCQ: The Clinical Features of the Qi-deficiency Constitution Questionnaire. MCF: Main Clinical Feature. MCF1. "Easily get tired" and MCF2. "Shortness of breath"; and SCF: Secondary Clinical Feature. SCF1. "Sweat easily," SCF2. "Weak voice," SCF3. "Not willing to talk" and SCF4. "Lack of energy". Analysis for the CFQCQ total score: [a] ITT analysis (using [a] Best-worst-case' scenario dataset and [b] Worst-best-case' scenario dataset) was conducted, analyzed datasets after missing data imputation, i.e., MJWB arm (n = 109), Control arm (n = 109). Analysis for both the CFQCQ total score and the CFQCQ sub-scores: [c] Complete case analysis was conducted, analyzed participants who completed the trial, i.e., MJWB arm (n = 98), Control arm (n = 100). The ANCOVA analysis analyzed both ITT analysis and complete case analysis. The results are reported as mean ± SD scores in each arm, the mean difference between arms, the 95% CI for the mean difference, and the p-value.

3.3.2 MJWB Effects on the Common Cold Incidence in Elderly

At least one common cold was reported among 40.8% (40/98) participants in the MJWB arm throughout the 3 months, as compared to 43.0% (43/100) in the control arm (odd ratio 0.9, 95% CI 0.5 to 1.6, p = 0.756) (Table 3). The two arms had no statistically significant difference in the common cold incidence.

Table 3 MJWB effects on the common cold incidence in the elderly.

Common Cold Incidence	MJWB arm (n = 98)	Control arm (n = 100)	Point estimate for the odds ratio	95% CI for the Odds Ratio	p
No	58 (59.2)	57 (57.0)	0.9	0.5 to 1.6	0.756
Yes	40 (40.8)	43 (43.0)			

Note: The common cold incidence was calculated from the "Yes" or "No" responses in Q2. "Did you have a common cold incident today?" This was one of the questions in the Patient Diary-the Common Cold Incidence Record (ICCR-P). A complete case analysis was conducted, analyzing participants who completed the trial, i.e., MJWB arm (n = 98) and control arm (n = 100). Complete case analysis was conducted using the Pearson chi-square (χ^2) test. The results are reported as frequency and percentage for the incidence in each arm and a point estimate for the odds ratio, the 95% CI for the Odds Ratio, and the p-value.

The common cold incidence across subgroups was compared to illustrate the potential key effect modifier(s), such as pre-existing comorbidities, shown in Table S4.

3.4 Secondary Outcomes

3.4.1 MJWB Effects on the Persistent Days of the Common Cold in Elderly

In the MJWB arm, 40 out of 98 (40.8%) participants reported at least one common cold, while 43 out of 100 (43.0%) in the control arm reported at least one common cold.

Throughout the 3-month prevention trial, the persistence of the common cold ranged from 1 to 34 days among the MJWB arm participants, compared to 1 to 30 days in the control arm. The mean ± SD number of persistent days for the MJWB arm participants was 2.8 ± 5.2 compared to 2.8 ± 5.3 in the control arm. There was no statistically significant difference between the two arms in the common cold, persistent days (mean difference 0.1, 95% CI -1.4 to 1.5, p = 0.929). The sensitivity analysis yielded consistent statistically insignificant results in its persistence (Table 4).

Table 4 MJWB effects on the persistent days of the common cold in the elderly.

Persistent Days of the Common Cold	Mean ± SD / Median ([Q1 and Q3])		Mean Difference	95% CI for the mean difference	p
	MJWB arm (n = 98)	Control arm (n = 100)			
Independent sample t test	2.8 ± 5.2[a]	2.8 ± 5.3[a]	0.1[a]	-1.4 to 1.5[a]	0.929[a]
Mann-Whitney U test	0.0 [0.0 and 5.0][b]	0.0 [0.0 and 4.0][b]	/	1.0 to 1.0[b]	0.990[b]

Note: The total persistent days (i.e., the sum of the days) of the first, second, and third months, which included responses indicating either a "Yes" or "No" common cold incidence, was calculated from the responses recorded in Q4. "Today is your day □□ for the incident common cold." This was one of the questions in the Patient Diary- the Common Cold Incidence Record (ICCR-P). Complete case analysis and sensitivity analysis were conducted, and participants who completed the trial, i.e., MJWB arm (n = 98) and control arm (n = 100). [a] Complete case analysis was conducted using the independent sample t-test. The results are reported as mean ± SD persistent days in each arm, the mean difference between arms, the 95% CI for the mean difference, and the p-value. [b] Sensitivity analysis was conducted using the Mann-Whitney U test. The results are reported as median [Q1 and Q3] in each arm and between arms with 95% CI and p-value.

3.4.2 MJWB Effects on the Symptoms of the Common Cold in Elderly

At least one common cold was reported among 40 out of 98 (40.8%) participants in the MJWB arm and 43 out of 100 (43.0%) in the control arm.

Throughout the 3-month prevention trial, the total score of the common cold symptoms for the MJWB arm participants ranged from 3 to 181, compared to 2 to 470 in the control arm. The mean ± SD TCMSSMQ total score in the MJWB arm was 19.7 ± 35.2, compared to 26.8 ± 64.0 in the control arm. There was no statistically significant difference between the two arms in the common cold symptoms (mean difference -7.1, 95% CI -21.6 to 7.4, p = 0.336). The sensitivity analysis yielded consistent statistically insignificant results in the symptoms' total score (Table 5).

Table 5 MJWB effects on the TCMSSMQ total score of the common cold in the elderly.

TCMSSMQ total score of the Common Cold	**Mean ± SD/Median ([Q1 and Q3])**		**Mean difference**	**95% CI for the mean difference**	**p**
	MJWB arm (n = 98)	**Control arm (n = 100)**			
Independent sample t test	19.7 ± 35.2[a]	26.8 ± 64.0[a]	-7.1[a]	-21.6 to 7.4[a]	0.336[a]
Mann-Whitney U test	0.0 [0.0 and 33.8][b]	0.0 [0.0 and 21.5][b]	/	0.9 to 1.0[b]	0.955[b]

Note: TCMSSMQ: The Traditional Chinese Medicine Syndrome Scoring Method Questionnaire. Complete case analysis and sensitivity analysis were conducted, and participants who completed the trial, i.e., MJWB arm (n = 98) and control arm (n = 100). [a] Complete case analysis was conducted using the independent sample t-test. The results are reported as mean ± SD total score in each arm, the mean difference between arms, the 95% CI for the mean difference, and the p-value. [b] Sensitivity analysis was conducted using the Mann-Whitney U test. The results are reported as median [Q1 and Q3] in each arm, between arms, with 95% CI and p-value.

3.4.3 MJWB Effects on Serum IgG, IgM, and IgA Concentrations

After the 3-month prevention period, improvements in the concentrations were identified: 65 out of 98 (66.3%) MJWB arm participants showed an increase in the IgG, 50 out of 98 (51.0%) in the IgM, and 51 out of 98 (52.0%) in the IgA concentrations. A statistically significant within-group

difference was shown in the before and after prevention IgG concentration (n = 98, Z = -3.4, p < 0.001) but not in the IgM (n = 98, Z = -0.8, p = 0.408) and IgA concentrations (n = 98, Z = -0.2, p = 0.819). There was a positive correlation and statistically significant difference between the before and after prevention IgG (r(96) = 0.3, p = 0.004) or IgM concentrations (r(96) = 0.3, p < 0.001), but a negative correlation and a statistically insignificant difference between the before and after prevention IgA concentration (r(96) = -0.0, p = 0.990) (Table 6).

Table 6 MJWB effects on the immune biomarkers' concentrations.

Effects on the concentration (mg/ml)	Wilcoxon signed rank test		Spearman's rank correlation
	Z	p	
IgG	-3.5[b]	<0.001	0.004
IgM	-0.9[b]	0.388	<0.001
IgA	-0.3[b]	0.795	0.990

Note: [b] Based on negative ranks.

3.5 Other Outcomes

3.5.1 Adverse Effects: AE & SAE

Throughout the 3-month prevention period, 21.4% (21/98) of participants in the MJWB arm reported at least one adverse event. Separately, 15.3% (15/98) participants reported 19 AEs in the first month, 5.1% (5/98) participants reported 7 AEs in the second month, and 5.1% (5/98) participants reported 5 AEs in the third month. All AEs were either mild or moderate. One participant (1.0%, 1/99) dropped out due to an AE of a moderately swollen and painful right gum in the first month. No serious adverse events were reported (Table 7).

Table 7 Adverse events during the first, second, and third months in the MJWB arm.

Adverse Event	MJWB arm (n = 98)
First month*	
Mild	
Bruise tongue, Bruise vein(s) underneath the tongue	1 (1.0)
Irregular bowel movement	2 (2.0)
Uncomfortable throat	2 (2.0)
Dry mouth	1 (1.0)
A sense of swollen tongue	1 (1.0)
Itchy skin, Raised skin and skin lumps	2 (2.0)
Feel nauseated and belching	2 (2.0)
Tension headache	1 (1.0)
Eczema	1 (1.0)
Dry throat, mild sore throat	1 (1.0)
Yellowish urine	1 (1.0)
Bitter mouth in the morning, Dry mouth and throat	1 (1.0)
Difficult to have deep sleep in the afternoon and at night	1 (1.0)

Total	17 (17.3)
Moderate	
Frequent nocturia	1 (1.0)
Palpitation and vertigo	1 (1.0)
Total	2 (2.0)
Second month	
Mild	
Bitter mouth in the morning, Dry mouth and throat	1 (1.0)
Dizziness	1 (1.0)
Dry throat, Tight vocal cords and difficult to speak, Deficiency of qi in the middle-energizer	1 (1.0)
Itchy throat and dry cough	2 (2.0)
Weak knees	1 (1.0)
Mild dry tongue and mild sore gums	1 (1.0)
Total	7 (7.1)
Third Month	
Mild	
Abdominal cramps and diarrhea	1 (1.0)
Irregular bowel movement, Difficult to falling asleep	1 (1.0)
Bitter mouth in the morning, Dry mouth and throat	1 (1.0)
Weak knees	1 (1.0)
Total	4 (4.1)
Moderate	
Urticaria	1 (1.0)
Total	1 (1.0)

Note: Results are reported as frequency and percentage. Results are reported as participants who encountered at least 1 episode of adverse events during the first, second, or third month. Each adverse event was counted separately. For example, during the first month, a participant encountered two different adverse events ("mild tension headache" and "moderate palpitation and vertigo"), which were categorized and counted as two separate incidences. Calculation = (Number of Adverse Events and Serious Adverse Events/Total number of participants in the MJWB arm) × 100%. * One participant (1.0%, 1/99) dropped out due to an adverse event (moderately swollen and painful right gum) in the first month.

AEs and SAEs were not recorded among the control arm participants.

3.5.2 Adverse Effects: Liver and Renal Function Herbal Safety Assessment

Before the trial, blood tests were done to confirm the eligibility of the participants in the MJWB arm. Based on the assessment criteria, when the "assessed index value" divided by the "maximum normal index value" was ≤1.5, participants would be assessed to have normal liver and renal function. All the 109 MJWB arm participants were assessed with normal liver and renal function to take MJWB for 3 months.

After the trial, 98 out of 109 (89.9%) participants in the MJWB arm completed the trial, 97 out of 98 (99.0%) finishers were assessed with normal liver and renal function (Table 8).

Table 8 Liver and renal function herbal safety assessment in the MJWB arm.

Indexes	Before Prevention (n = 98)	After Prevention (n = 98)
Urea	5.4 ± 1.3	5.7 ± 1.4
Creat	70.6 ± 15.0	69.9 ± 12.7
AST	22.9 ± 6.9	22.1 ± 6.7
ALT	20.9 ± 10.3	20.4 ± 11.2
T prot	74.0 ± 4.2	72.2 ± 4.1
Alb	41.9 ± 1.8	42.6 ± 1.9
UA	0.3 ± 0.1	0.3 ± 0.1

Note: Results are reported as mean ± SD. Creat: Creatinine, AST: Aspartate Transaminase, ALT: Alanine Transaminase, T prot: Total protein, Alb: Albumin, UA: Uric acid. Normal range for each index in Male: (1) 3.0-9.2 mmol/L for Urea, (2) 64-111 umol/L for Creat, (3) 5-34 U/L for AST, (4) <56 U/L for ALT, (5) 64-83 g/L for T prot, (6) 32-46 g/L for Alb and (7) 0.21-0.42 mmol/L for UA. Normal range for each index in Female: (1) 3.5-7.2 mmol/L for Urea, (2) 50-98 umol/L for Creat, (3) 5-34 U/L for AST, (4) <56 U/L for ALT, (5) 64-83 g/L for T prot, (6) 32-46 g/L for Alb and (7) 0.15-0.35 mmol/L for UA.

However, 1 participant was assessed with abnormal liver and renal function. This participant was assessed with elevated Aspartate Transaminase (AST) (assessed index value "62"/maximum normal value "34" = 1.82) and Alanine Transaminase (ALT) (assessed index value "85"/maximum normal value "<56" = 1.52) on 7 June 2022 (i.e., the initial blood test after taking 84 sachets of MJWB). To resolve the situation: (1) Two repeated blood tests were done monthly, on 7 July 2022 and 8 August 2022, respectively. On 7 July 2022, both AST (assessed index value "72"/maximum normal value "34" = 2.12) and ALT (assessed index value "104"/maximum normal value "<56" = 1.86) remained elevated. On 8 August 2022, both AST (assessed index value "60"/maximum normal value "34" = 1.76) and ALT (assessed index value "96"/maximum normal value "<56" = 1.71) were lowered down as compared to the last blood test. (2) The participant was also referred to our TCM clinic for follow-up and had the first consultation on 22 August 2022.

4. Discussion

4.1 Interpretation

The 3-month MJWB intake can significantly improve the clinical features of the Qi-deficiency Constitution, in particular the three clinical features, "easily get tired," "shortness of breath," and "lack of energy." From the perspective of "preventive treatment of disease," MJWB may prevent the common cold by regulating the Qi-deficiency Constitution among elderly participants [10]. Moreover, the IgG concentration was also improved in the MJWB arm. MJWB may also exert its preventive effectiveness through regulating the natural immunity among the participants [27]. IgG is closely related to the recurrent incidence of the common cold [17, 28-38]. While the elderly are susceptible to the common cold due to the increased exhaustion in IgG [39], improving the IgG

concentration may be good for the elderly population. The improvement in the Qi-deficiency Constitution clinical features and the IgG level may suggest that MJWB is beneficial for preventing participants from progressing to the related clinical symptoms and their complications.

There is no statistically significant difference between the two arms in the incidence of the common cold, the mean duration of persistence, or TCMSSMQ total score. This may be due to various reasons: (1) the need for a longer recuperation period for those with Qi-deficiency Constitution to achieve their constitutional balance, thus possibly preventing the common cold [40]. In particular, the elderly with underlying diseases usually have a weakened constitution, undermining their capacity to fight the common cold [41] and disabling them to overcome the common cold's long duration and severe symptoms [41]. (2) The trial was conducted overlapping the COVID-19 pandemic period. The COVID-19 and the alert to COVID might become confounders in evaluating the common cold results. (3) In any doubts, based on the literature findings and/or clinical judgment [42], the potential key effect modifiers such as the pre-existing comorbidities, the medications taken during the trial, and the liver and renal dysfunctions (however, no liver and renal function data was collected from the control arm participants for the between-group comparison) could also potentially affect the common cold results. (4) The null hypothesis, "there was no difference between the two arms concerning their ability to reduce the common cold incidence," might be incorrectly established. Based on the TCM theory, MJWB was used to nourish the Qi-deficiency Constitution; thus, adjusting its functional state could prevent the common cold. In other words, there is no direct correlation for MJWB in preventing the common cold but indirectly through improving the Qi-deficiency Constitution [10].

Our finding of a decrease in the CFQCQ mean total score was consistent with the result of Chan et al.'s randomized controlled trial (after the trial, the CFQCQ's total score was lower, as compared to that in the before trial ($p < 0.05$) between the two arms) [43]. The incidence of the common cold was not statistically significant, as found by Chan et al. [compared with the control arm in the post-treatment common cold numbers ($p < 0.05$)]. This may be due to the different targeted participants, as Chan et al. targeted a younger population (mean age for males 39.2 ± 13.1, females 38.9 ± 14.2) with a higher incidence of the common cold (≥4 times per year) [43]. Our controlled trial found a statistically significant between-group difference in the CFQCQ total score, while Song et al., via the randomized double-blinded trial, found there was no statistically significant difference for Qi-deficiency type, Deficiency of Qi and Yin type, Yin-deficiency type, and Yang-deficiency type ($p > 0.05$) [8]. Meanwhile, our trial yielded evidence of the improvement in IgG concentrations. Compared to this, Song et al. found the elevation of both the IgA and IgG levels ($p < 0.01$) in 294 participants aged 4 to 64 years old [8]. This variation could be attributed to differences in the targeted participants, among other factors.

4.2 Strengths and Limitations

Strengths of the study included (1) it is the first clinical trial to report the preventive effect of MJWB through the key concept of the constitution theory of TCM, i.e., from the perspective of "preventive treatment of disease," (2) the enrollment was initiated from our large-scale participants' database of Qi-deficiency Constitution, in which made the participants recruitment process efficient and ensured a sufficient sample size for the trial, (3) the implementation of standardized online data collection which also made data collection more efficient.

The study had several limitations. These included (1) the trial was not randomized, (2) no blood samples were drawn from the no-intervention control arm to compare the between-group differences in the liver and renal function and immunological functions, in which the liver and renal function might potentially affected the common cold prevalence, (3) the standardization of the common cold diagnosis would help improve the related outcome assessment [44]. For example, among participants [8.2% (8/98) in the MJWB arm, as compared to 3.0% (3/100) in the control arm] who reported COVID-19 cases during the prevention period, some of them reported that at the time of the onset they were diagnosed with the common cold but not the COVID-19, thus they filled in the patient diary as they had the incidence of the common cold. Though this issue was solved by remarking in the ICCR-P (i.e., it did not exclude the possibility of co-infections of the common cold and COVID-19) [45], the standardized and differential diagnoses of the common cold are still essential.

4.3 Prospect

This trial established a foundation for the TCM prevention study, contributing to the primordial prevention (addressing the root cause of the common cold, i.e., Qi-deficiency Constitution), primary prevention (administrating of a prophylactic herbal medication, i.e., MJWB) and secondary prevention (conducting periodic health examinations at an individual level, i.e., a yearly assessment of Qi-deficiency Constitution and preventing progression to symptomatic common cold), to relieve the complications of the common cold among HK elderly population [5].

Future directions in this area include but are not limited to (1) following up on the long-term improvements of the elderly participants, such as in terms of their constitutional changes common cold prevalence; (2) helping clinicians and participants clearly distinguish the common cold from other acute upper respiratory tract infections; (3) performing well-designed clinical trials on promising TCM preventive strategies with limited research evidence.

5. Conclusions

MJWB can significantly improve the clinical features of the Qi-deficiency Constitution and the IgG level. Specifically, it improved the “easily get tired,” “shortness of breath,” and “lack of energy” clinical features. The common cold incidence and the related persistent days or symptoms observed no statistical significance between the MJWB users and the non-users. The larger the sample size, the more likely a trial will find a truly significant relationship if one exists.

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Yiu Lin Wong: Conceptualization, Project facilitation, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing - original draft and Writing - review & editing. **Jialing Zhang**: Writing - review & editing. **Linda LD Zhong**: Writing - review & editing. **David Moher**: Resources and Writing - review & editing. **Zhaoxiang Bian**: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Project facilitation and Writing - review & editing. All authors reviewed and approved the final version of the manuscript.

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Competing Interests

The authors have declared that no competing interests exist.

Data Availability Statement

Study data were collected and managed using REDCap electronic data capture tools hosted at Hong Kong Baptist University [46, 47]. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

Additional Materials

The following additional materials are uploaded at the page of this paper.

1. Table S1: Inclusion and exclusion criteria.
2. Table S2: Prevalence of baseline pre-existing comorbidities.
3. Table S3: Prevalence of the potential key effect modified medications taken during the trial.
4. Table S4: The common cold incidence across subgroups.

References

1. Sun Y, Zhao Y, Xue SA, Chen J. The theory development of traditional Chinese medicine constitution: A review. J Tradit Chin Med Sci. 2018; 5: 16-28.

2. Lai T, Guan Y, Men S, Shang H, Zhang H. Resnet for recognition of qi-deficiency constitution and balanced constitution based on voice. Front Psychol. 2022; 13: 1043955.
3. Jiang QY, Li J, Zheng L, Wang GH, Wang J. Constitution of traditional Chinese medicine and related factors in women of childbearing age. J Chin Med Assoc. 2018; 81: 358-365.
4. Wong YL. The distribution of body constitutions and evaluation of the preventive effectiveness with Chinese medicine approaches in Hong Kong elderly population. Hong Kong, China: Hong Kong Baptist University; 2024.
5. AbdulRaheem Y. Unveiling the significance and challenges of integrating prevention levels in healthcare practice. J Prim Care Community Health. 2023; 14: 21501319231186500.
6. Zhang Hui NC, Zhang Rong-chun. Discussion on the original intension of constitutional conditioning of the jade screen powder and the strategy of its extending applications. Chin J Tradit Chin Med Pharm. 2014; 29: 3874-3877.
7. Zhang Hui Ling CSQ. Effect of Yu Ping Feng San on the upper respiratory infection children's immune function. Pharmacol Clin Chin Mater Med. 1995; 4: 37-38.
8. Cheng S, Xuan N, Li-Hua Z, Ying Z, Jing-Rong Z, Zhou C. "Ti Xu Gan Mao He Ji" preventing and treating deciency symdrome common cold 294 cases. Shaanxi Tradit Chin Med. 2003; 24: 505-507. doi: 10.3969/j.issn.1000-7369.2003.06.020.
9. Hong L. Theoretical study of “preventive treatment of disease” in traditional Chinese medicine. In: Healthy Aging. Singapore: World Scientific Publishing Co Pte Ltd; 2011. pp. 41-53.
10. Qiu J, Zhao J, Feng P, Zhou H, Li H. Relationship between traditional Chinese medicine constitution and pregnancy outcome in elderly primiparae. Trop J Pharm Res. 2023; 22: 1443-1449.
11. Liu R, Li M, Wang P, Yu M, Wang Z, Zhang GZ. Preventive online and offline health management intervention in polycystic ovary syndrome. World J Clin Cases. 2022; 10: 3060-3068.
12. Cheng CW, Wu TX, Shang HC, Li YP, Altman DG, Moher D, et al. Consort extension for Chinese herbal medicine formulas 2017: Recommendations, explanation, and elaboration. Ann Intern Med. 2017; 167: 112-121.
13. Lau JT, Leung PC, Wong EL, Fong C, Cheng KF, Zhang SC, et al. The use of an herbal formula by hospital care workers during the severe acute respiratory syndrome epidemic in Hong Kong to prevent severe acute respiratory syndrome transmission, relieve influenza-related symptoms, and improve quality of life: A prospective cohort study. J Altern Complement Med. 2005; 11: 49-55.
14. CountryReports. Hong Kong Geography [Internet]. Pleasant Grove, UT: CountryReports. Available form: https://www.countryreports.org/country/HongKong/geography.htm.
15. De Moor FC. The importance of voucher specimens. South Afr J Aquat Sci. 1996; 22: 117-118.
16. Culley TM. Why vouchers matter in botanical research. Appl Plant Sci. 2013; 1: 1300076.
17. Cong C. Clinical research on the effect of Yu ping feng granules preventing the recurrent common cold and recuperating the qi-deficient constitution. Beijing, China: Beijing University of Chinese Medicine; 2018.
18. Spronk I, Korevaar JC, Poos R, Davids R, Hilderink H, Schellevis FG, et al. Calculating incidence rates and prevalence proportions: Not as simple as it seems. BMC Public Health. 2019; 19: 512.
19. Yin dan L. Repair nourish activing in elderly deficiency cold again and again clinical research. Changchun, China: Changchun University of Chinese Medicine; 2013.

20. Thermo Fisher Scientific Inc. Thermo Fisher China | Homepage [Internet]. Shanghai, China: Thermo Fisher Scientific Inc.; 2024. Available from: https://www.thermofisher.com.
21. Yu Z, He-Ping Z, Xiao-Hui L, Xiao-Xia L, Ya-Ping X. Investigation of reference range of parameters of liver and renal function of old people in Beijing. Prog Mod Biomed. 2011; 11: 1734-1736.
22. Parker RA, Cook JA. The importance of clinical importance when determining the target difference in sample size calculations. Trials. 2023; 24: 495.
23. SPSS. Overview [Internet]. Kowloon, Hong Kong: Hong Kong Baptist University; 2024. Available from: https://ito.hkbu.edu.hk/services/software-licensing/spss.html.
24. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials-a practical guide with flowcharts. BMC Med Res Methodol. 2017; 17: 162.
25. Kim HY. Statistical notes for clinical researchers: Nonparametric statistical methods: 1. nonparametric methods for comparing two groups. Restor Dent Endod. 2014; 39: 235-239.
26. Kim N, Fischer AH, Dyring-Andersen B, Rosner B, Okoye GA. Research techniques made simple: Choosing appropriate statistical methods for clinical research. J Invest Dermatol. 2017; 137: e173-e178.
27. Panda S, Ding JL. Natural antibodies bridge innate and adaptive immunity. J Immunol. 2015; 194: 13-20.
28. Lei Z. Research on Yu Ping Feng San and its immune regulation. Chengdu, China: Chengdu University of TCM; 2006.
29. Tao CX. Immunomodulating activities and its mechanisms of fractioned polysaccharides from Yu-ping-feng-powder. Anhui, China: Anhui Medical University; 2006.
30. Xin-Yan C, Yan-Zhao L, Zhi-Min Y. Literature research of cold susceptible population treated with traditional Chinese medicine. J Guangzhou Univ Tradit Chin Med. 2019; 36: 1-6. doi: 10.13359/j.cnki.gzxbtcm.2019.01.001.
31. Bo LX. A research review on treating cold of qi xu in the integrative medicine. Clin J Chin Med. 2016; 28: 139-142.
32. NI Dong Min WBL, Wang Sheng Long. Research progress on the prevention of recurrent common cold. CJGMCM. 2016; 31: 3531-3534.
33. Ling W. Research progress on the treatment and prevention mechanisms of Yu Ping Feng San on recurrent upper respiratory infection. J Trop Dis Parasitol. 2012; 1: 59-61.
34. Zhang Liang CWH. Research progress on the treatment and prevention mechanisms of Yu Ping Feng San on recurrent upper respiratory infection. Mod J Integr Tradit Chin West Med. 2010; 22: 2852-2853.
35. Gao Rui Qing MXB. Research progress on the pharmarchology and clincal study of Yu Ping Feng San on the respiratory system diseases. Zhejiang J Tradit Chin Med. 2003: 318-319.
36. Xing-Ping L. Immunopharmacology research on Yu Ping Feng San. J Shaanxi Collage Tradit Chin Med. 2000; 23: 36-38. doi: 10.13424/j.cnki.jsctcm.2000.02.029.
37. Hou Lin Jiang XHT. Immunopharmacology research on Yu Ping Feng San. Chin J Integr Tradit West Med. 1998; 11: 701-703.
38. Xin Hong Tao HLJ, Xu Shao Hua, Zhou Xiao Hui. Immunopharmacology research on Yu Ping Feng San. China J Chin Mater Med. 1998; 8: 505-507.

39. Zhi Xia Yang RS, Yang Tian, Yan Zhang, Ying Shuai Li, Qi Wang. The correlation study between traditional Chinese medicine constitutions and immunology. Immunol Stud. 2014; 2: 23-32. doi: 10.12677/is.2014.23005.
40. Xue Li-yuan NC. Analysis of main medicine and prescription used in qi deficiency constitution. China J Tradit Chin Med Pharm. 2018; 33: 857-859.
41. Jian-Sheng L. Overview on the symdrome diffferention of traditinal Chinese medicine on elderly's common cold. Henan Tradit Chin Med. 2010; 30: 367-368. Available from: https://lib.cqvip.com/Qikan/Article/Detail?id=33370133.
42. Gorard S. Towards a judgement-based statistical analysis. Br J Sociol Educ. 2006; 27: 67-80.
43. Cong C, Qi W, Ze-Qi S, Li P, Jia-Lin L, Ting W. Clinical trial of Yu ping feng granules in recuperation of qi-deficient constitution with recurrent common cold. Chin J Exp Tradit Med Formulae. 2018; 24: 182-187. doi: 10.13422/j.cnki.syfjx.2018050183.
44. Watson A, Wilkinson TM. Respiratory viral infections in the elderly. Ther Adv Respir Dis. 2021; 15: 1753466621995050.
45. Eccles R. Common cold. Front Allergy. 2023; 4: 1224988.
46. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)-a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009; 42: 377-381.
47. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform. 2019; 95: 103208.