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Exploring heterogeneity of perimenopause with application of multivariable analysis approaches

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Abstract

Objectives Heterogeneity of clinical appearance had made it a challenge to make individualized and comprehensive management of perimenopause. This study aimed to estimate the profiles over heterogenous appearances of perimenopause with application of latent variable analysis methods over an optimized multidimensional assessing framework.

Methods A two-phase clinical study was designed and advanced in the research center in Guangzhou, China. The assessing framework was developed over the initial item pool as integration of 4 scales including Insomnia severity index, Modified Kupperman index, Self-rating anxiety scale, and Self-rating depression scale. Validity and reliability of the instrument were evaluated and the psychometric properties of the items were estimated with multidimensional item response theory(MIRT). And then computer adaptive testing(CAT) was developed with the estimated model. We used latent profile analysis (LPA) to cluster patients into subgroups as patterns characterized by multidimensional latent trait scores. Finally, interpretability and efficiency were analyzed via comparison between the two assessing strategies.

Result There were in total 336 patients diagnosed with perimenopause enrolled for the assessment. A conceptual framework was estimated consisting of 6 factors including sleep disturbance, mood swings, vasomotor symptoms, positive attitude towards life, multisystem abnormality, and fatigue. The construct validity was evaluated as optimized with CMIN/df = 1.814, GFI = 0.619, CFI = 0.721, TLI = 0.707 and RMSEA = 0.075. With scores in the simulated CAT, the 4 latent profiles model was estimated indicating the heterogeneity of perimenopause characterized by different severity of psychological and physical discomforts in the LPA.

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Conclusion The quantitative paradigm raised in this study revealed the potential patterns presenting heterogeneity of perimenopause offering better interpretation for clinical assessment.

Keywords Perimenopause, Computer adaptive testing, Factor analysis, Multidimensional item response theory, Latent profile analysis

Background

Perimenopause is defined as the period that extends from the onset of menopausal transition to 1 year after the final cessation of menses [1]. Women during perimenopause suffered from systemic discomforts that mainly caused by endocrine disorders resulting from insufficient maintenance of the hypothalamic-pituitary-ovarian axis [2–4]. Over the recent decades, studies have provided us with a chronology of reproductive and hormonal events that accompany the process of menopause transition. The chronology of ovarian aging has been clinically used in explaining the symptoms experienced by women undergoing the menopausal transition [5]. However, hormonal profiles between and within individuals were reported to be of wide variation out of fluctuations in hormone level [6].

Heterogeneity and variation of clinical appearances of perimenopause also led to difficulties in evaluation and management of perimenopause [7, 8]. To cope with perimenopause, clinicians need to make timely recognition of signs and symptoms together with their dynamic changes during the transition. Management of complex perimenopause symptoms including depressive symptoms, hot flashes, and sleep disturbances entails a careful assessment and consolidated interventions to achieve satisfactory efficacy [8]. Personalized assessment is to be developed for further assisting clinical management of perimenopause offering comprehensive measurement of symptom spectrum not only the disorder-specific symptoms, but also the prevalent somatic complaints [9, 10].

In previous research, some scales were designed and integratively used for making a comprehensive clinical assessment thereby discovering relationship between mental disorder and perimenopausal syndrome in China [11]. As a perimenopause specific scale widly applied around the world, modified Kupperman Index(mKI) [12] was designed for measuring severity of perimenopausal symptoms. Also, non-disease specific scales such as Self-rating anxiety scale(SAS) and Self-rating depression scale(SDS) were used for detecting mental disorder of perimenopause while Insomnia severity index (ISI) was used for measuring sleeping disorder of perimenopause. However, the mixture application led to confusion in both assessing and result interpretating period. For example, palpitation is one of the items in Modified Kupperman index (mKI) meanwhile the item *"I feel my heart beating fast."* is also included in both SAS and SDS. Without adequate cross-cultural adaptation, duplicated items with the same literal sense across scales leads to confusion and worsen compliance of patients during the assessment [13]. Moreover, the overlapping and replication across different scales reflected the matter that the results of mixture application of scales should be cautiously interpreted since independence hypothesis of assessment is violated. Without the luxury of developing a new multidimensional assessment from scratch, it is more feasible to re-construct the conceptual framework by disentangling the complex symptoms into distinct domain over the items from existing scales. In this way, it is possible to explore the heterogeneity of clinical appearance and further promote comprehensive individualized measurement of perimenopause.

As the process of assessment was concerned, in traditional practice, compensatory logic was normally used by which score of each item was accumulated as evaluation result. However, it leads to information reduction for making a comprehensive interpretation of the assessment for characterizing the examinees. Non-compensatory rule is to be integrated in the assessment design process [14]. Computer adaptive testing (CAT) over multidimensional item response theory (MIRT) shed light into the optimization of clinical assessment for evaluating latent traits of patients. As a core module of the assessment, item response theory was commonly used for bridging the gap between individual latent traits and psychometric properties of the scale [15]. By setting the items in a multidimensional framework, quantitative scores of multidimensional latent traits of individuals would benefit clinical practice with comprehensive clues for decision-making about diagnosis and treatment. And non-compensatory algorithm could also be designed in the testing. Therefore, it is possible for the evaluation about latent traits of patients and further estimation of disease profiles [16].

Taking advantage of multivariable analysis methods including CFA, MIRT and CAT, this study attempted to estimate profiles for presenting heterogeneity of perimenopause via quantifying latent traits over the complex clinical appearances.

Material and method

Two-stage design of clinical study

The clinical study consisted of two stages and was approved by the Ethics committee of Guangzhou Women and Children's Medical Center (NO.2021/028A01). In the first stage, a retrospective study was designed and

carried out for evaluating validity and reliability of scales so as to ensure adequacy of instrument selection for multidimensional traits assessment of perimenopause. Assessing data of 4 scales including mKI, SAS, SDS, and ISI about perimenopause patients from January 2020 to August 2020 was collectedin Guangzhou woman and child's medical center(GZWCMC). Integrating 60 items from the 4 scales, the original assessing framework was estimated covering 4 aspects including perimenopausal symptom, anxiety, depression and insomnia. The validity and reliability of the items were evaluated in R 3.4.2. Cronbach's alpha and split-half coefficient of each scale were evaluated. For better interpretability and more precise detection about multidimensional traits of patients, we attempt to optimize the framework with data-driven approaches in the next stage. In the second phase, a cross-sectional study was designed and carried out from October 2020 to August 2021. Assessing data with the 60-item assessing instrument was used for estimating psychometric properties and further estimation of latent profiles model.

Patient and public involvement

Inclusion criteria

Patients who diagnosed with perimenopause in the outpatient of the research center were recruited in this study. And the inclusion criteria were set as below:

Inclusion criteria: (a) women in age between 45 and 60 years; (b) diagnosed in the stage of perimenopause meeting either of the following criteria: (i) with a history of amenorrhea for the last 3-11months; (ii) Suffered irregular menstrual periods for the past one year (c)with the ability to complete the assessment independently.

Exclusion criteria: (a) anyone with a history of malignant tumors or with severe complications of other organs. (b) anyone who had been administered hormones or hormone analogues. (c) anyone with a severe psychiatric disease or mental disorder that could not finish the assessment independently.(d) anyone whom a researcher deemed to be unsuitable for the research.

Data collection and quality control

Patients meeting the inclusion criteria were asked to fill scales with informed consent under guidance of two trained nurses in case of any misunderstanding of the item content thereby ensuring correctness of the data records. A third practitioner was in response of quanlity control and cases with missing or mistaken data over 15% were deleted.

Statistics analysis

Sample size data imputation

Sample size of each stage was set as 100 referring to Gorsuch's [17] suggestion for the absolute minimum sample size demand of factor analysis. And the entire sample size was set as 300 that calculated as 5 times of the number of variables in the assessment.As a preprocessing procedure, data imputation was carried out with application of the k-nearest neighbours algorithm in R3.4.2 for the incomplete case. Demographic properties and symptoms intensity were analysis and that between different stages were compared with Student's t-test setting $p<0.05$ as statistically significant.

Factor analysis and conceptual framework re-construction

The conceptual framework of the assessment was reconstructed and the construct validity was evaluated with factor analysis methods. Firstly, exploratory factor analysis(EFA) was carried out and scree plots were printed with R package psych [18] to decide the initial number of factors to make the optimized multidimensional conceptual framework. Labeling of the factors was defined according to factor loadings and content of the clustered items. Discussion among 3 clinical experts was also carried out to modify the labeling of the latent factors. Secondly, confirmatory factor analysis(CFA) was applied to evaluate the adequacy of the setting of the conceptual framework in AMOS 21.0. Chi-Square Minimum Discrepancy(CMIN)/Degree of freedom(df), Root Mean Square Error of Approximation(RMSEA), Comparative Fit Indices(CFI), Goodness of Fit Indices(GFI), Tucker-Lewis Index(TLI), Root Mean Square Residual(RMR) and information criterion were used as indices to evaluate the goodness of fit about the model. The initial model was also evaluated as a comparison about the adequacy of setting for the multidimensional conceptual framework. Finally, following modification indications from AMOS, the relationship within the framework was modified and standardized factor loadings of each item on related latent trait were also estimated. Items without statistically significant correlation($p>0.05$) to the factors were eliminated and the others were drafted for further development of the CAT.

Multidimensional psychometric properties analysis

Referring to item-latent traits relationship in the re-constructed multidimensional conceptual framework of the assessment, psychometric properties of each item were evaluated with package mirt [19] in R 3.4.2. Quasi-Monte Carlo EM estimation was used as the core algorithm for estimating item parameters with the item type of setting as graded. Item characteristic curve, together with item information curve of each item were plotted as intuitive visual evaluation for the item settings.

Computer adaptive testing

Based on the calibrated parameters of the items estimated with MIRT, the CAT version of the assessment was

Table 1 Demographics of the perimenopause sample

Period	Characteristic	Values
Stage 1	N	192
	Age(year)	49.68±3.61[45, 60]
	45 ~ 49	48.96%
	50 ~ 54	38.54%
	55 ~ 59	10.42%
	60 ~ 65	2.08%
	Duration of symptoms(month)	17.43±14.77[1, 72]
	BMI	22.87±2.77[16.72, 34.21]
	Kupperman Index	7.04±4.18[1,27]
Stage 2	N	144
	Age	49.58±3.35[45,59]
	45 ~ 49	61.80%
	50 ~ 54	30.56%
	55 ~ 59	7.64%
	60 ~ 65	0%
	Duration of symptoms	18.69±15.02[1,72]
	BMI	22.59±2.77[17,31.43]
	Kupperman Index	9.23±4.66[1,30]

programmed for the multidimensional evaluation of perimenopause with the application of packages mirtCAT in R 3.4.2. The core logic of assessment was designed as follows: (a). Starting item was randomly selected among vasomotor symptoms including hot flush, irritating, and sweating. (b). The maximum determinant of the information matrix was set as adaptive criteria of the assessment for the latent trait scores calculation. (c). The stopping criteria of the test were set with the increment of latent trait scores as 0.05 and the minimum standard error of each dimension as 0.3. The test was also terminated when all items were answered. Furthermore, a web-based questionnaire was designed on basis of shiny framework as an interactive interface for the assessment. Since it is difficult to re-test every patient considering the compliance of patient and repeatability of the assessing situation, the efficiency of the CAT version of assessment was validated with 500 generated responses in simulation. By adjusting the limitation of standard error(SE) of the score of latent traits, the number of items required to finish the assessment was evaluated and regarded as efficiency indices of the instrument.

Latent profile modeling with computer adaptive test simulation

To further characterize the heterogeneity of perimenopause, subgroups of patients were identified with multidimensional latent traits scores that estimated in the CAT. TidyLPA [20] package was used for estimating the latent profile model of perimenopause in R 3.4.2. Fit indices of the modelling were evaluated including Bootstrapped likelihood ratio test(BLRT), Adjusted Lo-Mendell-Rubin test(Adjusted LMR), Akaike information criterion(AIC), Bayesian information criterion(BIC), Sample size-adjusted BIC(SABIC), Posterior classification probabilities and Entropy [21].

Table 2 Cronbach's alpha and split-half coefficient for the 4 scales

Scale	Cronbach's alpha	Split-half reliability
mKI	0.75	0.74
ISI	0.93	0.92
SAS	0.78	0.79
SDS	0.79	0.82

Notes mKI: modified Kupperman Index; SAS: Self-rating anxiety scale; SDS: Self-rating depression scale; ISI: Insomnia severity index

Result

Demographic

Data records of 192 perimenopause patients were collected in the first stage of the research. As shown in Table 1, the range of age was from 45 to 60 with the average of 49.68±3.61. The duration of symptoms of the patients varies from 1 to 72 months with the average of 17.43±14.77 months. In the cross-sectional study, 190 cases were recorded of which 46 cases were eliminated out of incompleteness of the assessment. Finally, 144 perimenopause patients were enrolled. And the age range of the sample was from 45 to 59 with the average of 49.58±3.35. The duration of symptoms varied from 1 to 72 months with average at 18.69±15.02 months. And comparison of the age and duration of symptoms of the two samples showed no statistical difference (t_{age}=0.225, p_{age}=0.822 and $t_{duration\ of\ symptoms}$=-0.689, $p_{duration\ of\ symptoms}$=0.491). The mKI score was evaluated with a large deviation and a wide score range, which indicated the potential heterogeneity of perimenopause not only in symptom spectrum but also in intensity.

Factor analysis and conceptual framework modification

Cronbach's alpha indices and split-half coefficient for each scale were estimated and listed in Table 2.

The initial conceptual framework consisted of 4 factors including menopausal discomforts, depressive disorder, anxiety disorder, and sleep disturbance referring to the original intension of the 4 scales. The validity and reliability of ISI was evaluated as good with Cronbach's alpha indice and split-half reliability coefficient over 0.9 while those of the other 3 scales were in a acceptable condition. With data collected in the second phase, the overall Measure of Sampling Adequacy(MSA) in KMO analysis was evaluated to be 0.76. And a modified conceptual framework with 6 factors was evaluated to be best fitting the data as the scree plot shown in Fig. 1.

As shown in Supplementary Table 1, most of relationship between item and factor were evaluated to be adequate with absolute value of the standardized factor

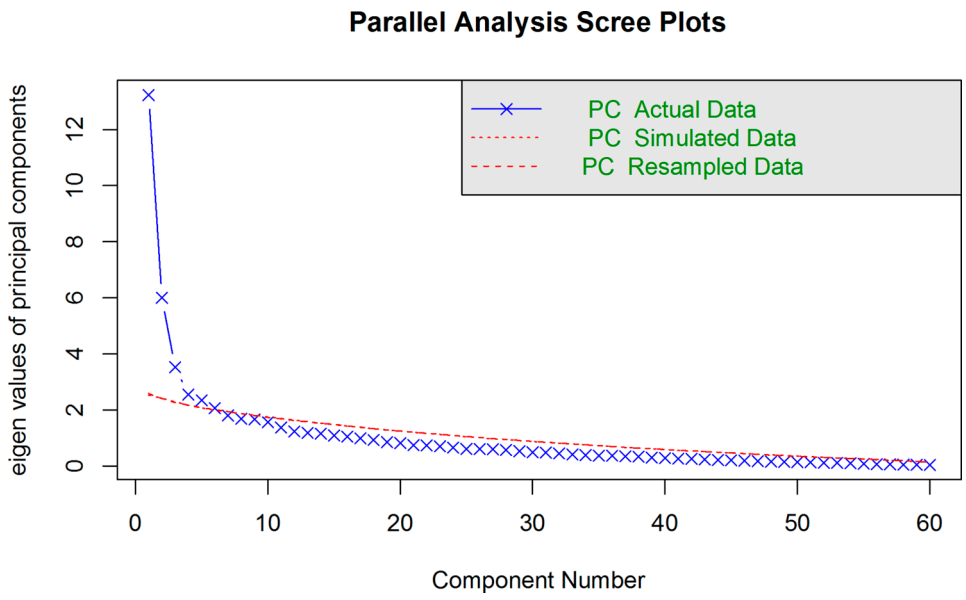

Fig. 1 Parallel analysis scree plot of the 60-item scale for perimenopause assessment. FA: Factor analysis

loadings over 0.3. To make initial interpretation of the framework, the 6 factors were summarized and labeled as sleep disturbance, mood swings, vasomotor symptoms, positive attitude, multisystem abnormality, and fatigue according to the factor loadings of the relevant items. In CFA, the construct validity of the initial 6-factor model was evaluated to be inadequate with CMIN/df=2.504, CFI=0.414, TLI=0.389, AIC=3634.679, BIC=3805.15, RMSEA=0.098.

To modify the conceptual framework, adjustment was made according to modification indications from AMOS together with suggestions for discussion among experts. In the optimized framework, SAS17 and SDS5 were dropped with their relation to the factors evaluated of no significance (p_{SAS17}=0.06, p_{SDS5}=0.6). And some items including SAS5, SAS9, SAS10, SAS13, SAS15, SDS14, SDS18, and SDS20 were refactored to related factor following modification indices. The standardized factor loading of each item to its related factor in the optimized model was listed in Supplementary Table 2. Comparing with the initial model, modification of construct validity was achieved with better goodness of fit(CMIN/df=1.814, GFI=0.619, CFI=0.721, TLI=0.707 and RMSEA=0.075) in CFA.

Item response theory and psychometric properties of the items

Psychometric properties of items in the conceptual framework were evaluated and coefficients were shown in Supplementary Table 3.

As the easiness indices shown in Supplementary Table 3, response of some options was missing in items including mKI2, mKI7, mKI8, mKI11, SAS6, SAS12, SDS19. Therefore, intercept parameters were not calculated for these items. Discrimination indices of most of the items were evaluated to be adequate with absolute value over 1 except items mKI11, mKI12, SAS13 and SDS8. As the item characteristic curves shown in Fig. 2, some of the items including mKI12, SAS17, SDS7, SDS8, and SDS9 were evaluated to be with inadequate psychometric property as the slopes of item information traces overlapped without showing separated boundaries for each option. And most items showed adequate discrimination and precision with a long and narrow slope along the axis of latent trait score. As the information curve shown in Fig. 3, most information could be provided with latent trait score in the range (-2, 2) for most of the items except items mKI1, mKI11, SAS13, and SAS17.

Simulation of computer adaptive test

In a CAT simulation, 500 responses with latent traits between −2 and 2 were generated on basis of the model estimated with MIRT. Logic of item selection of CAT was driven by both item psychometric properties and previous item responses. Association between CAT scores and sum scores of items in each dimension were evaluated to be of adequacy with $p<0.05$ and correlation indices over 0.85(Sleep disturbance $r=0.974$; Mood swings $r=0.961$; Vasomotor symptoms $r=0.861$; Positive attitude towards life $r=0.893$; Pain $r=0.857$; Fatigue $r=0.919$). Evaluation about the minimum items to be answered was carried out by adjusting SE as the precision parameter in the range 0.3 to 0.5. As shown in Table 3, setting restrict precision limitation with SE<0.3, all 58 items should be answered in the simulation. In a less restrict limitation with SE<0.4, an average of 57.6 items and a minimum of

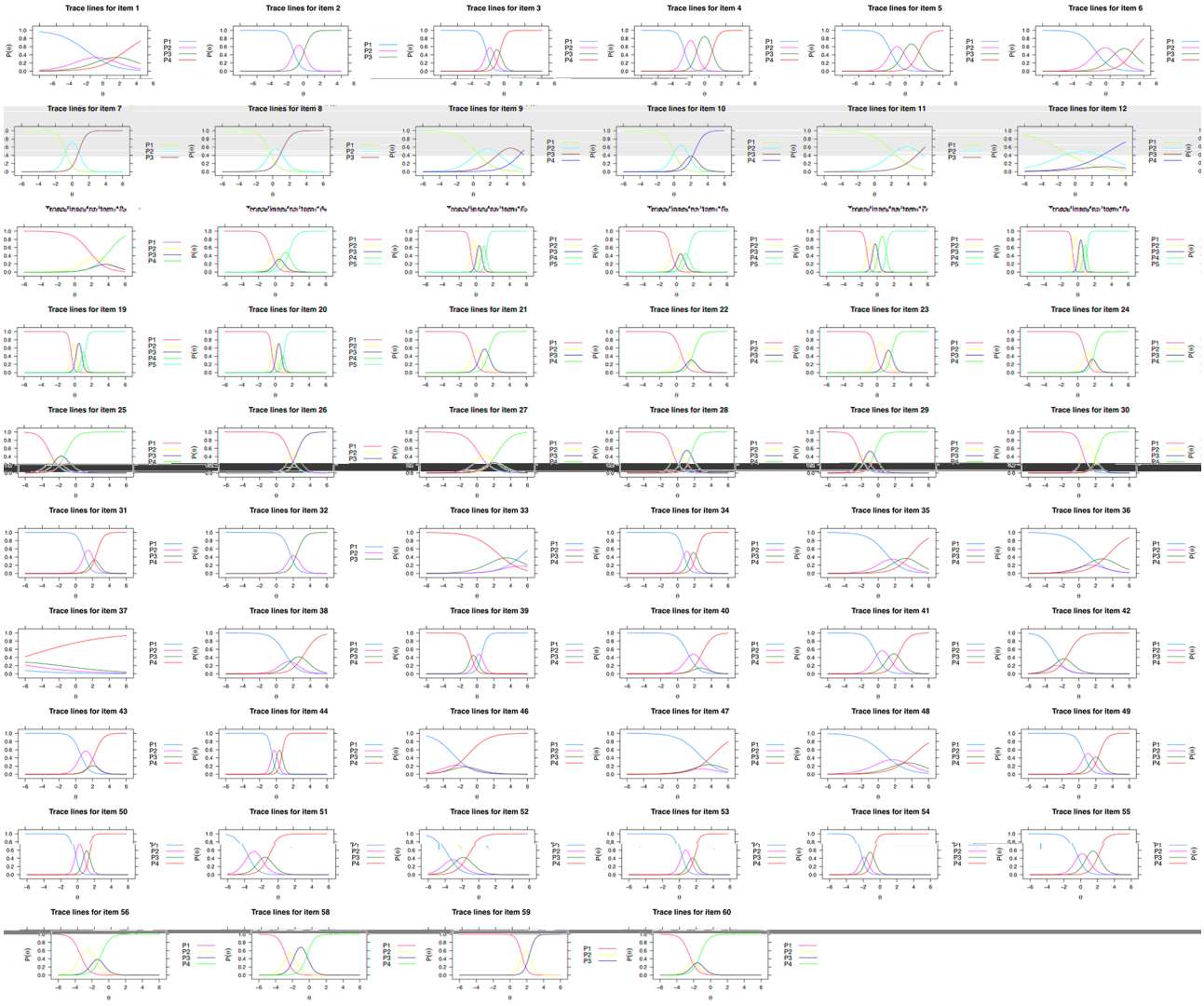

Fig. 2 Characteristic curve of the 58 items in the optimized conceptual framework for perimenopause assessment. Item *n*: The *n*th item in the conceptual framework

33 items were needed to finish the CAT. The association between the multidimensional original sum scores and the CAT latent trait scores were tested, the scatter plots showed an S-shape in Fig. 4, suggesting that the CAT performed with better discrimination especially at the high and low ends of the latent trait continuum.

Latent profile modelling

As individualized multidimensional scores evaluated, latent profile analysis was applied to characterize clinical subgroups of perimenopause. Comparison of models with different number of subgroups were shown in Supplementary Table 4. And the 5-profile model was evaluated with no optimized goodness of fit with p value of LMR and BLRT over 0.05 comparing with that of the 4-profile model. Therefore, the 4-profile model was proved to be most adequate for characterizing the data in the CAT simulation with AIC = 1997.98, BIC = 2110.78, Entropy = 0.78, p_{LMR}<0.05,p_{BLRT}<0.05.

As shown in Fig. 5, profiles estimated with multidimensional scores indicated that different subgroups of perimenopause could be divided according to the severity of their systemic discomforts. As the results were shown in Table 4, demographic properties including age, BMI, and duration of symptoms were evaluated to be without statistical significance among the 4 subgroups. The 1st Class showed the most severe in VAS, Sleep disturbance, mood swing, multisystem abnormality and fatigue and the lowest score in positive attitude towards life. Therefore, it was defined as the *severe discomfort group with low positive attitude towards life.* Oppositely, patients clustered in the 2nd Class showed the highest score in positive attitude and least discomforts int other aspects. Therefore, it was named with *low discomfort group with high*

Fig. 3 Information curve of the 58 items in the optimized conceptual framework for perimenopause assessment. Item *n*: The *n*th item in the conceptual framework. (items order by row.eg: item1-6 in the 1st row)

Table 3 Number of items to be answered in the computer adaptive testing within different precision limitation

	Standard error of the estimated trait scores				
	0.30	**0.35**	**0.40**	**0.45**	**0.50**
Min	58	58	33	21	23
25%	58	58	58	58	58
Median	58	58	58	58	58
Mean	58	58	57.6	56.45	55.35
75%	58	58	58	58	58
Max	58	58	58	58	58

Notes Min: minimum number of items; Max: maximum number of items

positive attitude towards life. For the 3rd class, defined as *high sleep disturbance and mood swings group with low comorbid discomfort*, as vasomotor symptoms and mood swings were the most obvious appearances, and comorbidities were less observed with lower scores. Patients in the 4th Class were labeled as the *moderate discomfort group with high positive attitude towards life* as it showed moderate severity of multidimensional discomforts and the highest score in positive attitude towards life. The property of each profile was plotted as an intuitive display of the estimated model.

To further assist the management of perimenopause, a web page of computer adaptive test on basis of the

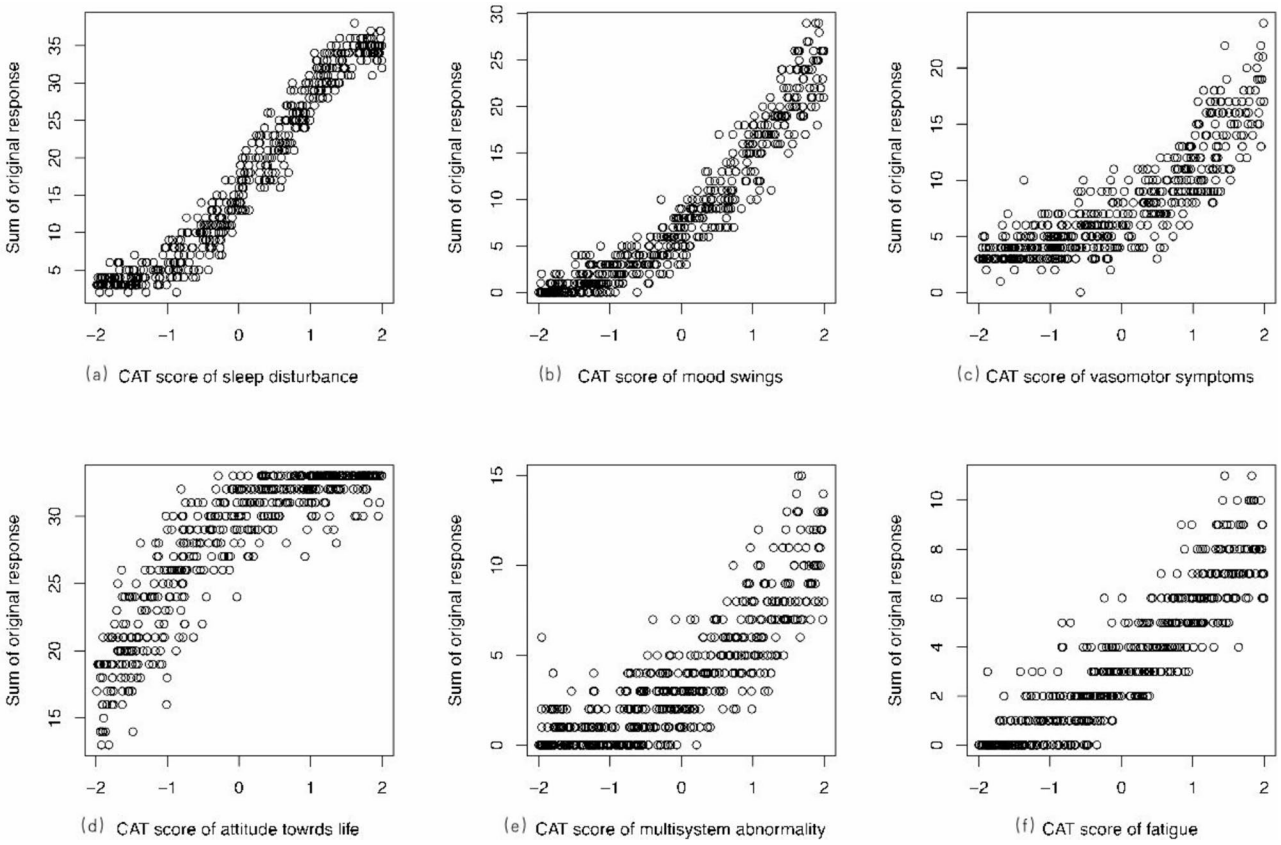

Fig. 4 Scatter plots for the simulated 6 factor scores and cumulated scores of original responses of items. CAT: Computer adaptive test

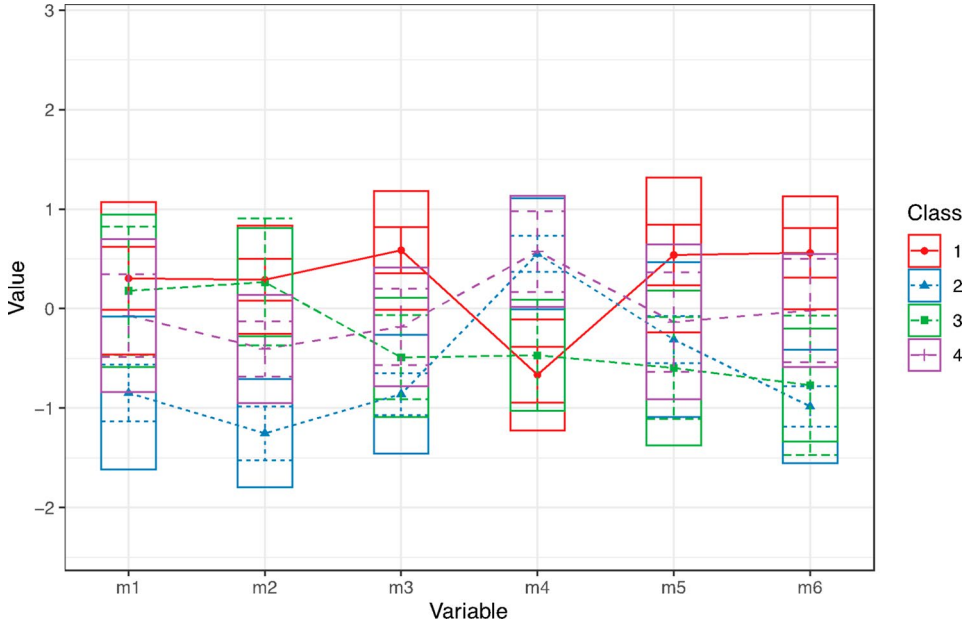

Fig. 5 Four profiles of perimenopause based on computer adaptive testing scores. m1: score of sleep disturbance; m2: score of mood swings; m3: vasomotor symptoms; m4: attitude towards life; m5: multisystem abnormality; m6: fatigue

Table 4 Mean, standard deviation for demographic properties and latent factor scores of the four latent profiles of perimenopause

Characteristic	Profile1 ($n=58$)	Profile2 ($n=30$)	Profile3 ($n=15$)	Profile4 ($n=41$)	*p*
n	58	30	15	41	
Age	49.69±3.55	48.63±3.21	48.53±2.07	49.22±3.03	0.58
Duration of symptoms	21.53±14.85	16.67±12.66	14.87±10.42	19.88±18.05	0.20
BMI	21.96±3.84	22.81±2.73	21.19±4.13	23.17±2.59	0.10
Sleep disturbance	0.32±0.89	-0.89±0.59	0.23±0.63	-0.10±0.72	***
Mood swings	0.28±0.59	-1.29±0.44	0.25±0.55	-0.39±0.53	***
Vasomotor symptoms	0.59±0.65	-0.87±0.53	-0.55±0.49	-0.19±0.57	***
Positive attitude towards life	-0.68±0.64	0.53±0.44	-0.45±0.45	0.67±0.44	***
Multisystem disnormality	0.53±0.84	-0.33±0.69	-0.62±0.56	-0.14±0.84	***
Fatigue	0.55±0.60	-1.01±0.37	-0.87±0.60	0.02±0.56	***

Note ***:<0.001; Profile 1 = severe discomfort group with low positive attitude towards life; Profile 2 = low discomfort group with high positive attitude towards life; Profile 3 = high sleep disturbance and mood swings group with low comorbid discomfort; Profile 4 = moderate discomfort group with high positive attitude towards life

estimated model was programmed to offer interactive interfaces for clinical assessment of patients with perimenopause. Item response history together with multidimensional quantitative result was presented to support interpretation of the assessment procedure and results.

Discussion

It is a conventional research paradigm to assess with different scales in clinical research about psychosomatic disease such as perimenopause [22]. However, mechanically integration of scales without refining conceptual framework brought confusion while interpreting the results of the assessment. As was shown in Table 2, although the validity and reliability of the scales were evaluated as acceptable indicating adequate internal consistency, the independence of traits was not satisfied due to overlapping of intension of items existed among the scales. Since there is no perimenopause-specific multidimensional assessment tool applied in clinical practice, it is of considerable importance for the development of an instrument for evaluating the multidimensional traits of perimenopause. And it is also an alternative approach to reconstruct the conceptual framework of assessment to deal with the situation.

Understanding the varied symptoms experienced by perimenopausal women could assist in creating a more effective diagnostic approach. However, it should be also noticed that comorbidities in this specific stage would introduce more complexity in clinical assessment. In this study, we focus on analyzing the systemic and psychosomatic dimensions of perimenopause. Therefore, symptoms indicating potential endometrial pathologies such as menorrhagia and abdominal pain were not included in the assessment although they are normally reported in research about peri- and postmenopausal women [23].

Attempting to disentangle symptoms and clinical subtypes of perimenopause, a quantitative instrument was developed based on a multidimensional conceptual framework in this study. EFA and CFA were integratively applied to enhance interpretation of the assessment based on both pragmatic and theoretical criteria [24]. An initial item pool containing 60 items within a 6-factor conceptual framework was finally developed for evaluating the density of perimenopause symptoms including vasomotor symptoms, mood swings, attitude towards life, sleep disturbance, multisystem abnormality, and fatigue. By refining items into several independent dimensions, the construct validity was evaluated to be optimized in CFA. As shown in Supplementary Table 2, all items except SAS17 were evaluated with an absolute value of loadings over 0.3. The interpretability of the assessment was enhanced through gathering items with consistent intension into the same factor. However, confusion could be realized in the cluster of items shown in Supplementary Table 2. For example, sexual disorder in sleep disturbance, constipation in mood swings, annoyance in vasomotor symptoms, hand dry and warm in positive attitude towards life, and heartbeats and weight loss in fatigue. The confusion could be resulted from the difference in individual comprehension about item content and assessing intention since all the scales were applied without adequate cross-cultural adaptation. Conservative moral values under influence of the traditional culture of China also played an important role when intimate question such as sex were assessed among Chinese women [25]. Therefore, cross-cultural adjustment is demanded in further research, thereby making optimization of the instrument setting for perimenopause assessment in China.

Psychrometric properties including discrimination and difficulty indices of most items were evaluated to be adequate. However, as to the items including mKI12, SAS17, SDS7, SDS8, and SDS9, mismatching between the option setting and discriminable thresholds of symptom density led to reduction in discrimination of the items. Limitation of sample data is another reason accounting for this phenomenon. It is also essential to make a practical evaluation with representative sample data in a larger

size. Considering the importance of items in the assessment and the demand of further procedure and time-cost to fix this issue, none of the items was removed from the item pool for the CAT in this study. Different from the identification of the different stages of perimenopause in the STRAW+10 [26], subtypes of perimenopause patients were defined according to the scores of latent traits in this study. Subgroups of patients were identified according to the the summarized score of clinical appearances emphatically. Within a multidimensional conceptual framework of assessment, the 4-profile model was evaluated to be of adequacy and interpretability. Characteristics of the profiling also indicated heterogenous patterns of clinical appearance. Patients clustered in Class3 showed higher score in sleep disturbance and mood swings together with a medium to low density of vasomotor symptoms and comorbid somatic symptoms. This subtype could be the characteristics of the early stage of ovarian aging as compensatory hormonal changed in the hypothalamic-pituitary-gonadal axis [27]. There is also another interesting finding that positive attitude seemed to be related to better quality of life for perimenopause. Patients with a higher score in positive attitude towards life were evaluated to be with lower density of both vasomotor symptoms and comorbid discomforts. Oppositely, in Class1, those with lower score in the dimension about the attitude towards life was evaluated to be with higher severity of vasomotor symptoms. And that is consistent with previous studies [28–30]. It was also reported that emotional stability and emotional intelligence were significant resilience factors for the physical health outcome of women. And that played an important role in women's cognitive appraisal and emotional experience of menopausal symptoms [31]. Since the difference in age and duration of symptoms among these subgroups were evaluated to be without statistical significance, the heterogeneity among profiles suggested that both adaptive and individualized approaches should be introduced into the clinical management of perimenopause. BMI was also reported to be associated with scores of menopausal symptom severity and menopausal-specific quality of life [32]. Since the difference in BMI among the subgroups was evaluated to be without statistical significance, no conclusion could be drawn in this study. Since contribution of etiology on the clinical appearances was not entirely parsed out, the causation of the relationship is not yet proved [33]. In the four subgroups, although age, BMI and symptom duration were evaluated to be non-statistically independent, this remind us the possibility to discover whether there are hidden patterns among the perimenopause subgroups with different appearance. However, it is only possible to make this discovery when extensive data from cohort study is available. In further study, inspection results, for example, hormone level, that reported as evidence for disentangling the complex bothersome and overlapping of the symptoms should be included for the model estimation and modification.

As to the efficiency of assessment, compliance of patients and precision of the assessment result were two major problems to be concerned. Compliance plays an important role in the promotion of clinical study especially those with cohort design. With the application of CAT, the number of items used to achieve considerable precision was reduced thus modified the efficiency of assessment. Providing a quantitative instrument for clinical assessment, the CAT also benefited practitioners with an adjustable adaptive assessing procedure to make a comprehensive evaluation of perimenopause patients. However, a larger number of items were required in the multidimensional assessment than that in the unidimensional design. And a larger sample was required for estimating the adequate psychrometric properties. Therefore, the balance between precision and efficiency were to be optimized in further research.

As to our knowledge, this is the first study to develop an instrument for perimenopause assessment through reconstruction over existing scales. To further improve the instrument, many limitations of the research should be addressed. Firstly, the scales used to form the item pool were limited. There were many other scales that used for perimenopause evaluation were to be supplemented after well validating their validity and reliability for regional application. In this way, the completeness and correctness of the items setting and further the conceptual framework could be optimized. As the clinical compliance was concerned due to the numerous items to be answered in assessment, CAT would then serve as a more efficient strategy. Secondly, the average age of the participants was about 49 in range from age 45 to 60 and that perimenopause commence 8–9 years prior to menopause, many women in the earlier stages of perimenopause may have been excluded in this study. Therefore, the CAT estimated in this study may be appropriate for capturing later stages of perimenopause. And re-validation with an optimized clinical design is required for further application of the instrument in clinical practice. Thirdly, since only clinical appearances were recorded as resources for subtyping the perimenopause patients, the interpretability between and within the subgroups was limited. Inspection evidence in a more microscopic scale should be taken into account for discovering the potential multiscale pattern of perimenopause. In this way, the interpretability of the causation underlying the mixture clinical appearance could be strengthened. Last but not least, with a cross-sectional design, the sample size of the study was so limited that extrapolation of the results is to be re-validated. Further research should be carried out with a large cohort study of perimenopause.

And we hope the methodological paradigm proposed in this study could be further optimized for comprehensive assessment for perimenopause.

Conclusion

This study applied multivariable analysis to propose a methodological paradigm for understanding the heterogeneous clinical presentations of perimenopause. Using advanced analytical approaches, such as factor analysis to reduce assessment dimensions and identify latent traits, MIRT to estimate multidimensional psychometric properties, and CAT to adaptively quantify individual latent trait scores, an individualized comprehensive assessment framework was developed. Latent profile analysis further identified 4 potential subgroups of perimenopause based on the means and variances of the six traits: sleep disturbance, mood fluctuations, vasomotor symptoms, positive attitude towards life, multisystem abnormality, and fatigue. In this way, this data-driven subgrouping model captured the heterogenous of psychosomatic properties in perimenopause. It also offered a foundation for refining clinical management strategies and personalizing care for perimenopausal patients.

Abbreviations

AIC	The Akaike information criterion
BIC	Bayesian information criterion
BLRT	Bootstrapped likelihood ratio test
BMI	Body Mass Index
CAT	Computer adaptive test
CFA	Confirmatory factor analysis
CFI	Comparative fit indices
CMIN	Chi-Square Minimum Discrepancy
df	Degree of freedom
EFA	Exploratory factor analysis
GFI	Goodness of fit indices
ISI	Insomnia severity index
KNN	k-nearest neighbors
LMR	Lo-Mendell-Rubin
LMR	Lo-Mendell-Rubin test
LPA	Latent profile analysis
MIRT	Multidimensional item response theory
mKI	Modified Kupperman index
RMR	Root Mean Square Residual
RMSEA	Root mean square error of approximation
SABIC	Sample size-adjusted Bayesian information criterion
SAS	Self-rating anxiety scale
SDS	Self-rating depression scale
STRAW	Stage of reproductive aging workshop
TLI	Tucker-Lewis index
$\chi 2$	Chi-square

Supplementary Information

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Supplementary Material 1

Author contributions

ZY.H, HZ.Y, ZP.L, LJ.L and YJ.H contributed toward the concept, data analysis, and manuscript writing, and manuscript review; S.W, XQ.Z, CY.Z, MQ.L contributed toward data collection. ZY.H, YJ.H contributed towards funding, data collection, concept and manuscript review. ZY.H, H.Y, HZ.Y, ZP.L, LJ.L and YJ.H contributed towards manuscript revision and review.

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Data availability

The data used to support the findings of this study are available from the corresponding author(mail: miracle_he@126.com) upon request.

Declarations

Ethics approval and trial registration

All patients enrolled in this study signed informed consent. This study was approved by the Ethics committee of Guangzhou Women and Children's Medical Center (NO.2021/028A01) in accordance with the Declaration of Helsinki. The research protocol was registered in The Chinese Clinical Trial Registry with registration number ChiCTR2100052587(2021-10-31).

Data sharing statement

The data used to support the findings of this study are available from the corresponding author(mail: miracle_he@126.com) upon request.

Competing interests

The authors declare no competing interests.

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