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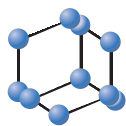
Early Age of Migraine Onset is Independently Related to Cognitive Decline and Symptoms of Depression Affect Quality of Life

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Abstract: ***Background:*** People with migraine experience cognitive decline more often than healthy controls, resulting in a significant functional impact. Early identifying influencing factors that contribute to cognitive decline in migraineurs is crucial for timely intervention. Although migraine may onset early in childhood and early onset migraine is related to significant disability, there is no research investigating the association between the age of migraine onset and migraineurs' cognitive decline. Therefore we aim to explore possible factors that correlate to the cognitive function of migraineurs, especially focus on age of migraine onset.

Methods: 531 patients with migraine were included. Data on demographics and headache-related characteristics were collected and evaluated using face-to-face interviews and questionnaires. We used the Montreal Cognitive Assessment scale to assess cognitive function. In addition, we analyzed independent correlations between cognitive decline and the age of migraine onset in patients with migraine. And all patients completed the Headache Impact Test-6 to evaluate their quality of life.

Results: Migraineurs with cognitive decline showed significant differences from those without in age (OR=1.26, *P*<0.0001), years of education (OR=0.89, *P*=0.0182), the intensity of headache (OR=1.03, *P*=0.0217), age of onset (OR=0.92, *P*<0.0001) and anxiety scores (OR=1.09, *P*=0.0235). Furthermore, there was no interaction in the age of onset between subgroups. Multivariate linear regression analyses of HIT-6 scores showed that the intensity of headache (β=0.18, *P*<0.0001) and depression scores (β=0.26, *P*=0.0009) had independent effects on decreased quality of life.

Conclusion: Our findings suggest that younger age of migraine onset is independently related to migraineurs' cognitive decline, and migraine accompanying anxiety symptoms significantly related to decreased quality of life in migraineurs.

Keywords: Migraine, headache, age of migraine onset, cognitive function, cognitive decline, quality of life, anxiety symptom, depression symptom.

1. INTRODUCTION

Migraine is a prevalent and disabling neurological disorder that occurs across all age groups. In the Global Burden of Disease Study 2017 (GBD2017) [1], migraine was ranked 7th based upon years lived with disability (YLDs), and migraine was ranked 2nd in the global burden of neurological disorders based upon YLDs [2], which was considerably higher than other neurological diseases such as epilepsy and Alzheimer's disease. Cognitive decline is more likely among patients with migraine than healthy controls [3, 4], and the eventual functional impact includes distractions and barriers to life and works for patients with migraine.

Previous studies have found obstacles for migraine patients with cognitive decline regarding duties that require intensive and continuous focus during headache attacks. For example, for migraineurs with cognitive decline, the likelihood of being interrupted and committing errors while reading, writing and doing arithmetic are generally higher, and these individuals experience difficulties handling interpersonal relationships [5, 6]. Consequently, it is crucial to analyze the potential influencing factors to help migraineurs cope with the stress of declined cognitive function.

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In recent years, the effects of migraine and its accompanying symptoms on cognitive function in migraine patients have been emphasized. Few studies have explored the influencing factors that may cause cognitive decline in migraineurs, and these studies are somewhat limited [7-9]. Therefore, we draw on the experiences from previous studies and address the existing deficiencies such as small sample size, the lack of a comprehensive analysis of factors and reliance on scales that are not internationally accepted, with the aim of delivering accurate results relevant for academic research and clinical use. Although migraine may onset early in childhood which is related to significant disability, there is no research investigating the association between age of migraine onset and migraineurs' cognitive decline [10, 11]. In the present research, we explore potential factors that associate with cognitive function of migraineurs. Moreover, we hypothesized the independent correlations between cognitive decline and the age of migraine onset in migraineurs. By early identifying the possible influencing factors, we aim to help alleviate the negative effects of cognitive decline in migraineurs as much as possible.

2. MATERIALS AND METHODS

2.1. Study Sites and Study Population

In this cross-sectional study, all patients came from the Department of Neurology or Psychiatry of West China Hospital from June 2016 to March 2019 and were evaluated by at least two neurologists and two psychiatrists. The diagnosis of migraine without aura was made according to the International Classification of Headache Disorders Ⅲ Edition (beta version) (ICHD-Ⅲ beta) and the International Classification of Headache Disorder Ⅲ Edition (ICHD-Ⅲ) [12, 13]. The diagnosis of migraine without aura in ICHD-Ⅲ beta does not differ from the diagnosis based on ICHD-Ⅲ. ICHD-Ⅲ beta was used to diagnose patients before 2018. All demographics data and headache-related characteristics were collected and evaluated using face-to-face interviews and questionnaires, including the Montreal Cognitive Assessment (MoCA) [14], Headache Impact Test-6 (HIT-6) [15], 24-item Hamilton Rating Scale for Depression (24-HRSD) [16], and 14-item Hamilton Anxiety Rating Scale (14-HAMA) [17]. Participants provided their subjective perception of average pain intensity on a visual analog scale (VAS) [18]. Body Mass Index (BMI) was calculated as weight in kilograms divided by the square of height in meters [19].

The MoCA total score is 30 points, with an additional point for people with ≤12 years of education and a normal score of ≥26 points. In this study, we used the MoCA to screen for cognitive decline at a cut-off score of <26. The HIT-6 is useful for assessing headache-related disability in migraine patients; the higher the score, the greater the impact of headache on life. The severity of depression symptoms was measured by the 24-HRSD. We used this scale to screen accompanying depression symptoms at a cut-off score of ≥8. Higher HRSD scores indicate increased depression levels. The 14-HAMA is characterized by 14 items. We used it to screen for accompanying anxiety symptoms in migraine patients with a cut-off score of ≥7. Higher HAMA scores indicate increased anxiety levels.

The study protocol was approved by the ethics committee of West China Hospital, Sichuan University (201652), and informed consent was provided by the patients.

2.2. The Inclusion and Exclusion Criteria

The inclusion criteria for all subjects were as follows (Fig. **1**):

1) diagnosed with migraine without aura according to the International Classification of Headache Disorders Ⅲ Edition (beta version) (ICHD-Ⅲ beta) or the International Classification of Headache Disorders Ⅲ Edition (ICHD-Ⅲ);

2) 18 years of age or older;

3) completed interviews and questionnaires;

4) showed no abnormalities in magnetic resonance imaging (MRI).

The exclusion criteria for all subjects were as follows:

1) primary or secondary headache disorder other than migraine;

2) suffering from major diseases that have been shown in previous studies to affect cognitive function, such as cerebral infarction [20, 21], epilepsy [22], hypertension [23], head injury [24], intracranial tumor [25], and Parkinson's disease [26];

3) incomplete information that could not be recovered;

4) refusal to participate in this project.

2.3. Statistical Analyses

All statistical analyses were performed using EmpowerStats (http://www.empowerstats.com) and the statistical package R (3.2.3 version). Categorical demographic and clinical variables were analyzed between patients with or without cognitive decline using the Chi-square test or Fisher's exact test. Continuous variables were expressed as the means±standard deviation or medians (interquartile range) and were analyzed using Student's t-test or the Mann-Whitney U test.

Univariate logistic regression was used to determine the association between potential determinants of and accompanying cognitive decline in migraineurs. Multivariate logistic regression models with adjustment for age, gender, type of work, years of education, BMI, systolic blood pressure (SP), diastolic blood pressure (DP), headache characteristics, sleep disorders, HAMA scores and HRSD scores were used to evaluate the influencing factors of cognitive decline associated with migraine, and adjusted odds ratio (OR) with 95% confidence interval (CI) were estimated to evaluate the effects. The consistency of effect of age of onset in various subgroups (age, years of education, VAS scores, history of migraine and HAMA scores) was also explored using stratified analysis. Besides, we performed further interaction tests to investigate the independent impact of age of migraine onset.

Univariate linear regression was used to detect the association between potential determinants and quality of life in migraineurs. Multivariate linear regression was employed to
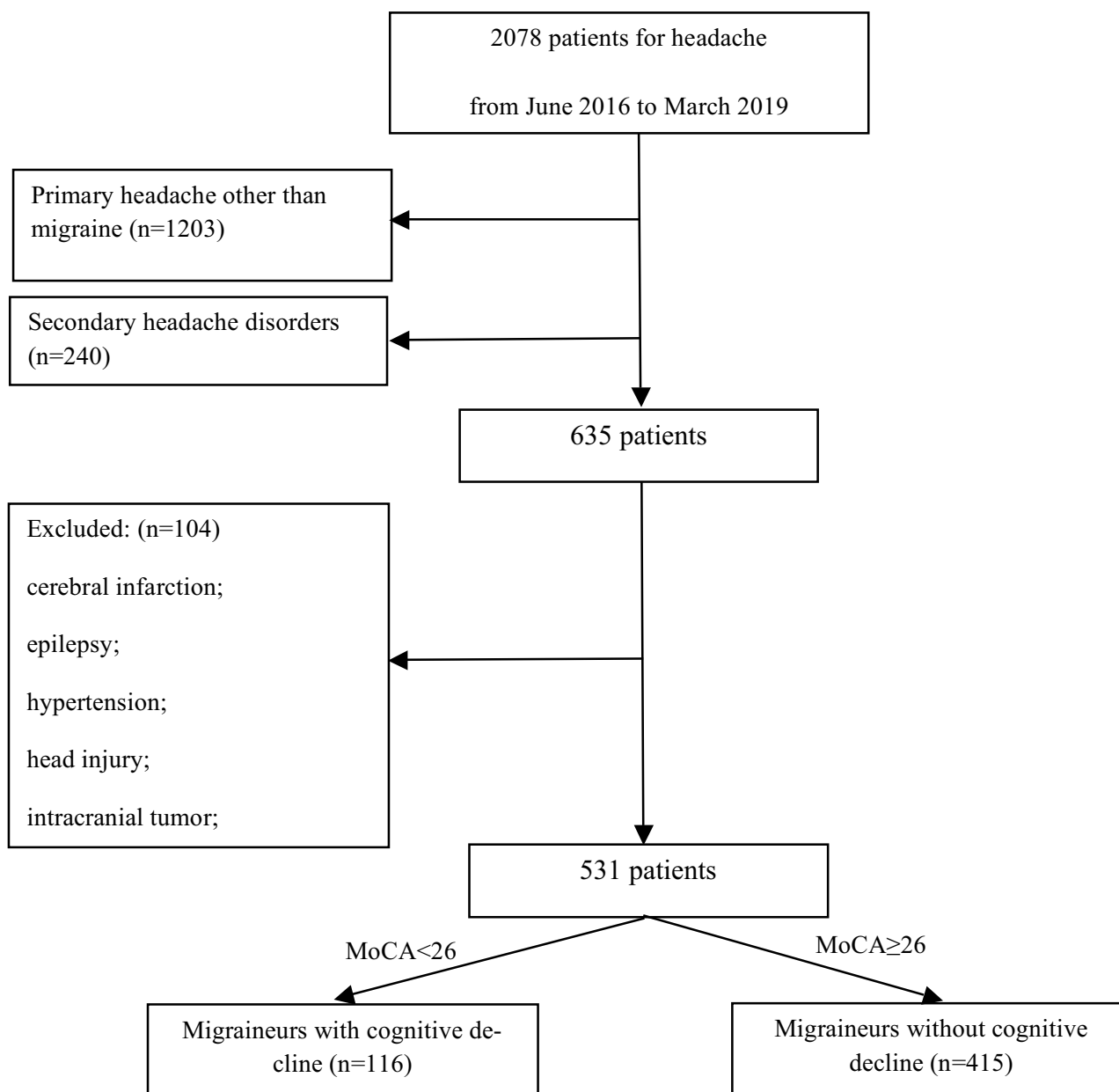
Fig. (1). Flow of the participants in the current study. Our headache database has 2078 headache patients from June 2016 to March 2019 and 635 of these patients are migraine patients. After strictly filtering migraine patients by inclusion and exclusion criteria, we ended up with 531 patients included in the study. Then we used the MoCA to screen for cognitive decline at a cut-off score of <26. There were 116 migraine patients with cognitive decline.

identify independent influencing factors for decreased quality of life. The measures of association were OR with 95% CI. This analysis was adjusted for age, gender, nationality, type of work, years of education, headache characteristics, sleep disorders, family history of migraine, MoCA scores, HAMA scores and HRSD scores.

In all statistical analyses, the significance level was *P*<0.05.

3. RESULTS

3.1. Demographic and Clinical Characteristics

Given the inclusion and exclusion criteria, we had a final sample size of 531 patients. Demographic and clinical char-

acteristics are reported in Table **1**. Cognitive decline was observed in 21.85% (n=116) of the migraineurs. The median anxiety scores for migraine with cognitive decline and without cognitive decline were 10.90 and 8.88, respectively. The median depression scores for migraine with cognitive decline and without cognitive decline were 13.65 and 11.59, respectively. The median age of migraine onset for migraine with cognitive decline and without cognitive decline was 31.77 years and 36.78 years. The proportion of subjects with sleep disorders was 51.29%.

3.2. Possible Influencing Factors for Cognitive Decline

We divided patients with migraine into 2 groups based on whether they had cognitive decline. The demographic and clinical characteristics are reported in Table **1**.

Table 1. Demographic and clinical characteristics of migraineurs with or without cognitive decline (n = 531).

Characteristic	Total Patients (n = 531)	Cognitive Decline		P value
		Yes (n = 116)	No (n = 415)	
Age, y, mean±SD	42.19 ± 11.62	53.55 ± 8.85	39.01 ± 10.24	<0.001*
Gender, n (%)				0.300
Male	158 (30.8%)	30 (25.86%)	128 (30.84%)	
Female	373 (70.2%)	86 (74.1%)	287 (69.2%)	
Han ethnicity, n (%)	503 (69.2)	110 (94.8%)	393 (94.7%)	0.956
Right-handed, n (%)	511 (96.2)	114 (98.3%)	397 (95.7%)	0.272
Type of work, n (%)				<0.001*
Manual workers, n (%)	267 (50.3%)	88 (75.9%)	179 (43.1%)	
Mental workers, n (%)	264 (49.7%)	28 (24.14%)	236 (56.87%)	
Education, y, mean ± SD	10.52 ± 4.18	7.73 ± 3.95	11.27 ± 3.94	<0.001*
BMI, mean ± SD	22.52 ± 3.37	23.39 ± 4.19	22.28 ± 3.07	0.002*
SP, mean ± SD	117.60 ± 14.52	122.47 ± 15.59	116.24 ± 13.92	<0.001*
DP, mean ± SD	76.00 ± 9.10	78.02 ± 9.24	75.44 ± 9.00	0.007*
Clinical Characters Of Migraine	-	-	-	-
CM, n (%)	111 (20.9)	32 (27.6%)	79 (19.0%)	0.045*
Attack frequency, per month, mean ± SD	7.80 ± 7.72	9.30 ± 8.79	7.38 ± 7.35	0.018*
Attack duration, h, mean ± SD	21.82 ± 18.51	22.86 ± 19.18	21.53 ± 18.33	0.494
Headache days, per month, mean ± SD	8.57 ± 7.76	10.30 ± 9.02	8.09 ± 7.31	0.025*
VAS score (0-100), mean ± SD	60.98 ± 11.89	61.72 ± 11.67	60.77 ± 11.95	0.446
Age of migraine onset, y, mean ± SD	32.87 ± 10.94	36.78 ± 11.56	31.77 ± 10.51	<0.001*
History of migraine, y, mean ± SD	9.34 ± 8.43	8.67 ± 6.92	9.53 ± 8.81	0.332
Sleep disorders, n (%)	275 (51.8)	70 (60.3%)	205 (49.4%)	0.037*
Family history of migraine, n (%)	136 (25.6)	33 (28.45%)	103 (24.82%)	0.429
Depression scores, mean ± SD	12.04 ± 7.01	13.65 ± 7.41	11.59 ± 6.84	0.005*
Anxiety scores, mean ± SD	9.32 ± 5.28	10.90 ± 5.25	8.88 ± 5.20	<0.001*
MoCA total score, mean ± SD	27.44 ± 2.49	23.67 ± 1.57	28.49 ± 1.47	<0.001*
HIT-6, mean ± SD	58.30 ± 8.37	57.01 ± 8.78	58.66 ± 8.23	0.060

*P value <0.05.

Abbreviations: BMI: Body Mass Index; SP: Systolic blood Pressure; DP: Diastolic blood Pressure; CM: Chronic Migraine; VAS: Visual Analogue Scale; HIT-6: Headache Impact Test-6; Montreal Cognitive Assessment; SD: Standard Deviation.

The results of the univariate logistic regression analysis are shown in Table **2**. Age (*P*<0.0001), type of work (*P*<0.0001), years of education (*P*<0.0001), BMI (*P*=0.0035), systolic blood pressure (*P*<0.0001), diastolic blood pressure (*P* = 0.0074), chronic migraine (*P*=0.0466), frequency of headache (*P*=0.0191), headache days/month (*P*=0.0073), age of migraine onset (*P*<0.0001), sleep disorders (*P*=0.0378), and anxiety scores (*P*=0.0055) showed differences between the group of migraineurs with and without cognitive decline.

After adjusting for potential confounders, the multivariate logistic regression analysis showed that age (OR=1.26, P<0.0001), years of education (OR=0.89, *P*=0.0182), in-

tensity of headache (OR=1.03, *P*=0.0217), age of migraine onset (OR=0.92, *P*<0.0001) and anxiety scores (OR=1.09, *P*=0.0235) had independent effects on cognitive decline (Table **2**).

Stratified analysis and interaction tests were used to investigate the potential impact of age of migraine onset. We found no interaction in the age of migraine onset between various subgroups (age, years of education, VAS scores, history of migraine and HAMA scores) (Table **3**). The results were consistent after the interaction test, showing that our result for age of migraine onset was stable.

Table 2.　　**Possible Influencing Factors of Migraineurs with Cognitive Decline.**

Characteristic	Non-adjusted		†Adjusted	
	OR Value (95%CI)	*P* Value	OR Value (95%CI)	*P* value
Age	1.17 (1.13, 1.21)	<.0001*	1.26 (1.20, 1.33)	<0.0001*
Male	0.78 (0.49, 1.25)	0.3003	0.98 (0.50, 1.91)	0.9553
Han ethnicity	1.03 (0.41, 2.59)	0.9562	0.33 (0.09, 1.17)	0.0861
Right-handed	2.58 (0.59, 11.30)	0.2070.	2.06 (0.33, 13.01)	0.4416
Type of work	4.14 (2.60, 6.61)	<0.0001*	1.86 (0.90, 3.82)	0.0925
Years of Education	0.79 (0.75, 0.84)	<0.0001*	0.89 (0.81, 0.98)	0.0182*
BMI	1.10 (1.03, 1.17)	0.0035*	1.06 (0.96, 1.18)	0.2471
SP	1.03 (1.01, 1.04)	<0.0001*	0.98 (0.95, 1.01)	0.1351
DP	1.03 (1.01, 1.06)	0.0074*	1.02 (0.98, 1.07)	0.3309
Clinical Characters				
CM	1.62 (1.01, 2.61)	0.0466 *	1.64 (0.50, 5.45)	0.4158
Attack frequency	1.03 (1.00, 1.06)	0.0191 *	0.97 (0.85, 1.11)	0.6444
Attack duration	1.00 (0.99, 1.01)	0.4939	0.99 (0.97, 1.01)	0.5142
Headache days/month	1.03 (1.01, 1.06)	0.0073*	1.03 (0.89, 1.18)	0.6971
VAS score (0-100)	1.01 (0.99, 1.02)	0.4451	1.03 (1.00, 1.06)	0.0217*
Age of migraine onset	1.04 (1.02, 1.06)	<0.0001*	0.92 (0.88, 0.95)	<0.0001*
History of migraine	0.99 (0.96, 1.01)	0.3322	1.01 (0.98, 1.05)	0.5176
Sleep disorders	1.56 (1.03, 2.37)	0.0378*	0.82 (0.42, 1.61)	0.5669
Family history	1.20 (0.76, 1.91)	0.4290	1.40 (0.73, 2.71)	0.3129
Depression scores	1.04 (1.01, 1.07)	0.0055*	1.00 (0.94, 1.06)	0.9726
Anxiety scores	1.07 (1.03, 1.12)	0.0003 *	1.09 (1.01, 1.18)	0.0235*

*P value < .05.

Abbreviations: BMI: Body Mass Index; SP=: Systolic blood Pressure; DP: Diastolic blood Pressure; CM: Chronic Migraine; VAS: Visual Analogue Scale; CI: indicates confidence interval; OR: odd ratio.

† Adjusted: adjusted for age, gender, type of work, years of education, BMI, SP, DP, headache characteristics, sleep disorders, HAMA scores and HRSD scores.

Table 3.　　**Interaction test for the association between age of migraine onset and cognitive decline.**

Characteristic	N(%)	Age of migraine onset	† Cognitive Decline	† P for Interaction
			OR (95%CI) P	
Age, y	-	-	-	0.0837
18-41	255 (24.11%)	25.99 ± 7.55	1.10 (0.95, 1.26) 0.1985	-
42-70	276 (23.92%)	39.22 ± 9.67	0.97 (0.94, 1.00) 0.0496	-
Years of education, y	-	-	-	0.8816
0-12	380(71.56%)	34.40 ± 10.71	0.92 (0.88, 0.96) 0.0001	-
13-22	151(28.44%)	29.01 ± 10.57	0.91 (0.84, 1.00) 0.0511	-
VAS	-	-	-	0.4141

Characteristic	N (%)	Age of migraine onset	† Cognitive Decline		† P for Interaction
			OR (95%CI) P		
40-50	164 (30.88%)	35.20 ± 10.38	0.92 (0.85, 1.00) 0.0381		-
60-70	293 (55.18%)	32.17 ± 11.15	0.89 (0.84, 0.94) <0.0001		-
80-100	74 (13.94%)	30.49 ± 10.53	0.96 (0.86, 1.08) 0.5144		-
History of migraine, y	-	-	-		0.2923
1-3	149(28.06%)	33.42 ± 11.21	0.91 (0.85, 0.98) 0.0089		-
4-8	145(27.31%)	32.18 ± 10.98	0.82 (0.71, 0.94) 0.0039		-
9-50	237(44.63%)	32.95 ± 10.76	0.91 (0.85, 0.97) 0.0052		-
Anxiety scores	-	-	-		0.1643
<7	181(34.09%)	33.77 ± 11.05	0.96 (0.90, 1.02) 0.1853		-
7-14	266(50.10%)	32.44 ± 10.60	0.91 (0.86, 0.96) 0.0008		-
>15	84(15.81%)	32.27 ± 11.72	0.86 (0.79, 0.94) 0.0015		-

Abbreviations:: VAS: Visual Analogue Scale; CI: Confidence Interval; OR: Odd Ratio.
† Adjusted: adjusted for age, gender, type of work, years of education, BMI, SP, DP, headache characteristics, sleep disorders, HAMA scores and HRSD scores.

3.3. Possible Influencing Factors for Decreased Quality of Life

The results of the univariate linear regression analysis of HIT-6 scores are shown in Table **4**. Age ($P<0.0001$), years of education ($P=0.0072$), BMI ($P=0.0299$), intensity of headache ($P<0.0001$), MoCA total score ($P=0.0257$), depression scores ($P<0.0001$) and anxiety scores ($P=0.0119$) were significantly different.

After adjusting for confounding variables using multivariate linear regression analysis, the intensity of headache ($\beta=0.18$, $P<0.0001$) and depression scores ($\beta=0.26$, $P=0.0009$) had independent effects on migraineurs' quality of life (Table **4**).

4. DISCUSSION

This study found that 21.85% of migraineurs showed a cognitive decline. To identify potential influencing factors of cognitive decline in migraineurs, we assessed the association between cognitive function and migraine characteristics. We found that the cognitive function of migraineurs was related to the migraineurs' age, years of education, intensity of headache, age of migraine onset and anxiety scores.

Consistent with previous studies, we found that migraineurs with cognitive decline were older than migraineurs without cognitive decline. This is because aging is positively associated with a decline in cognitive function, such as attention and memory [27, 28]. Many studies of age-related cognitive decline have suggested that cognitive decline begins in old age [29]. A study of neurogenetic effects on cognition in aging brains found that cognitive function declined slightly or did not decline before 55 years old [30]. Another study suggested that cognitive decline usually occurred at age 70 years or older [31]. Regrettably, these findings did not focus on migraineurs. There is no doubt that the time of cognitive function decline is preemptive in patients with migraine,

although the mechanism is unclear. We speculate that this phenomenon may have a cause. With the exception of migraine correlated with an increased risk of vascular disease, which is one of the risk factors for cognitive decline [20, 32, 33], repeated headache attacks could lead to cognitive decline [34]. Consequently, cognitive decline may begin much earlier for migraineurs than age-related cognitive decline. This finding also suggests that migraine may be a crucial risk factor for cognitive decline, and it requires further attention and research.

Many studies have shown that years of education is a protective factor that may reduce the chances of cognitive impairment, suggesting that individuals with a longer duration of education are less likely to experience cognitive impairment [35-37]. These studies did not focus on migraineurs, but our results provide support for the applicability of previous findings to migraineurs. Moreover, our findings confirm the previous conclusion that the intensity of headache is positively associated with declined cognitive function in migraine patients [38]. EP Calandre *et al.* [39] suggested that migraineurs with regional brain perfusion abnormalities had poorer performance in verbal and visual memory tests. Another study of 70 migraine patients found that regional cerebral blood flow (rCBF) changes correlated with the degree of migraine severity [40]. In other words, the more serious the migraine attack is, the more it changes in rCBF that were associated with poor cognitive performance.

However, in contrast to previous studies [7, 8, 41, 42], our study found that depression scores were not related to cognitive decline. Moreover, our research demonstrated that migraineurs with higher anxiety scores had an increased impact of cognitive decline. Interestingly, some recent studies in individuals with mood disorders have shown that negative mood status is a risk factor for declining cognitive function that could lead to cognitive impairment [43-47]. This showed that either anxiety symptom or depression symptom alone as

Table 4.   **Possible Influencing Factors of Life Quality.**

Characteristic	Non-adjusted		†Adjusted	
	OR value (95%CI)	*P* value	OR value (95%CI)	*P* value
Age	-0.13 (-0.19, -0.07)	<0.0001*	-0.09 (-0.22, 0.03)	0.1472
Male	-1.00 (-2.55, 0.56)	0.2102	-0.98 (-2.56, 0.59)	0.2217
Han ethnicity	-0.10 (-3.29, 3.09)	0.9527	0.17 (-2.97, 3.32)	0.9141
Right-handed	-0.10 (-3.85, 3.64)	0.9572	-0.06 (-3.69, 3.57)	0.9757
Type of work	0.69 (-2.11, 0.74)	0.3436	0.71 (-1.01, 2.44)	0.4167
Years of Education	0.23 (0.06, 0.40)	0.0072*	0.19 (-0.02, 0.41)	0.0818
BMI	-0.23 (-0.44, -0.02)	0.0299*	-0.06 (-0.28, 0.16)	0.5778
SP	-0.03 (-0.08, 0.02)	0.1877	-0.01 (-0.07, 0.04)	0.5939
DP	0.00 (-0.08, 0.07)	0.9125	0.00 (-0.08, 0.08)	0.9964
Clinical Characters	-	-	-	-
CM	1.13 (-0.62, 2.88)	0.2048	0.89 (-2.19, 3.97)	0.5704
Attack frequency	0.04 (-0.05, 0.14)	0.3652	-0.06 (-0.35, 0.24)	0.6967
Attack duration	-0.00 (-0.04, 0.03)	0.8074	-0.00 (-0.05, 0.04)	0.8390
Headache days/month	0.06 (-0.04, 0.15)	0.2309	0.10 (-0.19, 0.40)	0.4929
VAS score (0-100)	0.20 (0.14, 0.26)	<0.0001*	0.18 (0.12, 0.24)	<0.0001*
Age of migraine onset	-0.14 (-0.20, -0.07)	<0.0001*	-0.02 (-0.13, 0.08)	0.6558
History of migraine	-0.03 (-0.11, 0.06)	0.5244	-0.03 (-0.12, 0.05)	0.4239
Sleep disorders	0.85 (-0.58, 2.27)	0.2451	-0.24 (-1.89, 1.41)	0.7726
Family history	0.77 (-0.86, 2.40)	0.3547	-0.15 (-1.78, 1.47)	0.8522
MoCA total score	0.33 (0.04, 0.61)	0.0257*	0.02 (-0.42, 0.46)	0.9331
Depression scores	0.23 (0.13, 0.33)	<0.0001*	0.26 (0.11, 0.42)	0.0009*
Anxiety scores	0.17 (0.04, 0.31)	0.0119*	-0.09 (-0.29, 0.10)	0.3589

P value < 0.05.
Abbreviations: BMI: Body Mass Index; SP: Systolic blood Pressure; DP: Diastolic blood Pressure; CM: Chronic Migraine; VAS: Visual Analogue Scale; CI: Confidence Interval; OR: Odd Ratio.
† Adjusted: adjusted for age, gender, nationality, type of work, years of education, headache characteristics, sleep disorders, family history of migraine, MoCA scores, HAMA scores and HRSD scores.

a type of negative mood could trigger cognitive decline. Clearly, the relationship between cognitive decline and mood disorders in migraineurs deserves further study. In subsequent studies, we will continue to explore this issue by increasing the sample size.

Additionally, our research revealed that previous studies have not found younger age of migraine onset significantly associated with cognitive decline in migraineurs. Age of migraine onset may be an independent influencing factor of a dramatic decline in cognitive function. In fact, previous studies have suggested that migraine with cognitive decline correlated with neural networks linked to brain activation [48, 49]. Recently, researchers have found that migraine attack is an influencing factor for an alteration of the default mode network (DMN), which is one of the neural networks [34, 50-52]. Some prior studies on the DMN connectivity of migraineurs compared with age-matched healthy controls have indicated that patients with chronic migraine or epi-

sodic migraine had lower connection in the DMN [53-55]. Furthermore, the DMN is a cognitive cerebral network and is associated with episodic memory processing [56, 57]. X Michelle Androulakis et al. suggested that connections in the DMN were positively related to cognitive performance [54]. A study focused on rs-FC alterations in migraineurs during a transition state of brain development demonstrated more alterations of DMN connectivity in a group aged 12 to 18 years old with migraine than in a group aged 19 to 27 years old with migraine [34]. In short, migraineurs of different ages had different degrees of DMN connectivity changes, and younger age of onset might have a greater impact on DMN connectivity. On one hand the above findings might reveal part of the mechanism of migraine accompanying cognitive decline. These findings may as well explain the phenomenon in which migraineurs with younger age of onset had poorer cognitive function in our study. First, the younger the age of migraine onset is, the greater the impact on DMN connectivity will be, which is positively related to cognitive

performance. As a result, cognitive decline is more likely to occur in migraineurs with younger age of onset. Second, a study reported that alterations of rs-FC in young adult migraineurs may be related to the progression of migraine. Moreover, the peak prevalence of migraine is in late adolescence and early adulthood [34]. It is worth noting that rs-FC continues to change during the peak of migraine [58, 59]. Based on these findings, we speculate that migraine may have a greater influence on the brain functional network connectivity of younger-onset migraineurs as the disease progresses compared with later-onset migraineurs.

Based on the results of this study, the possible influencing factors on the quality of life of migraineurs include patients' intensity of headache and depression scores. Similar to previous researches [45], in terms of the severity of headache, we found that more severe the headache was, the worse was patient's quality of life. We assume that migraineurs need to take breaks from work or other events when they have headache attacks. Moreover, severe headaches lead to negative and irrational thoughts that affect interpersonal relationships and decrease the quality of life of migraineurs. Furthermore, consistent with the findings of previous studies [60, 61], we found that depression symptoms were influencing factors that had negative effects on migraineurs' quality of life. Interestingly, similar to the risk factors for cognitive decline in migraineurs, anxiety symptoms did not have a significant impact on migraineurs' quality of life.

To our knowledge, this is the first research to investigate the relationship between the age of migraine onset and cognitive decline in migraineurs. During data collection, we excluded patients with other diseases that affect cognition (such as brain injury, intracranial tumors, and metabolic diseases) to minimize interference as much as possible [20-26]. The result of the current study identified the factors that influence cognitive function in migraineurs. Furthermore, our study provided a scientific basis for the early assessment and intervention of migraineurs' cognitive decline, which might contribute to reducing the burden of disease in migraine patients.

Similar to most clinical studies, several limitations of this study should be acknowledged. First, our research is a cross-sectional study. Second, we did not use Polysomnography to quantify sleep disorders, therefore we did not have sufficient comprehensive data from patients with sleep disorders. To explore the mechanism of migraine-related cognitive decline related to age of migraine onset, more detailed data including functional magnetic resonance imaging (fMRI) data with a larger sample size would be added in further study.

CONCLUSION

Our study focused on exploring the potential influencing factors that contribute to cognitive decline and decreased quality of life in migraineurs. Our findings suggest that the age of migraine onset is independently positively related to migraineurs' cognitive function, and migraine accompanying anxiety symptoms significantly related to decreased quality of life in migraineurs. Therefore, it is necessary to pay more attention to migraineurs with younger age of onset or accompanying anxiety symptoms. The clearer mechanism between age of migraine onset and cognitive decline in migraineurs deserves further research.

LIST OF ABBREVIATIONS

GBD	=	Global Burden of Disease Study
YLDs	=	Years Lived with Disability
ICHD-III	=	The International Classification of Headache Disorders III
MoCA	=	The Montreal Cognitive Assessment
HIT-6	=	Headache Impact Test-6
HRSD	=	Hamilton Rating Scale for Depression
HAMA	=	Hamilton Anxiety Rating Scale
VAS	=	Visual Analog Scale
BMI	=	Body Mass Index
MRI	=	Magnetic Resonance Imaging
SP	=	Systolic Blood Pressure
DP	=	Diastolic Blood Pressure
OR	=	Odds Ratio
CI	=	Confidence Interval
rCBF	=	regional Cerebral Blood Flow
DMN	=	The Default Mode Network
fMRI	=	functional Magnetic Resonance Imaging

AUTHORS' CONTRIBUTION

Li He, Jiajia Bao and Mengmeng Ma designed the study. Jiajia Bao, Mengmeng Ma, Shuju Dong, Lijie Gao, Changling Li and Chaohua Cui acquired the date. Jiajia Bao, Ning Chen and Yang Zhang analyzed the data. Jiajia Bao wrote the article, which all authors reviewed. All authors approved the final version to be published and can certify that no other individuals not listed as authors have made substantial contribution to the paper.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical permission was granted by the Ethics Committee of West China Hospital, Sichuan University (Approval no. 201652).

HUMAN AND ANIMAL RIGHTS

No animals were involved in this study. All the humans procedures were followed in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013 (http://ethics.iit.edu/ecodes/node/3931).

CONSENT FOR PUBLICATION

Informed consent was obtained from all participants.

AVAILABILITY OF DATA AND MATERIALS

The data sets analyzed during the current study are available from the corresponding author [LH] upon reasonable request.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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