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Original Research

Risks and subgroups of cognitive impairment under different marital status among older adults: a latent profile analysis

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Abstract

Background and objective: With aging, cognitive impairment is severe in the aging society. This paper aimed to investigate the association between cognitive impairment and marital status and the empirical typology of cognitive impairment in Chinese aging population.

Methods: Descriptive statistics were performed by retrieving data from the China Health and Retirement Longitudinal Study (CHARLS) to test the relation between cognitive impairment and marital status with univariate linear regression and multivariate linear regression. The subgroups of cognitive impairment for included older subjects were identified with latent profile analysis (LPA).

Results: The sample included 13,149 participants aged 40 years or older. Both unmarried males and females suffer lower cognitive function than married males and females ($P < 0.001$). The declining trend remained consistent ($P < 0.05$) after adjustment for covariates. The participants who were illiterate or older or agricultural hukou had lower cognitive functions than their counterparts. LPA results showed that the cognitive function of participants could be divided into three subgroups.

Conclusions: Unmarried males and females had lower cognitive function than that of married counterparts due to the declined percentage of class two, who have high mental intactness and episodic memory.

Keywords

Cognitive impairment; Latent profile analysis; Marital status; Older adults

1. Introduction

The older adults account for the highest proportion of the population with cognitive impairment, such as dementia, attributed to a pivotal risk factor: age. An estimated 74.7 million people worldwide will suffer from dementia by 2030 [1]. The prevalence of dementia fluctuates in different studies concerning diagnostic criteria, races, regions, etc. [2–4]. In China, a weighted prevalence of dementia in people aged 65 years or older was 5.6% [5]. Furthermore, mild cognitive impairment (MCI), a symptomatic pre-dementia phase, still affects 10%–20% of human beings aged 65 years or older [6]. Treating cognitive impairment has become one of the greatest challenges. The high prevalence of cognitive impairment places a heavy burden on the aging society in China [7, 8]. Therefore, it is urgent to identify the relevant

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factors for cognitive impairment and its subgroups, which may control it more accurately in a simple and low-cost way.

Multiple risk factors for cognitive impairment involved age, genes, diabetes, smoking, and other risk factors like sleep [9–15]. However, surveys of marital status and cognitive impairment are limited for Chinese aging population. Liu *et al.* [16] claimed that participants with marriage-like relationships had lower odds of cognitive impairment than participants with non-marriage relationships. Other studies also reported that the single males had higher odds of cognitive impairment than the married males, not in females [17]. Among unmarried participants, the risks of dementia were detected in both males and females but in men the risks were greater than in women [18]. These studies disclosed that the risks of cognitive impairment vary with gender, which reflected internal differences in the population. What's more, previous studies mentioned above were principally performed in participants aged 55 years or older. There is no national investigation targeting Chinese aging population with different lifestyles and risk factors. Whether this kind of association still exists and the sources of internal differences are unclear.

In this study, the dataset from China Health and Retirement Longitudinal Study (CHARLS) was downloaded. CHARLS aimed at Chinese aging population to investigate the association between marital status and cognitive impairment. Moreover, latent profile analysis (LPA), an individual-centered algorithm, was adopted to identify the empirical typology of cognitive impairment. LPA can confirm the internal association with indiscrete manifest variables and classify individuals into common profiles [19, 20], which may assist controlling cognitive impairment in Chinese aging populations more accurately.

2. Methods

2.1 Data and study samples

CHARLS possessed a set of high-quality datasets representing the whole aging population across China [21]. The baseline dataset collected the information of 17,705 participants. After four steps to clear unqualified samples (**Supplemental Fig. 1**), a total of 13,149 participants comprising 6272 males and 6877 females were enrolled into further analyses. The participants were divided into the married group and the unmarried group. The married group referred to married couples living together. The unmarried group referred to married but not living with spouses, separated, divorced, widowed, and never-married. The "married but not leaving with spouses" means that the most of the time for these couples were not stayed together for reasons such as work. This study was reviewed and approved by the ethics committee of Peking University (IRB 00001052-11014). Written and oral informed consent was obtained from all participants prior to their enrollment in this study.

2.2 Covariates

Seventeen covariates were collected, including age (40–50, 50–60, 60–70 and ≥70), educational levels (illiteracy, elementary school, middle school, high school, and college degree or above), sleeping time (0–6 hours, 6–8 hours, and ≥8 hours), afternoon napping (yes or no), smoking (yes, no, and smoked but quitted), alcohol consumption (never drank, drank but less than once a month, and drank more than once a month), Body mass index (BMI, <18.5 kg/m^2; 18.5–24 kg/m^2; 24–28 kg/m^2; ≥28 kg/m^2) [22], abdominal obesity (waistline ≥90 cm for males and ≥85 cm for females) [23], hypertension, low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol (TC), triglyceride (TG), uric acid, blood urea nitrogen (BUN), glycosylated hemoglobin (Hba1c) and hukou types. Hukou is a household registration system used in China. Participants with agricultural hukou mainly settle in rural areas, while participants with non-agricultural hukou mainly live in urban areas. Hypertension was defined as systolic pressure ≥140 mmHg or diastolic pressure ≥90 mmHg [24]. Hyperuricemia was defined as the concentration of uric acid >420 mmol/L for males and >360 mmol/L for females [25].

2.3 Cognitive assessment

In CHARLS, cognition was evaluated from three cognitive domains, including the dimensions of orientation and attention, visuospatial abilities, and word recall, which were consistent with the American Health and Retirement Study [26]. First, orientation, attention, and visuospatial abilities were aggregated as mental intactness (MI), and assessed by some mental status questions of the Telephone Interview of Cognitive Status (TICS). TICS was a well-designed measure to capture one's MI [27] and it was also used elsewhere to describe one's orientation/attention abilities and visuospatial ability [28]. Participants were asked ten items, including interview date (year, month, day), day of the week, current season, and serial-7 number subtraction questions (up to five times). Then, participants were shown a picture of two pentagons overlapping each other and asked to draw the picture. The scores of MI ranged from 0 to 11 points. Second, word recall representing episodic memory (EM) was performed. EM indicates the memory for autobiographical events [29]. A list of 10 Chinese nouns was read to participants. Then, participants were asked to repeat these ten words (immediate recall), and five minutes later, the participants were asked again (delayed recall) [30]. Each item was assigned as 0 points (answered in error) or 1 point (answered accurately). The mean scores in immediate and delayed word recall were adopted as the final scores of EM (0–10 points). Finally, the scores of MI and EM were aggregated together to form the overall cognitive function scores (0–21 points). The questionnaire was also adopted in previous publications [27, 28, 31].

2.4 Statistical analysis

The continuous data were described using mean ± standard deviation (SD), and the categories of data were proportioned (%). Discrepancies between married and unmarried groups were measured by *t*-test or chi-squared test according to types of the data. The association between marital status and cognitive impairment was assessed by univariate linear regression and multivariate linear regression adjusted for covariates. After this, the latent subgroups of cognitive impairment in participants were identified with LPA. $P < 0.05$ (two-sided) was seen as an indicator of statistical significance. LPA was conducted using Mplus 7.4 (Muthén & Muthén Inc., Los Angeles, CA, USA). Analyses were performed using Stata 15.0 (Stata Corporation, College Station, TX, USA). Figures were made using GraphPad Prism 8.0 version (GraphPad Software Inc., San Diego, CA, USA).

3. Results

3.1 Baseline characteristics of participants

The study included 13149 participants, 52.30% of whom were females, and 11.72% males were unmarried, and 19.56% females were unmarried. The average age of male participants was 59.00 ± 9.28 years old, and that of female participants was 57.55 ± 9.56 years old. More specific descriptions are shown in Table 1.

3.2 Scores of cognitive functions and its components under different marital status

Scores of cognitive functions and its components in different groups are shown in Fig. 1. Fig. 1A shows the scores after adjustment for demographic characteristics, individual behaviours, and blood biomarkers. No declining trend was found in EM of married males and unmarried males ($P <$ 0.05). In Fig. 1B, after adjustment for all the covariates except age, cognitive functions between the married and the unmarried groups declined in all four age groups. In Fig. 1C, after adjustment for all the covariates except educational status, the declining trend of the married and unmarried groups is the same as age. Illiterate participants suffered lower cognitive functions in this study. In Fig. 1D, after adjustment for all the covariates except hukou types, participants with agricultural hukou have lower cognitive functions than people with non-agricultural hukou. Besides, in these two hukou types, a declining trend of cognitive functions still exists in males and females. The cognitive scores of married participants under different ages, education levels, and hukou types are higher than unmarried participants.

3.3 Association between marital status and cognitive functions

Four models were built using linear regression to assess the relationship between marital status and cognitive functions (Table 2). Univariate linear regression was performed in Model 0, displaying a significant association (β = –1.42, P < 0.001 for males & β = –1.56, $P < 0.001$ for females). In Model 1, results remained the same after adjustment for age and education ($P < 0.001$ for males and females). In Model 2, the discrepancy of EM between married and unmarried males was not found after adjustment for demographic characteristics and individual behaviors ($P > 0.05$), while for married and unmarried females, the difference still existed (β = –0.20, $P \leq 0.001$). In Model 3, all demographic characteristics, individual behaviors, and blood biomarkers were adjusted. However, the difference of EM was not found in males, and the discrepancy regarding the cognitive function and its other components was still statistically significant both in males and females ($P < 0.05$).

3.4 Fit indices of LPA for the subgroups of cognitive function in all the participants

The fit indices are shown in Table 3. Akaike information criterion (AIC), Bayesian information criterion (BIC), and adjusted BIC (aBIC) declined with the growing subgroups, indicating a better model. Lo-Mendell-Rubin likelihood ratio test (LMR) and bootstrap likelihood ratio test (BLRT) were all less than 0.0001. It indicated that the more subgroups in the model, the better the model fit; however, three subgroups of participants had the highest entropy index: 0.971, showing an optimal fitting with three class-model and the highest classification quality. Therefore, 3-class model was considered to be the best. Fig. 2 shows the properties of three subgroups. Item 1 to 11 was adopted to assess MI, and item 12 to 31 was adopted to assess EM. Class 2 is divided into high MI and high EM due to the highest mean of item response. Class 3 was divided as low MI and moderate EM due to the low mean of item response in items 8, 9, 10, and 11. Class 1 was divided into middle MI and low EM.

3.5 Alteration for percentages of males and females in three subgroups

Fig. 3 shows that the declining trend of cognitive functions between the married and unmarried groups results from the decreased percentage of class 2 (high MI and high EM), which remains the same trend both in males and females. The percentages of class 1 and class 3 are increased.

4. Discussion

Aging-related diseases like dementia and mild cognitive impairment are hitting high notes due to high prevalence and negative impact. CHARLS is a project aimed at investigating the aged population. It provides us an opportunity to examine the association between cognitive impairment and marital status, and the empirical typology of cognitive impairment in Chinese aging population.

Unmarried groups, including married couples but not living together, the separated, the divorced, the widowed, and the never-married in our study, were not separated into different groups mainly due to its small sample size. The previous study also showed that all unmarried groups share the same higher odds of dementia than the married counterparts [16]. This phenomenon may associate with the char-

TABLE 1. Baseline characteristics of participants.

Characteristics	Males				Females			
	Married	Unmarried	χ^2/t	*P*	Married	Unmarried	χ^2/t	*P*
	Cases (n%)	Cases (n%)			Cases (n%)	Cases (n%)		
Total	5537 (88.28)	735 (11.72)	-	-	5532 (80.44)	1345 (19.56)	-	-
Age group			−11.70	<0.001			23.33	<0.001
40–50	1271 (22.95)	111 (15.10)			1723 (31.15)	250 (18.59)		
50–60	2153 (38.88)	224 (30.48)			2207 (39.90)	361 (26.84)		
60–70	1504 (27.16)	223 (30.34)			1247 (22.54)	364 (27.06)		
>70	609 (11.00)	177 (24.08)			355 (6.42)	370 (27.51)		
Hukou			18.19	<0.001			1.43	0.488
Agricultural Hukou	4129 (74.57)	601 (81.77)			4292 (77.61)	1045 (77.70)		
Non-Agricultural Hukou	1371 (24.76)	131 (17.82)			1202 (21.74)	295 (21.93)		
Others	37 (0.67)	3 (0.41)			36 (0.65)	5 (0.37)		
Educational levels			104.71	<0.001			93.93	<0.001
Illiterate	1422 (25.69)	310 (42.18)			2811 (50.82)	873 (64.91)		
Elementary school	1479 (26.72)	194 (26.39)			1063 (19.22)	219 (16.28)		
Middle school	1598 (28.87)	157 (21.36)			1039 (18.79)	155 (11.52)		
High school	591 (10.68)	45 (6.12)			408 (7.38)	68 (5.06)		
College degree or above	446 (8.06)	29 (3.95)			210 (3.80)	30 (2.23)		
Sleeping time			5.31	<0.001			3.09	0.002
0–6 h	2615 (47.38)	399 (54.73)			2785 (50.74)	701 (53.11)		
6–8 h	2476 (44.86)	269 (36.90)			2290 (41.72)	497 (37.65)		
>8 h	428 (7.76)	61 (8.37)			414 (7.54)	122 (9.24)		
Afternoon napping			0.87	<0.001			0.23	0.8166
Yes	3336 (60.25)	419 (57.01)			2682 (48.48)	638 (47.43)		
No	2201 (39.75)	316 (42.99)			2850 (51.52)	707 (52.57)		
Smoking			0.81	0.666			23.41	<0.001
Yes	3185 (57.52)	428 (58.23)			312 (5.64)	107 (7.96)		
No	1452 (26.22)	182 (24.76)			5128 (92.71)	1196 (88.92)		
Quitted	900 (16.25)	125 (17.01)			91 (1.65)	42 (3.12)		
Alcohol consumption			13.67	0.001			3.25	0.196
Never	2381 (43.00)	369 (50.20)			4895 (88.49)	1168 (86.84)		
Less than once a month	602 (10.87)	70 (9.52)			280 (5.06)	73 (5.43)		
More than once a month	2554 (46.13)	296 (40.27)			357 (6.45)	104 (7.73)		
BMI (kg/m^2)			35.39	<0.001			36.70	<0.001
<18.5	276 (5.96)	55 (8.89)			261 (5.63)	89 (7.85)		
18.5–24	2717 (58.63)	416 (67.21)			2088 (45.00)	594 (52.38)		
24–28	1239 (26.74)	111 (17.93)			1581 (34.07)	322 (28.40)		
≥28	402 (8.68)	37 (5.98)			710 (15.30)	129 (11.38)		
Abdominal obesity			16.59	<0.001			6.40	0.011
Yes	1447 (30.91)	143 (77.05)			1568 (33.55)	340 (29.64)		
No	3234 (69.09)	480 (22.95)			3105 (66.45)	807 (70.36)		
Hypertension			27.08	<0.001			48.45	<0.001
Yes	1818 (37.80)	309 (48.51)			1830 (38.11)	577 (49.23)		
No	2991 (62.20)	328 (51.49)			2972 (61.89)	595 (50.77)		
Low density lipoprotein (LDL)			0.32	0.572			0.12	0.732
≤130 mg/dL	2710 (72.44)	347 (73.67)			2578 (65.41)	569 (64.81)		
>130 mg/dL	1031 (27.56)	124 (26.33)			1363 (34.59)	309 (35.19)		
Total cholesterol (TC)			2.07	0.151			1.32	0.251
≤200 mg/dL	2448 (65.31)	322 (68.66)			2252 (57.07)	483 (54.95)		
>200 mg/dL	1300 (34.69)	147 (31.34)			1694 (42.93)	396 (45.05)		
High density lipoprotein (HDL)			1.84	0.175			0.43	0.511
≤40 mg/dL	1059 (28.04)	119 (25.27)			862 (21.83)	183 (20.82)		
>40 mg/dL	2691 (71.76)	352 (74.73)			3087 (78.17)	696 (79.18)		
Triglyceride (Tg)			4.93	0.026			0.85	0.356
<150 mg/dL	2806 (74.85)	373 (79.53)			2789 (70.68)	635 (72.24)		
≥150 mg/dL	943 (25.15)	96 (20.47)			1157 (29.32)	244 (27.76)		
Uric acid			0.28	0.595			7.29	0.007
Non-hyperuricemia	3503 (93.41)	443 (94.06)			3782 (95.75)	823 (93.63)		
Hyperuricemia	247 (6.59)	28 (5.94)			168 (4.25)	56 (6.37)		
Blood urea nitrogen (BUN)			0.76	0.384			2.15	0.142
<21 mg/dL	3214 (85.75)	396 (84.26)			3629 (91.85)	794 (90.33)		
≥21 mg/dL	534 (14.25)	74 (15.74)			322 (8.15)	85 (9.67)		
Glycosylated hemoglobin (Hba1c)			7.73	0.005			0.08	0.784
≥6%	252 (6.70)	16 (3.39)			303 (7.64)	65 (7.37)		
<6%	3512 (93.30)	456 (96.61)			3663 (92.36)	817 (92.63)		

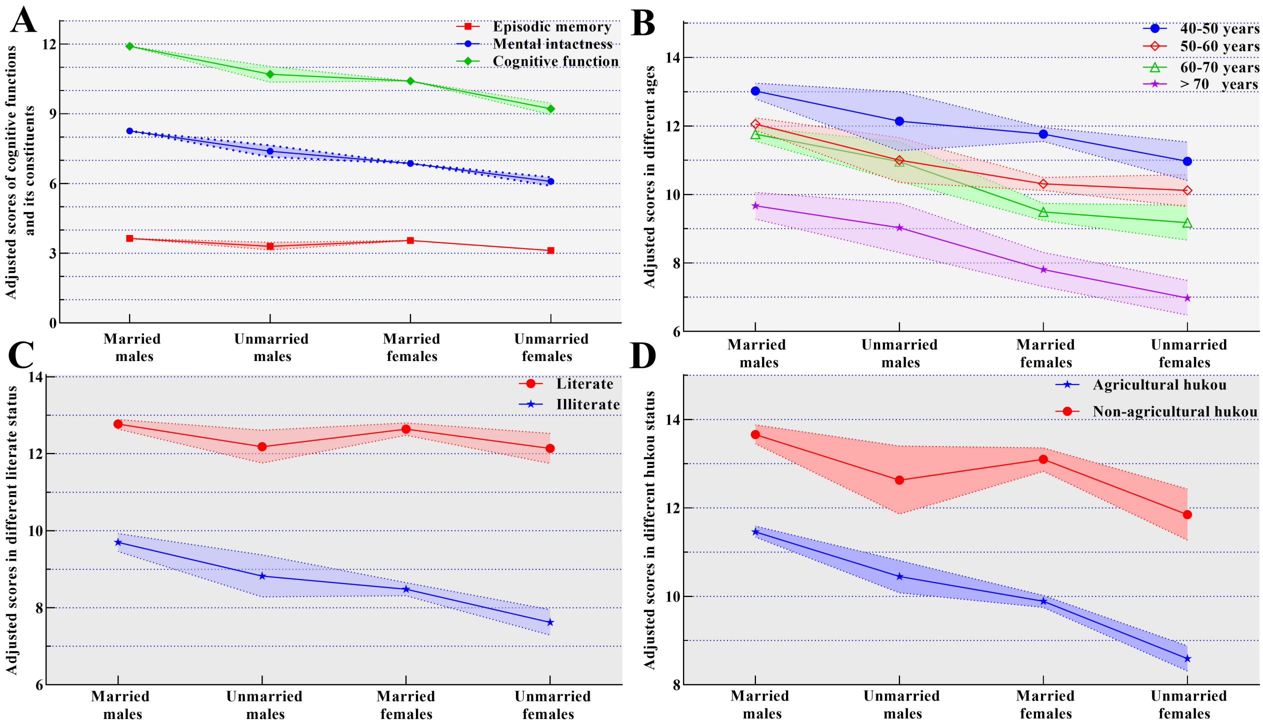

FIG. 1. Adjusted scores of cognitive functions and its constituents in different age, educational levels and hukou status.
Notes: The light colour area meant the 95% confidence interval of cognitive function scores. (A) shows the scores after adjustment for demographic characteristics, individual behaviors, and blood biomarkers. (B) shows the scores after adjustment for all the covariates except age. (C) shows the scores after adjustment for all the covariates except educational status. (D) shows the scores after adjustment for all the covariates except hukou types.

TABLE 2. Associations between marital status and cognitive functions.

Males			Females		
Variables	β (95% confidence interval)	*P*	Variables	β (95% confidence interval)	*P*
Model 0			**Model 0**		
Mental intactness	−0.99 (−1.19 to −0.78)	<0.001	Mental intactness	−1.03 (−1.21 to −0.85)	<0.001
Episodic memory	−0.43 (−0.57 to −0.29)	<0.001	Episodic memory	−0.53 (−0.64 to −0.41)	<0.001
Cognitive functions	−1.42 (−1.70 to −1.13)	<0.001	Cognitive functions	−1.56 (−1.81 to −1.30)	<0.001
Model 1			**Model 1**		
Mental intactness	−0.55 (−0.74 to −0.36)	<0.001	Mental intactness	−0.43 (−0.59 to −0.27)	<0.001
Episodic memory	−0.15 (−0.29 to −0.02)	<0.05	Episodic memory	−0.19 (−0.34 to −0.25)	<0.01
Cognitive functions	−0.70 (−0.96 to −0.44)	<0.001	Cognitive functions	−0.62 (−0.84 to −0.40)	<0.001
Model 2			**Model 2**		
Mental intactness	−0.41 (−0.61 to −0.20)	<0.001	Mental intactness	−0.34 (−0.52 to −0.17)	<0.001
Episodic memory	−0.01 (−0.15 to −0.13)	0.903	Episodic memory	−0.20 (−0.32 to −0.08)	<0.01
Cognitive functions	−0.41 (−0.70 to −0.13)	<0.01	Cognitive functions	−0.54 (−0.79 to −0.30)	<0.001
Model 3			**Model 3**		
Mental intactness	−0.37 (−0.62 to −0.11)	<0.01	Mental intactness	−0.27 (−0.48 to −0.06)	<0.05
Episodic memory	−0.00 (−0.18 to −0.17)	0.969	Episodic memory	−0.15 (−0.29 to −0.01)	<0.05
Cognitive functions	−0.37 (−0.72 to −0.03)	<0.05	Cognitive functions	−0.42 (−0.71 to −0.13)	<0.01

acteristics of the unmarried, who have more possibilities of loneliness at home, leading to cognitive impairment [32, 33]. Furthermore, reduced sexual intercourse may contribute to cognitive impairment. Marriage-like relationships, including the married and the cohabitated, shared similar lower risks of cognitive impairment due to more sexual intercourse possibly [34]. L Scheunemann *et al.* [35] showed that Sperm peptides could enhance long-term memory by stimulating neurons in the uterus of female Drosophila, indicating that sexual intercourse could be a barrier to cognitive impairment.

Our study reveals that unmarried males and unmarried females have lower cognitive function than married counterparts, consistent with a previous study [16]. However, Feng *et al.* [17] found that only men had higher odds of cognitive impairment statistically but not women in Singapore. Social engagement may explain this difference. A previous study indicated that women might have higher intimate relationships and social engagement with their friends than men

TABLE 3. Indices of latent class analysis for cognitive classes in all the participants.

Class	k	AIC	BIC	aBIC	Entropy	LMR	BLRT	Class probability (%)
1	31	491470.74	491702.75	491604.23	-	-	-	-
2	63	447923.28	448394.78	448194.57	0.957	<0.0001	<0.0001	50.70/49.30
3	95	433161.43	433872.42	433570.52	0.971	<0.0001	<0.0001	11.41/45.98/42.61
4	127	427565.84	428516.32	428112.72	0.921	<0.0001	<0.0001	44.27/24.11/20.45/11.17
5	159	422486.45	423676.42	423171.13	0.883	<0.0001	<0.0001	20.04/15.51/33.10/23.44/7.92

k, number of free parameters; AIC, Akaike information criterion; BIC, Bayesian information criterion; aBIC, adjusted Bayesian information criterion; LMR, Lo-Mendell-Rubin likelihood ratio; BLRT, parametric bootstrapped likelihood ratio test.

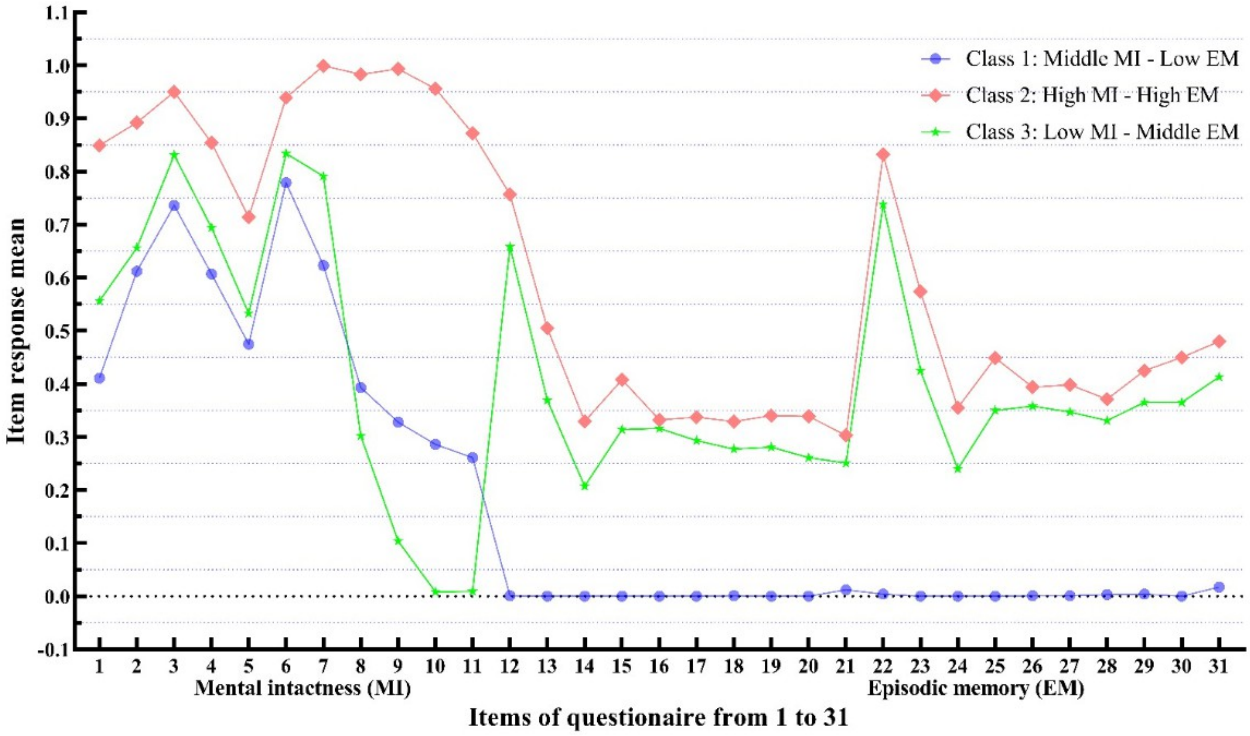

FIG. 2. Item response mean of the three different cognitive function classes.

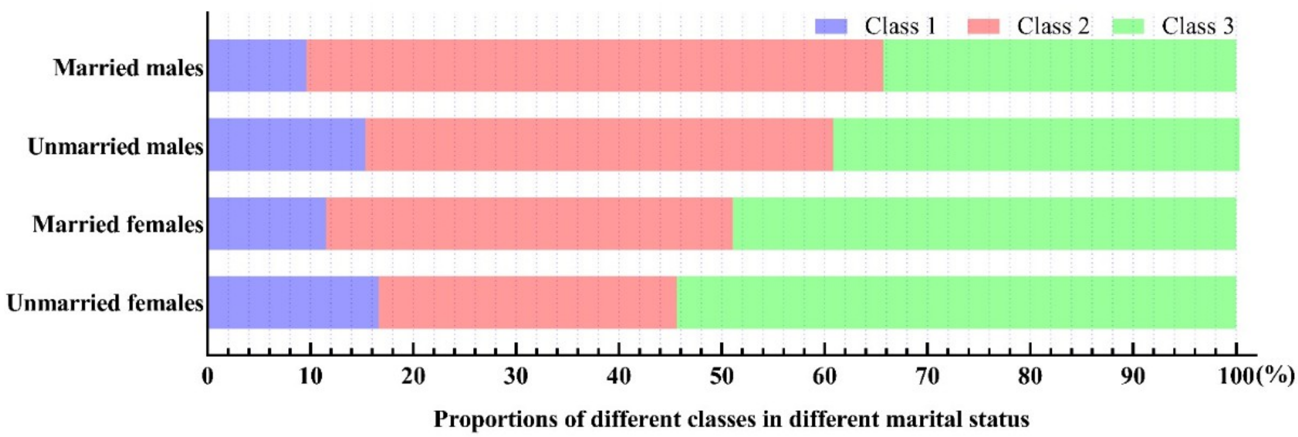

FIG. 3. Alteration for percentages of males and females in three subgroups.

[36]. Loneliness could contribute to the increased risk of dementia in Chinese citizens aged 65 years or older [37]. Further prospective cohort investigation in Chinese should be performed to evaluate the discrepancy.

Gender differences should be further highlighted in the current study. Hormones, such as estrogen, progesterone and androgen, are crucial factors in initial cognitive impairment with gender differences [38, 39]. The decline of estrogen level in menopausal women will arouse the higher prevalence of cognitive impairment and Alzheimer's Disease (AD), but the change of hormones is more moderate in men amid this process [40]. In the clinical report, women have shown an overall and rapid decline of cognition after bilateral ovariectomy with the decrease of estrogen in pathological conditions [41]. In the rat experiment, the relationship between hypothalamus pituitary-gonad axis (HPGA) and cognition has been attached to neuroscience [42]. It was found that the female mice perform the worse spatial memory ability when they were in the concentration of high luteinizing hormone [42]. From the perspective of sociology, it has been showed that females have a positive association with high press, depression, poor education and exercise, as well as more chronic disease accounted for cognitive decline than males [43–46]. However, smoking habit is a major risk for cognition in males [47]. Therefore, gender difference and gender modification should be paid more attention between marital status and cognitive impairment based on previous neuroscience researches.

Declining trends of cognitive functions were also observed in different literature status, and hukou types in this study. Literate participants showed higher scores of cognitive functions than illiteracy as previous surveys performed in Chinese aging population [48]. This may be attributed to better lifestyles, compliance with doctors, and more social resources possibly. In our study, participants with agricultural hukou mainly living in rural areas have lower scores of cognitive functions than participants with non-agricultural hukou, who mainly settle in urban areas. A study performed in Chinese aged 65 years old and above indicated that inadequate access to healthcare in rural areas might be the cause why rural settlers had worse cognitive impairment [49]. More active healthcare for the older adults, improved education, and balanced medical resources should be considered to reduce cognitive impairment.

This study still has some limitations. First, the percentage of different marital status in different age groups is unevenly distributed, which may bias the final results. Additionally, it should be noted that this cross-sectional study cannot examine the causality between marital status and cognitive impairment. In future studies, longitudinal cohort studies and endeavors targeting the high-risk subgroups in Chinese older adults should be made. Moreover, due to the small size of these subgroups like the divorced, the widowed and etc. in the unmarried group, subgroups are not taken into analyses separately, which limits a further understanding of full spectrum.

This study firstly identifies the latent subgroups of cognitive impairment in Chinese aging population with a representative sample dataset. It provides a novel perspective to decrease the high prevalence of cognitive impairment in the aged. Targeting the identified high-risk subgroups may facilitate to contain the high prevalence of cognitive impairment.

5. Conclusions

For Chinese aging population, unmarried males and females had lower cognitive functions than the married counterparts. A comprehensive cognitive assessment of the high-risk subgroup who have high mental intactness and episodic memory should be evaluated earlier and more frequent than other subgroups. Additionally, more active prevention endeavors including intelligent exercises, nutrition support etc., before and/or after admitted to hospital should be considered.

Author contributions

YX and YCZ carried out the data analyses and drafted the manuscript; FXZ, CJW, XYZH and FQ helped to revise the manuscript; JHY conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Ethics approval and consent to participate

This study was reviewed and approved by the ethics committee of Peking University (IRB 00001052-11014). Written and oral informed consent was obtained from all participants prior to their enrollment in this study.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://jomh.org/articles/10.31083/jomh.2021.092.

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