



# An evidence-based validation of traditional Chinese medicine syndromes<sup>☆</sup>

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## KEYWORDS

Kidney deficiency syndrome;  
Menopause;  
Factor analysis;  
Structural equation modelling;  
Acupuncture

## Summary

**Objectives:** A standard description regarding the diagnosis of traditional Chinese medicine (TCM) syndromes based on validated evidence is needed for education, practice and evaluation of TCM syndrome-specific treatments. We studied whether an evidence-based four-step approach proposed for the validation of TCM syndromes could validate Kidney-Yin deficiency syndrome (KDS-Yin) and Kidney-Yang deficiency syndrome (KDS-Yang) in middle-aged women with menopausal symptoms.

**Methods:** TCM classic and contemporary literature were reviewed for the symptoms and the domain changes of KDS-Yin and KDS-Yang. Factor analysis was used to explore whether these symptoms could be grouped according to their mutual relationships in a sample of women. Latent tree models were constructed based on the factor loadings and justifiability by the theory, and were tested by structural equation modelling on another sample of women.

**Results:** The symptoms and domain changes were reviewed from the TCM literature. Exploratory factor analysis (EFA) identified symptom patterns on a sample of 236 women. Based on the findings and the TCM literature, latent tree models of KDS-Yin and KDS-Yang, showing their domain changes and domain symptoms, were constructed and could be confirmed by structural equation modelling on a sample of 323 women.

**Conclusion:** KDS-Yin and KDS-Yang in middle-aged women with menopausal symptoms were validated and the four-step approach may be used to validate TCM syndromes.

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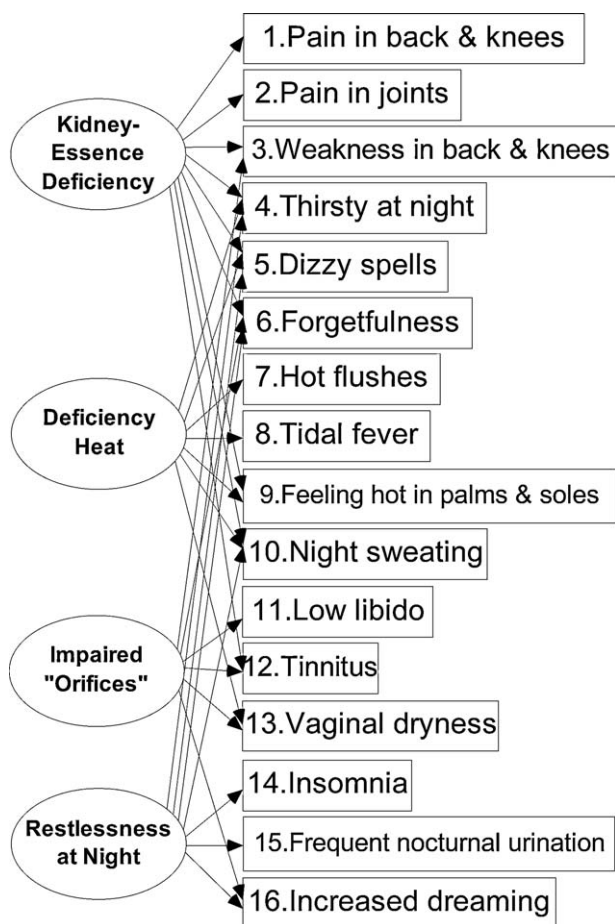
## Introduction

Traditional Chinese medicine (TCM) applies Chinese ancient philosophies to discover knowledge regarding health.

Guided by the TCM theory, a medical condition may be differentiated into the TCM syndromes of Yin, Yang, excess, deficiency, cold, heat, etc., and the condition is managed by a TCM syndrome-specific treatment.<sup>1</sup> TCM theory comprises schools of thought<sup>2</sup> and TCM syndromes are defined by expert opinion,<sup>1,3,4</sup> which may explain why the description of syndrome is vague and varies in TCM textbooks and references.<sup>5</sup> Consensus on diagnostic theory is low<sup>1–5</sup> and diagnosis is subjective which is believed to have contributed

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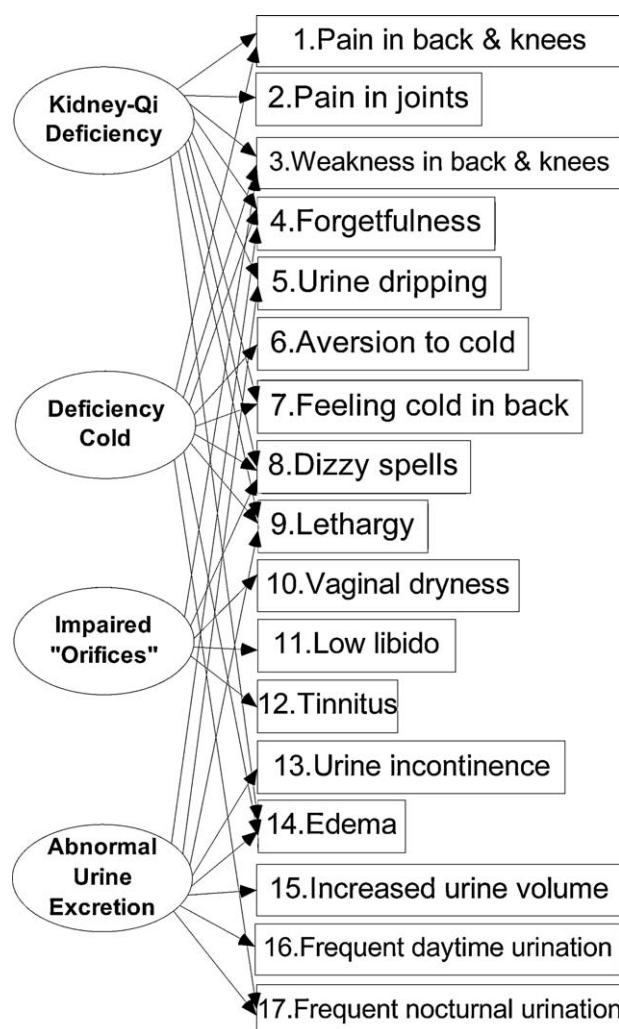


**Figure 1** The symptoms and the domain changes of KDS-Yin. Construction of this model was based on the four symptom factors (factor 1, items 1–6; factor 2, items 7–10; factor 3, items 11–13; factor 4, items 14–16) and the factor loadings were identified by EFA in the second step, and the theory was reviewed in the first step.

to the low diagnostic consistency of about 30% among TCM practitioners.<sup>6</sup> This makes it difficult to interpret and repeat TCM syndrome-specific treatments reported in clinical trials.

For decades, TCM experts have attempted to standardise terminology and description of TCM syndromes based on expert opinion.<sup>1,3,4,7</sup> However, as Birch et al. have reported,<sup>5</sup> consensus on the description of TCM syndromes is found to be low in the literature,<sup>1,3,4,7</sup> indicating that experts have different opinions regarding the standardisation of TCM syndromes.

Alternatively, researchers have attempted to validate TCM syndromes with statistical methods<sup>8–10</sup> based on which TCM syndromes can be presented as latent tree models.<sup>8</sup> A latent tree model shows its latent variables each of which manifests with, or is measured by, multiple observed variables.<sup>11</sup> In the case of a TCM syndrome, the domain changes in TCM pathogenesis are the latent variables and the domain symptoms are the observed variables (Figs. 1 and 2). Validation of TCM syndromes may be confirmed by structural equation modelling (SEM)<sup>9</sup> or explored by exploratory factor analysis (EFA).<sup>10</sup> SEM is a powerful statistical method



**Figure 2** The symptoms and the domain changes of KDS-Yang. Construction of this model was based on the five symptom factors (factor 1, items 1–5; factor 2, items 6–9; factor 3, items 10–12; factor 4, items 13–15; factor 5, items 16 and 17) and the factor loadings were identified by EFA in the second step, and the theory was reviewed in the first step. The domain “abnormal urine excretion” had merged factors 4 and 5, for they were found to be highly correlated (>0.90).

used to confirm models of hypothesis constructed, based on theory or data, to compare alternative models and to develop models.<sup>11</sup> In practice, researchers define the latent tree model of a syndrome by referring to TCM literature and expert opinion, and validation is determined by whether this model can be confirmed by SEM on a clinical sample.<sup>9</sup> In exploratory validation, researchers attempt to discover simple patterns among the many more-or-less related symptoms of a syndrome by EFA or to construct the latent tree model of a syndrome by machine learning on a clinical sample.<sup>8,10</sup> Validation is determined by experts regarding whether the symptom patterns or the model corresponds to the characteristics of the syndrome.

However, it is not possible to establish a uniform model of syndrome from TCM literature for confirmatory validation, whereas exploratory validation is still determined by expert opinion. Further, weaknesses are observed in these studies:

some symptoms of other syndromes were included into the syndrome of study; no measures were used to ensure the reliability of clinical information gathered despite the fact that clinical signs, subjectively assessed by TCM practitioners, may not be reliable<sup>6,12</sup> and the sample sizes were small or not justified in some of the studies. These data may be biased, but can still be interpreted as corresponding to the TCM theory.

We propose a four-step approach for an evidence-based validation of TCM syndromes: to review TCM classic and contemporary literatures for the domain symptoms and changes of a syndrome; to explore the symptom patterns of the syndrome by EFA on the symptoms reviewed; to construct latent tree models of the syndromes based on the EFA data, provided that the models are justifiable by the TCM theory; and to test whether the models can be confirmed or rejected by SEM.

The present study attempted to find out whether this four-step approach could be used to validate Kidney-Yin deficiency syndrome (KDS-Yin) and Kidney-Yang deficiency syndrome (KDS-Yang) in Hong Kong Chinese women, aged 40–60 years, with menopausal symptoms.

Menopause is the permanent cessation of menstrual periods.<sup>13</sup> Based on TCM gynaecology described in the classic literature,<sup>14</sup> the contemporary textbook for tertiary education<sup>15</sup> and a TCM expert opinion on menopause,<sup>16</sup> Kidney deficiency explains the occurrence of menopause in middle-aged women. Kidney deficiency primarily includes KDS-Yin, KDS-Yang and their concurrent existence (KDS-YY).<sup>1,3,4,7</sup> KDS is found to be prevalent in women aged 40 years and older, and increases with age.<sup>17</sup> KDS-Yin is common in women with menopausal hot flushes.<sup>18</sup> KDS-Yin starts to increase in middle-aged women from pre-menopausal to perimenopausal years, whereas KDS-Yang increases in their post-menopausal years and KDS-YY is most prevalent in all menopausal women.<sup>16</sup> KDS-Yin, KDS-Yang and KDS-YY are the basic TCM syndromes of menopausal symptoms.<sup>15,16</sup>

## Methods

Human research ethics approval was obtained from Institutional Review Board of the University of Hong Kong and Hospital Authority, Hong Kong West Cluster and written informed consents were obtained from the study participants.

### Participants and screening of menopausal symptoms

We recruited Chinese women aged 40–60 years, whose primary residence was in Hong Kong, and who could read and write Chinese for questionnaire evaluation. Women were excluded if they had life-threatening diseases, traumatic injuries or were currently taking anti-inflammatory, hormone replacement therapy or Chinese medicines because the inclusion of such women would confound the interpretation of the symptom reporting. As the study design did not allow for hormonal measurements to be performed, we took a pragmatic approach to classify women as pre-menopausal, if their self-reported menstrual periods had been regular; perimenopausal, if their self-reported men-

strual periods had been irregular or absent for less than 12 months; post-menopausal, if their self-reported menstrual periods had been absent for 12 months or longer and induced menopause for women, who had undergone hysterectomy or ovariectomy.

The present study was part of a project studying menopause and Chinese medicine, for which we conducted a health seminar and a postal survey. We recruited a sample of women from attendants of the seminar, who were respondents to a newspaper article describing the study, and another sample of women from the survey, who were respondents to a second newspaper article about the research. These samples of women were screened for menopausal symptoms using the 21-item standard Greene Climacteric Scale (GCS) (Hong Kong Chinese)<sup>19</sup> and a three-item urogenital scale.<sup>19,20</sup> Women, who reported to have either mild, moderate or severe grades to any of the 24 menopausal symptoms, were included in the tests.

### The four-step approach

The first step was reviewing the TCM theory and questionnaire construction. The symptoms and domains of KDS-Yin and KDS-Yang were reviewed from TCM classic<sup>14</sup> and the contemporary literature widely used in TCM education, practice and research: the textbook for TCM tertiary education on diagnosis,<sup>1</sup> the China national standard on diagnosis of TCM syndromes,<sup>3</sup> the guidelines for TCM clinical research<sup>4</sup> and the World Health Organization (WHO) international standard terminologies on TCM.<sup>7</sup>

We constructed a KDS item-reduction list by including the symptoms of KDS-Yin and KDS-Yang described in these classic and contemporary literature.<sup>1,3,4,7,14</sup> The first author and the third author, who had over 20 years experience in TCM teaching, research and practice, identified items for a KDS questionnaire, aiming to improve content validity. The items included were those directly related to KDS-Yin and KDS-Yang in middle-aged women. The items excluded were those directly related to syndromes other than KDS-Yin and KDS-Yang; those having a weak consensus in the literature (i.e., listed in only one or two of the references)<sup>1,3,4,7,14</sup>; and the small number of signs appearing in the contemporary literature,<sup>1,3,4,7</sup> but not in the classic literature.<sup>14</sup> Exclusion of the signs facilitated a patient-reported outcome (PRO) design of the KDS questionnaire. The items included were given indicative guidelines for severity scores ranging from 0 (absent) to 1 (mild), 2 (moderate) and 3 (severe), and pilot-tested on 10 participants, who fulfilled the inclusion and exclusion criteria. Finally, three senior TCM experts, who had over 40 years experience in TCM teaching, research and practice, reviewed the items for appropriateness and completeness for content validity.

The second step was an exploratory test of TCM syndromes. We administered the KDS questionnaire, together with the GCS and the urogenital scale, to the seminar sample of women. The symptom characteristics of KDS-Yin and KDS-Yang were explored by EFA on data.

The third step was model construction. Based on the symptom patterns and the factor loadings (an EFA index showing the strength of correlation of a symptom and a symptom pattern) identified by the EFA, we constructed

the latent tree models of KDS-Yin and KDS-Yang showing their domains and domain symptoms. These models would be adopted if they were justifiable by the theory<sup>1,3,4,7,14</sup>; if not, we would reject the models.

The fourth step was model validation by SEM. The participants of the survey were sent a copy of the subject information sheet, the subject consent form, the KDS questionnaire, together with the GCS and the urogenital scale and a stamped reply envelope.

### Statistical analysis

EFA was used to discover simple patterns among the many more- or less-related symptoms of KDS-Yin or KDS-Yang in the second step because the domains and domain symptoms had not been determined previously and there was no general agreement in the theory.<sup>21</sup> The symptom patterns (factors) were yielded with eigen values exceeding unity and were obtained by Varimax rotation with Kaiser normalisation.<sup>22</sup> The sample size was estimated from 4 to 10 participants per variable, with a minimum number of 100 to ensure stability of the variance–covariance matrix.<sup>23</sup> We recruited over 200 participants to increase the chance of reproducing the factor pattern in the population.<sup>24</sup>

For model testing by SEM in the fourth step, the sample size was estimated with the rule of thumb of 10–20 cases per measured variable,<sup>25</sup> and many studies used the sample sizes of 200–500 in the literature.<sup>26</sup> The sample size would be adequate for testing the models if the models' Hoelter's critical *N* values were greater than 200 at the 0.01 levels of significance.<sup>27</sup> The models could be confirmed if the comparative fit index (CFI) and the incremental fit index (IFI) were  $\geq 0.09$ ,<sup>11,27</sup> and the root mean square error of approximation (RMSEA) was  $\leq 0.05$ <sup>11,27,28</sup> and 90% confidence interval (CI) of RMSEA ranged from 0 to 0.08.<sup>11</sup> Otherwise, the models would be rejected.

Data were processed by statistical package for social science (SPSS) 16.0 and asset management operating system (AMOS) 16.0. In the fourth step, missing data were handled in AMOS. AMOS uses maximum likelihood imputation to estimate means and intercepts for missing data, which several studies have shown to have the least bias than other approaches, in handling missing data.<sup>29</sup>

### Results

Of the 311 women who attended the seminar, 294 were invited to complete the KDS questionnaire, the GCS and the urogenital scale after excluding 17 women, who were on medications ( $n=16$ ) or younger than 40 ( $n=1$ ). To process the data with EFA, the returned KDS questionnaires with missing data ( $n=4$ ) and no response to the question on libido because of the absence of a sex partner ( $n=54$ ) were excluded. Except for marital status, the demographic characteristics for those who did ( $n=236$ ) and did not ( $n=54$ ) complete the question pertaining to libido were similar. In the survey, 435 women were sent the survey documents, and 343 sets of the documents were returned. After excluding eight sets not delivered due to incorrect mailing address, the response rate was 78.5%. Of the returned KDS questionnaires ( $n=335$ ), 12 were excluded due to missing data ( $n=3$ ),

**Table 1** Demographic characteristics of the samples.

	Seminar ( $n=236$ )	Survey ( $n=323$ )
Age (mean (SD) years)	49.7 (4.8)	48.2 (5.6)
BMI (kg/m <sup>2</sup> , mean (SD))	22.2 (2.8)	22 (2.8)
Menopausal status		
Pre-menopausal	25.8%	46.7%
Perimenopausal	33.5%	21.1%
Post-menopausal	33.0%	24.8%
Hysterectomy	4.7%	2.8%
Ovariectomy	3.0%	4.6%
Marital status		
Now married	90.3%	71.1%
Not married	9.7%	28.9%
Educational level		
Primary	14.0%	11.2%
Secondary	69.5%	63.3%
Tertiary	16.5%	25.5%
Employment		
Employed	39.8%	74.5%
Retired/house wife/ unemployed	60.2%	25.5%

Between the samples, BMI and education were similar ( $p > 0.05$ ) but age, menopausal status, marital status and employment were different ( $p < 0.05$ ). SD, standard deviation.

blank scales marked with 'not suitable' ( $n=4$ ), women being younger than 40 ( $n=2$ ) or older than 60 ( $n=3$ ).

All the women were identified with menopausal symptoms as measured by the 21-item GCS and the three-item urogenital scale. The median symptom score (range) was 18 (2–49) for the seminar sample ( $n=290$ ) and 17 (1–43) for the survey sample ( $n=323$ ). Demographic characteristics of the samples are shown in Table 1.

### The four steps

In the first step, discrepancies on the symptoms of KDS-Yin and KDS-Yang were found in the literature.<sup>1,3,4,7,14</sup> We included 39 symptoms for a KDS item-reduction list after excluding the items appearing only in children (retarded growth and development), men (impotence, nocturnal emission, premature ejaculation and infertility) and women of reproductive stage (infertility and oligomenorrhoea), and the signs that required TCM practitioners' assessment of the pulse, tongue and facial complexion (KDS-Yin: reddened tongue with scanty coating, rapid and fine pulse; KDS-Yang: pale facial complexion, pale tongue, deep and weak pulse).<sup>1,3,4,7</sup> Of the 39 items, we excluded nine that were recognised to be directly related to the syndromes of other visceral organs or causes but not the kidney and have weak consensus in the literature<sup>1,3,4,7,14</sup> (lung: cough, asthmatic breathing; heart: fearfulness; spleen: loose stools, bowel incontinence; cold invasion: stiffness in the low back or knees; excess heat: constipation, high libido; and excessive water intake: clear urine).

The remaining 30 items were pilot-tested on 10 women, who were teachers, office clerks and housewives conveniently recruited, and they recalled to have experienced 23



of the items in the past month, except vaginal dryness and the six items usually observed in old women and men (hearing impairment or loss, hair turning grey and wither, hair loss, dried teeth, loose teeth and teeth fall). Since vaginal dryness is reported by Hong Kong Chinese women aged 40–60 years,<sup>20</sup> we included vaginal dryness and the 23 items to the KDS questionnaire aiming to assess KDS-Yin (Fig. 1) and KDS-Yang (Fig. 2) in the participants. Finally, the three senior TCM experts approved the KDS questionnaire.

We found the description on the domain changes of KDS-Yin and KDS-Yang to be unclear and imprecise in the classic and contemporary literature.<sup>1,3,4,7,14</sup> We interpreted the literature as follows: Kidney-Essence deficiency and Kidney-Qi deficiency were the essential domains of KDS-Yin and KDS-Yang, respectively. KDS-Yin might also include the domains of deficiency heat and restlessness at night. KDS-Yang might also include the domains of deficiency cold and abnormal water metabolism and urine excretion. The ears and the genitals that are termed as the Kidney 'orifices' might be impaired by Kidney-Essence deficiency or Kidney-Qi deficiency.

In the second step, EFA on the seminar sample ( $n=236$ ) identified four symptom factors for KDS-Yin (Fig. 1) and five symptom factors for KDS-Yang (Fig. 2). With reference to the theory,<sup>1,3,4,7,14</sup> the four factors of KDS-Yin were found to correspond to Kidney-Essence deficiency, deficiency heat, impaired Kidney orifices and restlessness at night; whereas the five factors of KDS-Yang corresponded to Kidney-Qi deficiency, deficiency cold, impaired Kidney orifices, abnormal water metabolism and abnormal urine excretion. Kidney-Essence deficiency or Kidney-Qi deficiency was found to have accounted for about 25% of the variance in the data set and the other domains accounted for less than 10%, indicating that these two domains were more important than the other domains. On the other hand, 'loose stools' included as a control item was not found to group with any of the domains. An initial EFA on the data, without vaginal dryness, showing the same patterns has been reported elsewhere.<sup>30</sup>

In the third step, we constructed two latent tree models showing the relationships between the domains and the domain symptoms of KDS-Yin (Fig. 1) and KDS-Yang (Fig. 2). In KDS-Yang, the domain 'abnormal urine excretion' was formed by merging 'water metabolism' and 'urine excretion' because they were found to be highly correlated ( $>0.90$ )<sup>31</sup> in an initial modelling, and the merge was justifiable by the TCM theory.<sup>1,3,4,7,14</sup> Some of the symptoms were connected to two or more domains because these symptoms were found to be highly related with the domains based on the EFA factor loadings, and these multi-collinear relationships were justified by the TCM theory.<sup>1,3,4,7,14</sup>

In the fourth step, the sample size ( $n=323$ ) was found to be adequate for testing the models because the models' Hoelter's critical  $N$  values were all  $>200$  at the 0.05 and 0.01 levels of significance.<sup>11</sup> The model of KDS-Yin (Fig. 1) could be confirmed by the data (CFI, 0.96; IFI, 0.96; RMSEA, 0.04; 90% CI of RMSEA, 0.02–0.05). The correlation coefficients between the domains ranged from 0.40 to 0.86. The model of KDS-Yang (Fig. 2) could also be confirmed by the data (CFI, 0.90; IFI, 0.90; RMSEA, 0.05; 90% CI of RMSEA, 0.04–0.06). The correlation values between the domains ranged from 0.17 to 0.58.

## Discussion

We propose a four-step approach for evidence-based validation of TCM syndromes and report that KDS-Yin and KDS-Yang in Hong Kong Chinese women aged 40–60 years with menopausal symptoms can be validated with the four-step approach. TCM syndromes that can be presented as latent tree models may be validated with the four-step approach.

The four-step validation of TCM syndromes is determined by evidence because scientific evidence is recognised to be the higher form of knowledge in comparison with authority and experience.<sup>31</sup> This is a more rigorous design than the exploratory validation determined by expert opinion.<sup>8,10</sup> Further, we use both expert opinion and the EFA data to construct evidence-supported and theory-justifiable latent tree models of TCM syndromes, whereas the confirmatory validation is based only on expert opinion to construct latent tree models.<sup>9</sup>

We attempted to review the 'original TCM theory' of KDS-Yin and KDS-Yang from TCM classic literature in Huangdi's *Internal Medicine* that is recognised to have established the foundation of TCM theory.<sup>14</sup> TCM schools of thought produced by scholars of the past 2000 years<sup>2</sup> and the TCM contemporary literature compiled by groups of experts, who have national or international fame in TCM,<sup>1,3,4,7</sup> are based on the classic literature.<sup>14</sup> These references<sup>1,3,4,7,14</sup> were carefully selected from a long list of TCM publications because they had been most widely used in TCM education, practice and research, and thus might be considered as representative of TCM theory for the study of KDS-Yin and KDS-Yang. Guidelines for the selection of TCM references are yet to be established in future studies.

We set criteria to exclude symptoms that are not directly related to the syndromes of study from all symptoms and signs listed in the literature.<sup>1,3,4,7,14</sup> Those symptoms excluded may be tested to determine if the exclusion is supported by evidence, especially for symptoms that are unclear, as whether to include or exclude to validation. For instance, the present study tested 'loose stools' as a control item in the EFA that was not found to be grouped with any domain of KDS-Yang as defined in the textbook.<sup>1</sup> We interpreted the finding as 'loose stools' to be rather directly related to spleen deficiency, and that was justifiable by other literature.<sup>3,4,7,14</sup>

The four-step validation will improve consensus on TCM syndromes for diagnosis and assessment in practice, research and education. There are limitations in the interpretation of our report.

The participants were found to have experienced menopausal symptoms. All the women were respondents to news articles about the study and were interested in having a consultation or increasing their knowledge of menopause in Chinese medicine. These women were found to have experienced more severe menopausal symptoms than a community sample of Hong Kong Chinese women aged 40–60 years<sup>20</sup> and thus were a symptomatic health-seeking group of women. Validation of KDS-Yin and KDS-Yang in these women may not be generalisable to children, men and women of reproductive and aged stages. Whether this validation can be generalised to middle-aged women without menopausal symptoms is subject to study.

That Kidney deficiency causes permanent cessation of menstrual periods in middle-aged women is documented in Huangdi's *Canon of Internal Medicine*<sup>14</sup> and in contemporary literature.<sup>15,16</sup> This opinion is challenged by another expert opinion that Kidney deficiency causing menopause is a product of modernisation of TCM by copying oestrogen deficiency of menopause in biomedicine during the China Cultural Revolution.<sup>32</sup> We compared KDS-Yin and KDS-Yang by menopausal status on women pooled from the seminar sample and the survey sample because the difference of symptoms by the GCS domains and the KDS domains were not found to be statistically significant between the samples by menopausal status ( $p > 0.05$ ). Our data show that the domains of KDS-Yin and the domains of KDS-Yang were more severe in the post-menopausal women ( $n = 191$ ) and the perimenopausal women ( $n = 145$ ) than in the pre-menopausal women ( $n = 225$ ) ( $p < 0.001$ ), except restlessness at night of KDS-Yin and deficiency cold of KDS-Yang ( $p > 0.05$ ). Women, who had hysterectomy ( $n = 27$ ), ovariectomy ( $n = 23$ ) and missing data on the GCS ( $n = 2$ ), were excluded from this comparison. This finding supports Kidney deficiency and the menopause described in the TCM literature.<sup>14–16</sup> Future studies may examine this issue with larger samples of participants.

The KDS questionnaire was developed with a PRO design because the KDS domains could be measured only by the self-reporting symptoms (Figs. 1 and 2) and the reliability of signs assessed by TCM practitioners was low or uncertain.<sup>6,12</sup> The PRO design has been shown to improve the reliability of clinical information.<sup>33</sup> We may include the signs to study when diagnostic methods for the assessment of signs with confirmed reliability are available.

We conveniently recruited 10 participants to the pilot test. This small sample size limited our ability in the initial evaluation of items that could measure KDS-Yin and KDS-Yang in the participants. Future studies may recruit more participants for the pilot test.

## Conclusion

The four-step approach proposed for the validation of TCM theory is evidence-based. KDS-Yin and KDS-Yang in Hong Kong middle-aged women with menopausal symptoms were validated with the four-step approach. TCM syndromes that can be presented as latent tree models may be validated with the four-step approach.

## Conflict of interest statement

The authors are academic and teaching staff of The University of Hong Kong. No competing financial or other interests exist.

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