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Correlation between menopausal symptoms and everyday cognition in Chinese (peri)menopausal women

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ABSTRACT

Objective: The aim of this study was to evaluate the relationship between the severity of menopausal symptoms and everyday cognitive decline in Chinese peri and postmenopausal women.

Methods: The peri and postmenopausal Chinese Han female who first visited the menopausal clinic of Shanghai Jiao Tong University Affiliated Sixth People's Hospital was selected as the study participants. The general questionnaire was used to obtain the sociodemographic characteristics of the study participants. The menopausal rating scale (MRS) was used to assess the severity of menopausal symptoms. The short version of the Everyday Cognition (ECog-12) scales was used to assess everyday cognitive performance.

Results: A total of 295 women were included, with an average age of 51.12 ± 5.15 years. The average ECog scores were 1.51 ± 0.49 and the average MRS scores were 6.89 ± 4.77. In multiple linear regression analysis, after adjusting for confounding factors age, body mass index (BMI), monthly income, occupational status, education level, menopausal status, parity, regular exercise, and history of chronic diseases, complaints of anxiety and physical/mental fatigue were positively correlated with everyday cognitive decline.

Conclusions: Menopausal anxiety and physical/mental fatique were the independent predictors of everyday cognition.

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KEYWORDS

Menopausal symptoms; everyday cognition; Chinese women

Introduction

After entering the menopausal transition period, with the fluctuation and decrease of estrogen level, women have a series of symptoms, including hot flashes and night sweat, sleep disturbance, mood disorders and urogenital atrophy, and so on [1]. A large-scale study from 20 provinces in China showed that the five most common menopausal symptoms in peri and postmenopausal women were fatigue (75.84%), insomnia (69.39%), irritability (67.02%), palpitation (62.78%), and melancholia (61.88%). The prevalence of hot flashes and sweating was 43.51% and 42.61%, respectively. Among the 14 symptoms evaluated by the modified Kupperman Menopausal Index scale, the prevalence was higher than 40%, except for the symptom of formication (19.92%) [2]. It can be seen that most Chinese menopausal women suffer from menopausal symptoms. However, due to the lack of understanding of menopause and the fear of menopausal hormone therapy (MHT), most Chinese menopausal women do not treat menopausal symptoms in time and actively, which may seriously affect their quality of life.

The risk of cognitive impairment may increase after entering menopausal transition [3-5]. The causes of cognitive decline during menopause, however, are still not clear. Menopauseassociated symptoms (e.g. hot flashes, depression, anxiety, and sleep disorders) may be the basis for these cognitive changes independently or cumulatively. The results of studies about the relationship between menopausal symptoms and cognitive decline are inconsistent. One study showed that subjective reported hot flashes were related to cognitive decline [6], while another study [7] showed that only hot flashes measured objectively were related to verbal memory. Studies assessing the effect of depressive symptoms on processing speed are conflicting, consistent with either a positive association [8], or a lack of association [9]. In addition, menopausal symptoms rarely occur independently and are often multiple concurrent. The interaction of menopausal symptoms suggests that the adverse effects of menopausal symptoms on cognitive function are more complex.

A limited number of studies assessing the correlation between menopausal symptoms and cognitive function, especially in Chinese mainland women. In order to make the conclusion that the severity of menopausal symptoms has an adverse effect on cognitive function more comprehensive and reliable, the purpose of this study is to evaluate the correlation between the severity of menopausal symptoms and cognitive decline in peri and postmenopausal Chinese women at a clinic setting.

Method

Sample

Women who first visited the menopausal clinic of Shanghai Sixth People's Hospital from October 2018 to October 2019 were

enrolled. Inclusion criteria: (1) 40-65 years old; (2) perimenopausal (consecutive irregularities for >7 d of their normal cycle), early postmenopausal (at least 12 months amenorrhea, but <5 years), or late postmenopausal (>5 years amenorrhea) women [10,11]; (3) no history of tumor, uncorrected thyroid disease, neurogenic/psychiatric disease, and serious head injury; and (4) no history of MHT. Exclusion criteria: (1) irregular bleeding in menstrual cycle due to polycystic ovary syndrome or other reasons; (2) pregnancy or lactation; (3) smoking or drinking chronically; and (4) missing data. Finally, 295 women were included in this study. This study protocol was approved by the ethics committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital (ethical batch number: 2020-R05). Informed consent has been signed by all study participants.

Sociodemographic variables

The sociodemographic characteristics were obtained using a general questionnaire, which was administered by well-trained staff through face-to-face interview with the study participants. The questionnaire included questions variables of age, height, weight, monthly income, occupational status, education level, menopausal status, parity, regular exercise, and history of chronic disease. Body mass index (BMI)=body weight (kg)/height² (m²).

Menopausal symptoms

The severity and intensity of menopausal symptoms are assessed using the menopausal rating scale (MRS) [12]. MRS is composed of 11 items, including hot flashes, heart discomfort, sleep disturbance, depressive mood, irritability, anxiety, physical/mental fatigue, sexual problems, bladder discomfort, vaginal dryness, and joint and muscle discomfort. For each item, a scale of 0-4 points is used to evaluate the severity of the complaint (0: none; 1: mild; 2: moderate; 3: severe; and 4: very severe). The total score of MRS is the sum of the scores of each item. The severity of menopausal symptoms is divided into 4 degrees based on the MRS scores: 0-4 points are asymptomatic, 5-8 points are mild, 9-15 points are moderate, and ≥ 16 points are severe [13]. In addition, consistent with the study of Jaff et al. [9], we also evaluated the MRS six symptoms related to cognition (hot flashes, sleep disturbance, depressive mood, irritability, anxiety, and physical/mental fatigue).

Everyday cognition

Everyday Cognition (ECog) scales are an informant-rated questionnaire designed to assess cognitive decline. This study used a short version of ECog scales (12 items) [14]. The short version of ECog can well identify dementia people and normal people (AUC under ROC curve = 0.95, CI = 0.94 \sim 0.97), and it is hoped that normal elderly people can be identified from those with cognitive impairment (mild cognitive impairment or dementia). The correlation between the ECog-12 and demographic variables (age and education level) can be ignored, and the correlation coefficients with age and education are 0.03 and 0.01, respectively. For each item, informants compare the patient's current level of functioning with his or her abilities 10 years ago. The ECog-12 divides the degree of cognitive decline into four grades: 1 = better or no change compared to 10 years earlier, 2 = questionable/occasionally worse, 3 = consistentlya little worse, and 4 = consistently much worse. In addition, the option 'don't know' is reserved. Add the scores of all completed items to get a total score, and then divide by the number of completed projects. The range of total scores is 1-4. A higher ECog score indicates worse every day cognitive performance.

Statistical analysis

Data are expressed as mean (M) ± standard deviation (SD), number (N), or percentage (%). Kolmogorov-Smirnov test is used to evaluate whether the variables are normally distributed. Mann-Whitney (two independent samples) or Kruskal-Wallis H (multiple independent samples) tests were used to compare between groups. Spearman rank correlation test was used to evaluate the correlation between the six categories of MRS and ECog scores. Multiple linear stepwise regression analysis was used to further evaluate menopausal symptoms related to everyday cognitive function (ECog scores). SPSS version 22.0 software (SPSS Inc., Chicago, IL) was used for data analysis, and p<.05was set as statistically significant.

Results

Table 1 presents sociodemographic characteristics of the study participants. The average age of 295 women was 51.12 ± 5.15 years old and 70.2% of them lay in the 40-55 age group. The average BMI was 22.24 ± 2.87 kg/m² and 4.4% of the

Table 1. Sociodemographic characteristics of the study participants.

Variables	$M \pm SD$ or N (%)	p Value*	
Age (years)	51.12 ± 5.15		
40–44	26 (8.8)	_	
45–55	207 (70.2)	_	
56–65	62 (21.0)	_	
Body mass index (kg/m ²)	22.24 ± 2.87	.907ª	
<18.5	17 (5.8)	_	
18.5–23.9	210 (71.2)	_	
24–27.9	55 (18.6)	_	
≥28	13 (4.4)	_	
Monthly income (yuan)		.191ª	
<3000	53 (18.0)	_	
3000-5000	65 (22.0)	_	
5000-10,000	101 (34.2)	_	
>10.000	76 (25.8)	_	
Occupation status		.276 ^a	
Employed	204 (69.2)	_	
Unemployed	16 (5.4)	_	
Retired	75 (25.4)	_	
Educational levels		.688ª	
Primary school	13 (4.4)	_	
High school	100 (33.9)	_	
University and above	182 (61.7)	_	
Menopausal status		.592°	
Perimenopausal	152 (51.5)	_	
Early postmenopausal	91 (30.8)	_	
Late postmenopausal	52 (17.6)	_	
Parity		.217 ^a	
0	20 (6.8)	_	
1	233 (79.0)	_	
2–3	42 (14.2)		
Regular exercises		.521 ^b	
Yes	103 (34.9)	_	
No	192 (65.1)	_	
Chronic diseases			
Hypertension		.782 ^b	
Yes	46 (15.6)	_	
No	249 (84.4)		
Diabetes		.512 ^b	
Yes	11 (3.7)	_	
No	284 (96.3)	_	

^{*}Comparison of ECog scores between the sociodemographic groups.

^aKruskal-Wallis H test; ^bMann-Whitney test.

Table 2. The characteristics of ECog scores (item and overall).

ECog items	1 Point, N(%)	2 Points, <i>N</i> (%)	3 Points, <i>N</i> (%)	4 Points, N(%)	M ± SD
1. Remembering where he/she has placed objects.	48 (16.3)	100 (33.9)	85 (28.8)	61 (20.7)	2.54 ± 0.99
2. Remembering the current date or day of the week.	164 (55.6)	86 (29.2)	34 (11.5)	11 (3.7)	1.63 ± 0.83
3. Communicating thoughts in a conversation.	188 (63.7)	75 (25.4)	25 (8.5)	7 (2.4)	1.49 ± 0.75
4. Understanding spoken directions or instructions.	206 (69.8)	69 (23.4)	15 (5.1)	4 (1.4)	1.38 ± 0.65
5. Reading a map and helping with directions when someone else is driving.	208 (70.5)	56 (19.0)	22 (7.5)	4 (1.4)	1.39 ± 0.69
6. Finding one's way around a house/building that he/she has visited many times.	205 (69.5)	67 (22.7)	16 (5.4)	6 (2.0)	1.40 ± 0.69
7. Anticipating weather changes and planning accordingly.	233 (79.0)	52 (17.6)	5 (1.7)	1 (0.3)	1.22 ± 0.48
8. Thinking ahead.	219 (74.2)	60 (20.3)	15 (5.1)	1 (0.3)	1.32 ± 0.58
9. Keeping living and work space organized.	229 (77.6)	51 (17.3)	13 (4.4)	2 (0.7)	1.28 ± 0.58
10. Balancing the checkbook/account without error.	150 (50.8)	106 (35.9)	27 (9.2)	5 (1.7)	1.61 ± 0.73
11. Doing two things at once.	183 (62.0)	73 (24.7)	28 (9.5)	9 (3.1)	1.53 ± 0.79
12. Cooking or working, and talking at the same time.	220 (74.6)	60 (20.3)	10 (3.4)	5 (1.7)	1.32 ± 0.62
ECog scores	31 (10.5)				1.51 ± 0.49

Table 3. Correlation between the six independent menopausal symptoms and

MRS	Rho	<i>p</i> Value	
Hot flashes	0.159	.006	
Sleep disturbance	0.244	.000	
Depressive mood	0.181	.002	
Irritability	0.141	.015	
Anxiety	0.293	.000	
Physical/mental fatigue	0.321	.000	

Spearman rank correlation test.

women were obese. About 30.8% of the women were early postmenopausal and 17.6% were late postmenopausal. ECog scores showed no statistical significance between the sociodemographic groups (age, BMI, monthly income, education level, menopause status, parity, regular exercise, and history of chronic diseases).

Table 2 presents the characteristics of ECog scores (item and overall). The average score of ECog was 1.51 ± 0.49 . For item 1 of the ECog scales, only 16.3% of women were better or no change compared to 10 years earlier, and more than 20% of women were consistently much worse, while for other items, 50% or more women scored 1 point and less than 4% scored 4 points. In addition, compared with other items, items 1 and 2 regarding everyday memory had the highest average scores $(2.54 \pm 0.99 \text{ and } 1.63 \pm 0.83, \text{ respectively})$. Therefore, in our study, everyday memory decline is the most common cognitive problem of peri and postmenopausal women.

Table 3 presents the correlation between the six independent menopausal symptoms of MRS and everyday cognition. In bivariate analysis, six menopausal symptoms (hot flashes, sleep disturbance, depressive mood, irritability, anxiety, and physical and mental fatigue) of MRS were positively correlated with everyday cognitive function (ECog scores). Among the six symptoms, the correlation between physical/mental fatigue and everyday cognitive function was the strongest (rho = 0.321, p<.001).

Table 4 presents regression analysis for independent menopausal symptoms related to everyday cognition. Age, BMI, monthly income, occupational status, education level, menopausal status, parity, regular exercise, and history of chronic diseases were considered as confounding factors in this study. Symptoms of hot flashes, sleep disturbance, depressive mood, irritability, anxiety, and physical and mental fatigue were the independent factors. ECog scores were the dependent factor. After adjusting the confounding factors, regression analysis showed that anxiety and physical/mental fatigue were still positively correlated with everyday cognitive function, while the correlation of hot flashes, sleep disturbance, depressive mood, and irritability with everyday cognition were no longer statistically significant. In addition, the adjusted R^2 of regression analysis

Table 4. Multiple linear regression analysis for independent menopausal symptoms related to everyday cognition.

Variables	В	SE	Beta	T	p Value	Adjusted R ²
Anxiety	0.122	0.039	0.194	3.125	.002	0.105
Physical/mental fatigue	0.109	0.034	0.197	3.165	.002	

Covariables: hot flashes, sleep disturbance, depressive mood, irritability, anxiety, physical/mental fatigue, age, BMI, monthly income, occupational status, education level, menopausal status, parity, regular exercise, and history of chronic diseases.

was 0.132. Therefore, menopausal anxiety and physical and mental fatigue are independent predictors of everyday cognitive function.

Discussion

The aim of this study was to evaluate the relationship between menopausal symptoms and everyday cognition in Chinese peri and postmenopausal women. We found that changes in everyday cognition were very common in Chinese peri and postmenopausal women, only 10.5% of these women were better or no change compared to 10 years earlier. Everyday memory decline was more complaint by the study participants, nearly a half of them were consistently a little/much worse compared to 10 years ago according to the question 'remembering where he/she has placed objects.' Our result is similar to the findings of the Seattle Midlife Women's Health Study (SMWHS) [15], for example, about 60% of 233 middle-aged women aged 40-60 years noticed undesirable memory changes over the past few years. A crosssectional study from the Study of Women's Health Across the Nation (SWAN) [3] showed that of 16,065 middle-aged women aged 40-55 years, 44.0% complaint self-reported forgetfulness in early or late perimenopause and 42% in natural menopause. Hispanic reported the highest rate (46.0%), African American followed (43.0%), and Japanese was the lowest, but the rate of forgetfulness was also up to 33.0% [3]. Therefore, even in different cultural backgrounds and races, memory problems are the most common perceived cognitive problems in middleaged women.

Different menopausal stages have different menopausal problems. However, there was no statistically significant in everyday cognition between the three menopausal stages (perimenopausal, early, and late postmenopausal) in our study. This result may be influenced by many factors, such as the tool of cognition, age, background of education, and so on. Although there were statistically significant differences in age and education among the three menopausal stages in our study (no shown in this article), the correlation between age, education, and ECog-12 could be ignored [14]. Thus, our result may be affected by the tool of

cognitive function. In addition, our study did not include middle-aged women with regular menstruation as the control group. Evidences from studies demonstrated that premenopausal women transitioned to perimenopause, their cognitive function may decline. The Kinmen Women-Health Investigation (KIWI) [16] conducted an 18-month follow-up longitudinal cognitive performance study of 694 rural premenopausal women aged 40-54 years in Kinmen, Taiwan. Women who entered perimenopause during the follow-up period performed worse verbal fluency than those who were still in premenopausal stage. SWAN found that peri and postmenopausal women were about 1.4 and 1.3 times more likely to be forgetful than premenopausal women after adjusting for demographic factors, lifestyle factors, irritability, depression, and tense/anxious [3]. A SWAN 4-year follow-up longitudinal study showed that menopausal transition was positively correlated with decreased processing speed and verbal memory [4].

We found that anxiety is an independent predictor of everyday cognitive function. Anxiety symptoms have adverse effects on cognitive function. A study of 400 women aged 25-64 years showed that anxiety and depressive symptoms are the main predictors of subjective memory impairment, and the relationship between subjective memory function and psychological distress is closer than menopause or age [17]. A number of cross-sectional studies [8,9, 18] showed that menopausal anxiety symptoms were significantly associated with decreased processing speed. Although the variety of the tools assessing menopausal anxiety and methods measuring cognitive functioning, the results show that anxiety has adverse effects on cognitive function (general or certain domains), further indicating that anxiety an independent risk factor for cognitive decline.

Our study also found that physical/mental fatigue symptoms were related to everyday cognitive decline. This result is similar to another study which included 3202 community residents over 60 years old from seven cities in China [19]. In addition, the review of Sargent and Brown also shows that fatigue is related to the general cognitive status [20]. Physical/mental fatigue can lead to a decrease in the ability and efficiency of physical or mental activity. Fatigue is often accompanied by special discomfort, the desire to rest, and the weakening of motivation. Fatigue can be manifested in the potential impairment of cognitive function, which has been proved to involve more complex neural mechanisms related to cognitive task performance [21]. For example, executive function decline is a common feature of mental fatigue; among the various components of executive function, selective attention, particularly conflict-controlling selective attention (response inhibition), is highly vulnerable to mental fatigue [21]. Physical/mental fatigue is a common menopausal symptom in menopausal women. Therefore, menopausal women may be more prone to fatigue-related cognitive decline.

In the multiple linear regression analysis of this study, after adjusting the confounding factors, hot flashes were no longer closely related to everyday cognitive function. Previous studies have reported that the effects of hot flashes on cognitive function are inconsistent. The hot flashes of self-report [6] or objective measurement [7] are the predictors of the decline of verbal memory. In contrast, other studies have shown a limited [22] or no association [8] between hot flashes and cognitive impairment. Interestingly, a study of 52 postmenopausal women showed that the occurrence of hot flashes during late reproductive years may have a long-term beneficial effect on cognitive function during postmenopausal years. These women were asked to recall vasomotor symptoms experienced during their menopause and their cognitive status was evaluated by the Mini-Mental State Exam (MMSE). These postmenopausal women who had never experienced hot flashes were more likely to develop cognitive impairment than those who reported having menopausal hot flashes (MMSE < 21, 37.8%, and 11.2%, respectively). The authors propose a hypothesis that a hot flash triggers a counterregulatory mechanism of the central nervous system to the insufficiency of glucose delivery to the brain and thus prevents an initiation of a sequel of insults to brain neurons, and consequently reduces neuronal degeneration and cognitive impairment. The discrepancies between the above studies on the effects of hot flashes on cognitive function may be due to the use of various methods to evaluate hot flashes and measure cognitive function, or hot flashes are only closely related to certain cognitive domains.

Sleep disturbance is very common in peri and postmenopausal women. Our study did not find the relationship between sleep disturbance and everyday cognition. The relationship between sleep disturbance and cognition is discrepancy [8, 23,24]. The discrepancy may be affected by whether participants were functionally impaired by sleep problems, different approaches to assessing sleep disturbance (objective or selfreported), or different domains of cognitive function assessed.

This study has several limitations. First, this study is a crosssectional design, which cannot determine the causality. Second, the presence or not and intensity of each menopausal symptom were simply assessed using five options (none, mild, moderate, severe, and very severe) instead of using more complex and specific scales. For certain symptoms (e.g. hot flashes), objective measurement rather than self-repotting may be related to cognitive decline. However, consistent with Jaff et al. [9], our study also used the MRS to assess the six selected symptoms related to cognitive function. The validity and reliability of MRS in assessing the prevalence and severity of menopausal symptoms are internationally recognized [12, 25]. Last, our study evaluated everyday cognitive function using the short version of ECog scales, which can only reflect the overall cognitive status, but cannot evaluate specific domains of cognitive function. Certain menopausal symptoms may be related to certain cognitive domains, but not other cognitive domains. These deficiencies may limit the reliability of the conclusions. Therefore, future research needs to examine different cognitive domains, and longitudinal studies are needed to further clarify the correlation between menopausal symptoms and cognitive function.

Conclusion

Everyday memory decline is the most common cognitive problem in peri and postmenopausal women. Our study showed that the severity of menopausal symptoms (anxiety and physical/mental fatigue) was positively correlated with the decline of everyday cognitive function. If peri and postmenopausal women often complain of suffering from menopausal symptoms, especially severe menopausal symptoms, which should be actively treated to prevent or reduce possible short-term or long-term adverse effects of menopausal symptoms on cognitive function.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Author contributions

WH participated in data collection, statistical analysis and drafted the manuscript. SJ participated in revision of manuscript. LG and CL participated in data collection. MT participated in research design and review of manuscript. The final version of the manuscript has been read and approved by all authors. WH and SJ contributed equally to this article.

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