## Original Article Different factors influence the natural menopausal ages of Uygur, Han and Kazak women in Xinjiang Autonomous Region of China

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Abstract: Aims: The present study is to analyze the natural menopausal ages of women of Uygur, Han and Kazak ethnic groups in Xinjiang Autonomous Region, as well as factors that influence menopausal ages. Methods: A total of 3382 volunteered women (40-60 years old) in Urumqi, Kashi, Ili, and Xinyuan of Xinjiang Autonomous Region were chosen between July 2013 and June 2014 for the present study. Among these subjects, 941 were Uygur, 1019 were Han, and 1422 were Kazak. All subjects completed questionnaires by one-on-one questioning by gynecologists. The questions included general social demographics, economic characteristics, menstrual history, premenstrual syndrome (PMS), marital status, family life happy degrees, reproductive history, contraceptive methods, psychiatric history, lifestyle, work status and age at natural menopause. Single factor analysis and multiple linear regression analysis were performed to investigate the risk factors that affected natural menopausal ages of Uygur, Han and Kazak women. Results: The ages of natural menopause for Han, Uygur and Kazak were not significantly different from each other. Some factors independently affected the age of natural menopause of all subjects. Natural menopausal ages were significantly different among subjects from the three ethnic groups. Natural menopausal age of subjects from each ethnic group was affected by different combinations of multiple factors. Conclusions: The present study demonstrates that the natural menopausal ages of Uygur and Kazak women are younger than that of Han women in Xinjiang Autonomous Region. The different menopausal ages of the three ethnic groups are caused by different combinations of influencing factors. Distinct measures should be taken for different ethnic groups for the prevention of earlier menopause.

Keywords: Natural menopausal age, Uygur ethnic group, Han ethnic group, Kazak ethnic group, influencing factors

#### Introduction

Menopause is a life stage of women for the transition from reproductive age to non-reproductive age [1]. It includes the time from the appearance of menopause-related endocrine. biological and clinical features, to one year after the last menstruation [1]. The ages of menopause for women in different countries or ethnic groups are different, but it is shown that that menopause usually occurs between 50 to 51 years old [1]. Menopause has a great influence on the physiology and psychology of women, and early menopause may result in high mortality [2]. Recent studies show that the menopausal ages for Chinese women tend to be younger and younger [3], and the menopausal ages of women in minority ethnic groups are usually younger than those of Han ethnic group [4]. Early menopause can cause osteoporosis, cardiovascular disease, cognitive dysfunction and sexual life difficulties, finally leading to increased mortality of menopausal women [5-8]. In Xinjiang Autonomous Region of China, the health of middle and old age women of Uygur, Han and Kazak ethnic groups is important for the stability and development of the society of the multi-ethnic region. It is crucial to study the factors that may affect natural menopause age. In the present study, we use crosssectional study to analyze the natural menopausal ages of women of Uygur, Han and Kazak ethnic groups in Xinjiang Autonomous Region, as well as factors that influence menopausal ages.

#### Materials and methods

#### Subjects

A total of 3382 volunteered women (40-60 years old) in Urumqi, Kashi, Ili, and Xinyuan of Xinjiang Autonomous Region were chosen between July 2013 and June 2014 for the present study. Among these subjects, 941 were Uygur, 1019 were Han, and 1422 were Kazak. The inclusion criteria were: i) 40-60 years old Uygur, Han and Kazak women; ii) subjects had uterus and at least one ovary; iii) normal mental status; and iv) subjects were able to complete questionnaires. Exclusion criteria were: i) age < 40 or > 60 years; ii) history of total hysterectomy, bilateral ovarian resection, gynecological tumor, psychosis, or drug taking; iii) pregnancy; or iv) lactation. This study was approved by the institutional ethics committee of Xinjiang Medical University. All participants provided written informed consent prior to participating in the study.

### Study methods

All subjects completed questionnaires by oneon-one questioning by gynecologists. The questions included general social demographics, economic characteristics, menstrual history, premenstrual syndrome (PMS), marital status, family life happy degrees, reproductive history, contraceptive methods, psychiatric history, lifestyle, work status and age at natural menopause. The subjects were followed up by telephone in the form of random sampling. The rate of follow-ups was 10%, and the coincidence rate was 95%. Body mass index (BMI) was classified according to World Health Organization classification standards for adults: low body weight (athrepsia),  $< 18.5 \text{ kg/m}^2$ ; normal body weight, 18.5-24.9 kg/m<sup>2</sup>; overweight, 25.0-29.9 kg/m<sup>2</sup>; obesity,  $\geq$  30 kg/m<sup>2</sup> [8].

#### Statistical analyses

Epidata3.1 was used to construct database. The data were input by two persons, and were subjected to logic proofreading to ensure the accuracy of data. Statistical analyses were performed using SPSS 17.0 software (IBM, Armonk, NY, USA). Normally distributed data were presented as means  $\pm$  standard deviations. Data with skewed distribution were described using medians and interquartile ranges ( $P_{75}$ - $P_{25}$ ).

Single factor analysis was performed to screen independent variables. For data with normal distribution, homoscedasticity, and independence, t-test and one-way ANOVA were used to compare differences between two groups or among three or more groups, respectively. For other data, Mean-Whitney U test and Kruskai-Wallis H test were used. Colinearity diagnosis was performed for independent variables with significance. Variance inflation factor (VIF) > 10 and tolerance < 0.1, or condition index > 30was used as diagnostic standards for identifying independent variables with colinearity. If no colinearity existed, multiple regression analysis was performed; otherwise, ridge regression analysis was used. Inspection levels were 0.05 for the above analyses. P < 0.05 was considered statistically significant.

### Results

#### The age of natural menopause for Han is significantly older than Uygur and Kazak

To collect information regarding natural menopausal ages of women from the three ethnic groups, 3500 questionnaires were issued, but 62 were rejected and 56 guit halfway. Finally, a total of 3382 subjects (96.63%) completed the questionnaire, including 1019 Han (30.13%), 941 Uygur (27.82%), and 1422 Kazak (42.05%). The number of subjects with natural menopause was 2484, including 802 Han, 687 Uygur, and 995 Kazak (Figure 1). The overall mean age of natural menopause was 46.19 ± 3.54 years, with the mean age for Han being  $48.3 \pm 2.68$  years, that for Uygur being  $45.73 \pm$ 3.63 years and that for Kazak being 45.26 ± 3.49 years (P > 0.05). The result suggests that the age of natural menopause for Han is significantly older than Uygur and Kazak.

# Some factors independently affect the age of natural menopause of all subjects

To screen independent variables that may affect menopausal age, single factor analysis was performed. The data showed that menarche age, lactation duration, work pressure, PMS, marital status, parity, means of contraception, number of abortion, ethnic group, occupation, education level, monthly income, happiness of family life, menstrual cycle, and menstrual period were correlated with natural menopausal age. The result indicates that



**Figure 1.** The number of natural menopausal and premenopausal subjects from Han, Uygur, and Kazak ethnic groups.

some factors independently affect the age of natural menopause of all subjects.

#### Natural menopausal ages are significantly different among subjects from the three ethnic groups

After single factor analysis, multivariate regression analysis was carried out. The data showed that natural menopausal age was delayed as monthly income was increased (B = 0.20, P < 0.001). The natural menopausal age of subjects with oral contraceptives was delayed for 2 years compared with subjects with intrauterine contraceptive rings (B = -0.20, P = 0.03). The natural menopausal age of subjects with menstrual period  $\geq$  8 days was 1.5 years earlier than those with menstrual period < 3 days (B = -0.87, P < 0.001). The natural menopausal age of Kazak and Uygur subjects was 3 years earlier than that of Uygur subjects (B = -0.87, P < 0.001). The natural menopausal age of subjects who were peasants and free professionals was at least 1 year earlier than that of subjects who were cadres (B = -0.27, P = 0.03). The natural menopausal age of subjects who had university or above education levels was 3 years earlier than that of subjects who had primary school education (B = -0.42, P < 0.001). The natural menopausal age of subjects who did not have happy family life was 2 years earlier than that of subjects with happy family life (B = -0.40, P = 0.01) (Table 1). The fitted regression equation ( $R^2$  = 0.424, and adjusted  $R^2$  = 0.422) was:  $\hat{Y} = 50.93 + 0.20X_{\text{oral contraceptives}}$ 0.99X<sub>menstrual period</sub> - 0.86X<sub>ethnic groups</sub> - 0.27X<sub>occupations</sub> - 0.39X<sub>education level</sub> + 0.21X<sub>monthly income</sub> - 0.35X<sub>family</sub> life happiness. These results suggest that the natural menopausal ages are significantly different among subjects from the three ethnic groups.

Natural menopausal ages of subjects from different ethnic groups are affected by different combinations of influencing factors

Since the natural menopausal ages were significantly different among subjects from the three ethnic groups, multivariate regression analysis was performed for individual ethnic groups. The natural menopausal age of Han subjects who had university or above education levels was 2 years earlier than that of Han subjects who had primary school education (B = -1.403, P < 0.001). The natural menopausal age of Han subjects who did not have happy family life was 2.5 years earlier than that of Han subjects with happy family life (B = -0.673, P = 0.02). The natural menopausal age of Han subjects who never had lactation was 2.1 years earlier than that of Han subjects who had lactation < 12 months (B = -0.437, P = 0.004). The natural menopausal age of Han subjects with oral contraceptives was delayed for 3 years compared with Han subjects with intrauterine contraceptive rings (B = 0.156, P < 0.01). The natural menopausal age of Han subjects without work pressure was delayed for 3 years compared with Han subjects with work pressure (B = 2.056, P < 0.01) (Table 2). The fitted regression equation ( $R^2 = 0.147$ , and adjusted  $R^2 =$ 0.110) for Han subjects was:  $\hat{Y} = 3.759$ -  $1.043X_{education \ level}$  -  $0.673X_{family \ life \ happiness}$  +  $2.056X_{work \ pressure}$  -  $0.437X_{lactation}$  +  $0.156X_{oral \ contrat}$ 

ceptives. The natural menopausal age of Uygur subjects who had university or above education levels was 5 years earlier than that of Uvgur subjects who had primary school education (B = -0.723, P < 0.001). The natural menopausal age of Uygur subjects who were peasants and free professionals was 2 years earlier than that of Uvgur subjects who were cadres (B = -0.682). P < 0.001). The natural menopausal age of Uygur subjects who did not have happy family life was 3 years earlier than that of Uygur subjects with happy family life (B = -0.577, P = 0.001). The natural menopausal age of Uygur subjects with menstrual cycle  $\ge$  37 days was 3 years earlier than that of Uygur subjects with menstrual cycle < 23 days (B = -0.384, P = 0.015). The natural menopausal age of Uygur subjects with monthly income  $\geq$  3000 RMB was 1 year earlier than that of Uygur subjects with monthly income < 500 RMB (B = -0.237, P = 0.005). The natural menopausal age of Uygur subjects without work pressure was delayed for 1 year compared with Uygur subjects with work

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Factors	Non-standard- ized coefficients		B'	t	Р	Colinearity statistics	
	В	S			•	Tolerance	VIF
(Constants)	52.24	0.99		52.86	0.00		
Menarche age staging	0.25	0.14	0.03	1.82	0.07	0.97	1.03
Lactation staging	-0.62	0.13	-0.10	-4.75	0.00	0.80	1.25
Work pressure	0.36	0.20	0.04	1.85	0.06	0.73	1.36
Premenstrual syndrome	0.03	0.24	0.00	0.13	0.90	0.35	2.87
Marital status	-0.09	0.07	-0.03	-1.33	0.19	0.96	1.04
Means of contraception	-0.20	0.09	-0.04	-2.21	0.03	0.97	1.03
Number of abortion	-0.14	0.09	-0.03	-1.53	0.13	0.78	1.28
Ethnic group	-0.82*	0.07	-0.30	-11.07	0.00	0.49	2.04
Parity staging	0.22	0.10	0.06	2.28	0.02	0.56	1.80
Occupation	-0.27	0.12	-0.07	-2.23	0.03	0.34	2.95
Education level	-0.42	0.12	-0.09	-3.47	0.00	0.51	1.96
Monthly income	0.20	0.07	0.08	2.85	0.00	0.50	1.99
Happiness of family life	-0.40	0.16	-0.05	-2.56	0.01	0.84	1.18
Menstrual cycle	-0.03	0.13	0.00	-0.20	0.84	0.70	1.42
Menstrual period	-0.87*	0.17	-0.11	-5.01	0.00	0.78	1.28

**Table 1.** Multivariate linear regression analysis of factors that affect

 the natural menopausal age of all subjects

Note: \*The dependent variable was menopausal age. VIF, variance inflation factor.

Table 2. Multivariate linear regression analysis of factors that affect
the natural menopausal age of Han subjects

Factors	Non-standard- ized coefficients		B'	t	Р	Colinearity statistics	
	В	S	-			Tolerance	VIF
(Constants)	42.93	1.90		0.00	0.05		
Menarche age staging	-0.13	0.18	0.49	0.88	0.48	0.61	1.26
Lactation staging	-0.44*	0.15	8.13	0.65	0.00	0.48	0.87
Work pressure	2.06*	0.21	92.67	7.81	0.00	5.14	11.88
Premenstrual syndrome	0.30	0.31	0.93	1.35	0.33	0.73	2.19
Marital status	-2.33	0.15	2.58	0.79	0.11	0.60	1.05
Means of contraception	-0.16	0.06	7.13	0.86	0.01	0.76	0.96
Number of abortion	0.00	0.11	0.00	1.00	0.98	0.81	1.25
Body mass index	-0.11	0.10	1.16	0.90	0.28	0.74	1.01
Parity staging	-0.20	0.17	1.35	0.82	0.25	0.58	1.15
Occupation	-0.07	0.14	0.26	0.93	0.61	0.70	1.23
Education level	-1.04*	0.00	26.73	0.35	0.00	0.24	0.52
Monthly income	0.05	0.10	0.19	1.05	0.66	0.86	1.28
Happiness of family life	-0.67	0.02	5.40	0.51	0.02	0.29	0.90
Menstrual cycle	-0.03	0.13	0.05	0.97	0.83	0.75	1.26
Menstrual period	0.03	0.28	0.01	1.03	0.92	0.60	1.78

0.292, P = 0.006). The natural menopausal age of Uygur subjects without PMS was delayed for 0.5 year compared with Uygur subjects with PMS (B = 0.787, P = 0.004) (Table 3). The fitted regression equation  $(R^2 = 0.124, and$ adjusted  $R^2 = 0.079$ ) for Uygur subjects was:  $\hat{Y} =$ 40.150 - 0.682X<sub>occupation</sub> -0.723X<sub>education</sub> -0.237X monthly income - 0.577X<sub>family life hap-piness</sub> + 0.962X<sub>work</sub> pressure + 0.787X<sub>PMS</sub> - 0.384X<sub>menstrual</sub> + 0.292X<sub>parity</sub>. The natural menopausal age of Kazak subjects who had university or above education levels was 4 years earlier than that of Kazak subiects who had primary school education (B = -1.143, P < 0.001). The natural menopausal age of Kazak subjects who were peasants and free professionals was 3 years earlier than that of Kazak subjects who were cadres (B = -0.316, P = 0.002). The natural menopausal age of Kazak subjects who did not have happy family life was 0.5 year earlier than that of Kazak subjects with happy family life (B = -0.448, P = 0.002). The natural menopausal age of Kazak subjects with number of abortion  $\geq$  2 was 0.5 year earlier than that of Kazak subjects without abortion (B = -0.486, P < 0.001). The natural menopausal age of Kazak subjects who were widowed was 3 years earlier than that of Kazak subjects who were married (B = -0.202, P = 0.007). The

subjects with 0 parity (B =

Note: \*The dependent variable was menopausal age. VIF, variance inflation factor.

pressure (B = 0.962, P < 0.001). The natural menopausal age of Uygur subjects with parity  $\geq$  2 was delayed for 4 years compared with Uygur

natural menopausal age of Kazak subjects who were smoking was 3 years earlier than that of Kazak subjects who never smoked (B = -0.062,

Factors	Non-standard- ized coefficients		B	t	Р	Colinearity statistics	
	В	S	_			Tolerance	VIF
(Constants)	40.15	2.52		0.00	1.00		
Menarche age staging	0.01	0.17	0.00	1.01	0.96	0.72	1.42
Lactation staging	-0.08	0.18	0.19	0.93	0.66	0.65	1.31
Work pressure	0.96*	0.23	17.74	2.62	0.00	1.67	4.09
Premenstrual syndrome	0.79*	0.27	8.22	2.20	0.00	1.28	3.76
Marital status	-0.08	0.09	0.71	0.93	0.40	0.78	1.11
Means of contraception	0.10	0.07	2.20	1.11	0.14	0.97	1.26
Number of abortion	-0.02	0.11	0.03	0.98	0.87	0.79	1.23
Body mass index	-0.06	0.08	0.44	0.95	0.51	0.80	1.11
Parity staging	0.29*	0.11	7.50	1.34	0.01	1.09	1.65
Occupation	-0.68*	0.14	22.91	0.51	0.00	0.38	0.67
Education level	-0.72*	0.16	20.37	0.49	0.00	0.36	0.66
Monthly income	-0.24*	0.85	7.80	0.79	0.01	0.67	0.93
Happiness of family life	-0.58*	0.18	10.42	0.56	0.00	0.40	0.80
Menstrual cycle	-0.38*	0.16	5.96	0.68	0.02	0.50	0.93
Menstrual period	0.24	0.21	1.27	1.27	0.26	0.84	1.92
Smoking	-0.36	0.28	1.68	0.70	0.20	0.41	1.20
Psychiatric history	-18.56	0.26	0.00	0.00	1.00	0.00	0.00

**Table 3.** Multivariate linear regression analysis of factors that affectthe natural menopausal age of Uygur subjects

Note: \*The dependent variable was menopausal age. VIF, variance inflation factor.

Table 4. Multivariate linear regression analysis of factors that affe	ect
the natural menopausal age of Kazak subjects	

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Factor	Non-standard- ized coefficients		B	t	p	Colinearity statistics	
	В	S	-		-	Tolerance	VIF
(Constants)	-2.32	0.95		1.12	0.27		
Menarche age staging	-0.04*	0.14	0.06	0.97	0.80	0.74	1.27
Lactation staging	0.24	0.15	2.49	1.27	0.12	0.94	1.71
Work pressure	-0.31	0.21	2.21	0.73	0.14	0.49	1.10
Premenstrual syndrome	0.85*	0.19	19.16	2.33	0.00	1.60	3.40
Marital status	0.20*	0.08	7.17	1.22	0.01	1.06	1.42
Means of contraception	0.44*	0.05	96.46	1.56	0.00	1.43	1.70
Number of abortion	-0.49*	0.09	28.93	0.62	0.00	0.52	0.73
Body mass index	-0.03*	0.07	0.19	0.97	0.66	0.85	1.11
Parity staging	-0.09	0.09	0.85	0.92	0.36	0.76	1.10
Occupation	-0.32*	0.10	9.38	0.73	0.00	0.60	0.89
Education level	-1.14*	0.13	79.17	0.32	0.00	0.25	0.41
Monthly income	0.14	0.07	3.43	1.15	0.06	0.99	1.32
Happiness of family life	-0.45*	0.14	9.64	0.64	0.00	0.48	0.85
Menstrual cycle	0.11	0.16	0.43	1.11	0.51	0.81	1.53
Menstrual period	-0.06	0.15	0.16	0.84	0.69	0.70	1.27
Psychiatric history	2.23	0.84	7.0	9.29	0.01	1.78	48.52
Smoking	-0.06*	0.71	0.77	0.94	0.38	0.82	1.08

Note: \*The dependent variable was menopausal age. VIF, variance inflation factor.

P = 0.380). The natural menopausal age of Kazak subjects with menarche age  $\geq$  14 was 1.2 years delayed compared with that of Kazak subjects with menarche age  $\leq$  13 (B = 0.529, P = 0.016). The natural menopausal age of Kazak subjects with body mass index  $\geq$  30 kg/m<sup>2</sup> was 1.5 years delayed compared with that of Kazak subjects with body mass index <  $18.5 \text{ kg/m}^2$  (B = 0.401, P < 0.001). The natural menopausal age of Kazak subjects without PMS was delayed for 0.5 year compared with Kazak subjects with PMS (B = 0.845, P < 0.001). The natural menopausal age of Kazak subjects with oral contraceptives was delayed for 4 years compared with Kazak subjects with intrauterine contraceptive rings (B = 0.444, P < 0.001)(Table 4). The fitted regression equation ( $R^2 = 0.197$ , and adjusted  $R^2 = 0.169$ ) for Kazak subjects was:  $\hat{Y} =$ 45.6 + 0.529X<sub>menarche age</sub> + 0.40X body max index - 0.316X occu-pation - 1.143X education level -0.448X<sub>family</sub> life happiness + 0.845X<sub>PMS</sub> - 0.202X<sub>marital sta-</sub> + 0.444X marital sta-tus + 0.444X oral contraceptives -0.486X number of abortion -0.062X moking. These results indicate that the natural menopausal ages of subjects from different ethnic groups are affected by different combinations of influencing factors.

#### Discussion

Natural menopause that is considered a symbol of aging and the occurrence of chronic diseases, is a physiological process affe-

cted by multiple factors such as gene, ethnicity, environment, lifestyle, fertility status, oral contraceptives, body mass index, education level and social economy [9-13]. Women in different locations or ethnic groups have distinct menopausal ages [14-17]. The natural menopausal age for Asian women is 48.0-52 years old, that for African women is 48.0-49.0 years old, that for Southeastern Asian women is 51 ± 1.09 years old [18], and that for Arabic women is 47-49 years old [15]. The natural menopausal age for Chinese women is 48.7-49.3 years [1], and that of Han women is 47.5-49.5 years [19]. The natural menopausal age for women in Chinese minority ethnic groups ranges between 46 and 48.2 years [4]. The present study shows that the natural menopausal age of Han women in Xinjiang Autonomous Region is 48.3 ± 2.68 years, being similar with Han women in other places of China [20, 21]. The natural menopausal ages of Uygur and Kazak women are 45.73 ± 3.63 and 45.26 ± 3.94 years, respectively, being significantly earlier than that of Han women. This result is consistent with a previous study [4].

Multivariate linear regression analysis shows that high education level, work pressure and family life happiness deficiency are factors that lead to younger natural menopausal ages. Some studies show that low education level is a risk factor for earlier menopause [11, 18, 22]. However, our study demonstrates that Uygur, Han and Kazak women with high education level have earlier menopause, being consistent with the study by Parazzini et al. [23]. Women with high education level usually have high work pressure that stimulates hypothalamicpituitary-ovarian axis [16, 24]. In addition, the result that women with family life happiness deficiency, divorce and widowhood have earlier menopause suggests that emotional factors may cause pituitary ovary axis disorders, leading to earlier menopause.

The present study also shows that the menopausal ages of Han women who have oral contraceptives or never have lactation are 3 years delayed compared with those of Han women who use other contraceptive means or have lactation, being consistent with reports by Dvornyk et al. [25-29]. Oral contraceptives may prolong the inhibition time of follicular hormone, which causes delayed natural menopause [30]. In addition, our results show that Kazak and Uygur women with parity  $\geq$  2 have older age of menopause, being consistent with previous studies [7, 31, 32]. Increased parity reduces the number of ovulatory cycles and delays the loss of oocytes, resulting in postponed natural menopause. Our result on the correlation of menopausal age with menarche age shows that Kazak women with menarche age  $\geq$  14 and longer menstrual cycle have delayed menopause, being consistent with some previous studies [33-35]. This may be related to delayed ovulation time and ovarian follicular exhaustion time [23].

In the present study, Uygur and Kazak women who are peasants have earlier menopause, being consistent with the report by Delano et al. [36]. In addition, Kazak women with PMS, psychiatric history, and widowhood have earlier menopause due to dysfunction of hypothalamic-pituitary-ovarian axis caused by emotional factors [16, 24, 37, 38]. Our result shows that Kazak women with higher body mass index have delayed menopause, being consistent with the report by Yasui et al. [39]. This might be due to the elevated estrogen levels in women with high body mass index [40]. Furthermore, the menopausal ages of Kazak women who smoke are younger than those who never smoke, possibly because the toxicity of tobacco constituents affects the synthesis of estrogen and leads to low levels of estrogen [41, 42]. In addition, tobacco smoke constituents may also reduce the activity of estrogen [43]. In summary, the present study presents factors that may affect the natural menopausal ages of Uygur, Han and Kazak women in Xinjiang Autonomous Region, and provides basis for carrying out menopausal health protection and clinical diagnosis. The study is only a cross-sectional investigation that uses retrospective information, which may be influenced by memory bias. More factors such as environment, gene, dietary habits, childbirth age, and activities remain to be studied. Therefore, larger scale prospective social survey is needed in the future, in order to more objectively find out the risk factors that influence the natural menopausal ages of women in minority ethnic groups in Xinjiang Autonomous Region.

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#### Disclosure of conflict of interest

None.

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