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•ORIGINAL RESEARCH ARTICLE•

The Study of White Matter Hyperintensity (WMH) and Factors Related to Geriatric Late-Onset Depression

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Background: Geriatric depression is one of the most common and harmful mental illnesses seen in the elderly. However, there are few studies focusing on the relationship between late-onset depression (LOD) and social and psychological factors, as well as brain structure.

Aims: To explore factors related to late-onset depression (LOD) in elderly patients.

Methods: 24 first onset LOD patients over 60 years old (meeting ICD-10 diagnostic criteria for depression) and 23 non-depressed elders were selected for inclusion into this study. Scale assessments, including Fazelas-scale for white matter hyperintensity (WMH) high signal level and the MTA-scale for medial temporal lobe atrophy levels, were combined with general demography and sociology data to find factors related to LOD.

Results: There was no significant difference in age (t=0.419, p=0.678), gender (X^2=1.705, p=0.244), or years of education (t=1.478, p=0.146) between the two groups. However, statistical differences were shown on scores on the WMH, (X^2=7.817, p=0.008), periventricular white matter hyperintensity (PWMH)(Fisher exact test: p=0.031), having or not having religious beliefs (Fisher exact test: p=0.265) and family harmony (yes or no) (Fisher exact test: p=0.253) between the LOD group and control group. The results of linear regression analysis showed that the total score for WMH, religious beliefs (with or without) and family harmony (yes or no) were associated with depressive symptomology.

Conclusion: Scores on the WMH, religious beliefs and family harmony are all potentially related to LOD in elderly patients.

Key words: Geriatric depression, Late onset, MRI, White matter hyperintensity, Religious belief, Family harmony

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1. Background

With the rapid aging of China's population, far more attention in research has been given to mental illness in the elderly. Geriatric depression is one of the most common and harmful mental disorders seen in the elderly. Studies outside of China reported a 3.7%-10% risk of geriatric depression in those over 65 years old [1], whereas in China this number was 39.86%.[2] As this disorder can bring serious psychological and financial burden to families and society it is a serious public health problem. First episode depression in the elderly (i.e. late-onset depression [LOD]) is a special subtype of

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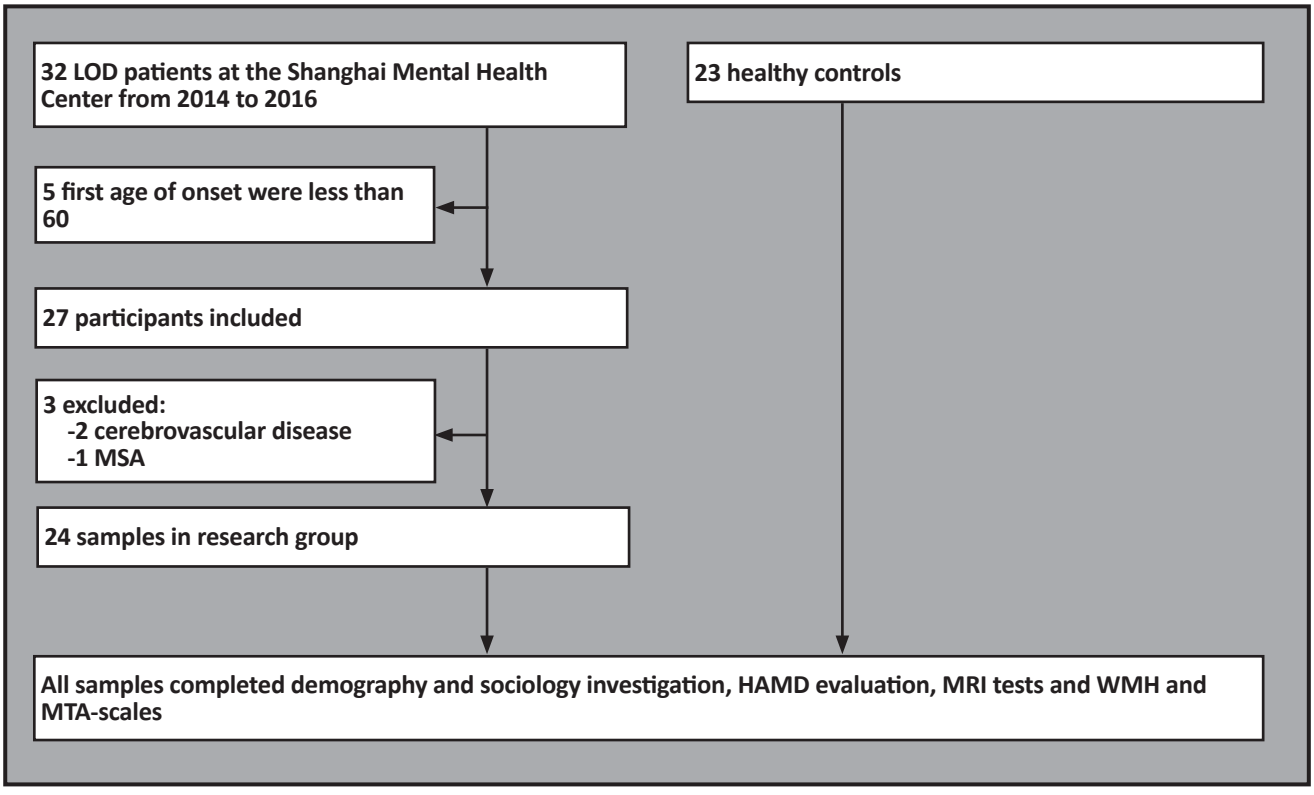
depression seen in the elderly. Features of LOD include cognitive impairment with multiple mood symptoms.[3] The latest studies show that LOD has similar pathology to dementia, and could be regarded as a risk factor for Alzheimer's disease (AD).[4] Currently, little research has been published on LOD, and there are no clinical drugs or diagnostic biomarkers for LOD.[5] Previous research reported lesion of frontal lobes and impairment of basal ganglia in LOD.[6] However, white matter hyperintensity (WMH) was also reported as a key factor in LOD.[7] Compared with early onset depression (EOD) patients, LOD had more WMH and cognitive disorder.[8] Because previous results with multiple social and psychological factors were not considered, our study explores the relationship between LOD symptoms and brain structure (WMH and medial temporal lobe atrophy) to find factors related to LOD prognosis and regression.

2. Methods

2.1 Research participants

For the process of this study please refer to figure 1. Patients with LOD were selected from the Shanghai Mental Health Center between 2014 and 2016. Inclusion criteria were the following: (a) meeting diagnostic criteria for depression according the International Classification of Diseases tenth edition (ICD 10); (b) age of onset of depression over 60; (c) Scores over 20 on the Hamilton Depression Rating Scale (HAMD-17); (d) Mini-Mental State Examination (MMSE) scores for the following educational levels: illiterate≥17, primary school education≥20, middle school or above education≥24; (e) No history of hypomania or mania. Exclusion criteria were the following: (i) depressive disorder caused by psychoactive substances, somatic disorders, dementia and other mental disorders; (ii) having early onset depression or bipolar disorder; (iii) comorbidity with a serious organic disease (such as disease of cardiovascular, lung, liver, kidney, endocrine, or hematopoietic systems), or, tobacco or alcohol dependence; (iiii) unable to conduct MRI due to metal implants. All participants were clinically evaluated by 2 experienced psychiatrists. The total sample was 32 participants, however 5 were excluded because their age of first episode was less than 60; 2 were unable to complete the imaging test and 1 had an organic mood disorder. There were 24 participants included in the final sample. 23 healthy controls (HC) were also recruited for participation. There was no significant difference between the two groups in gender (X^2=1.705, p=0.244), age (t=0.419, p=0.678), years of education (t=1.478, p=0.146), somatopathy (Risk factors of cerebral vessels, X^2=0.171, p=0.766; hypertension, X^2=1.733, p=0.248; cardiopathy, X^2=0.865, p=0.416; diabetes, X^2=3.179, p=0.137; hyperlipidemia, X^2=0.865, p=0.416; stroke, X^2=0.001, p=1, cancers, X^2=0.979, p=1). Patients or guardians signed informed consent before the study. This study was approved by the Ethics Committee of the Shanghai Mental Health Center.

Figure 1. The flowchart of the study



2.2 Research methods

2.2.1 Head MRI test

MRI tests using Siemens 3.0 Tesla high field MRI HVI (Germany). Scanning coils were 12 channels. MRI tests, including T1, T2 weighted and FLAIR weighted scanning, were used to observe subjects' brain morphology for excluding organic disease in patients. Parameters were the following: spin-echo (SE) T2-weighted imaging (T2WI): repetition time (TR)/time of echo (TE)=400/117 ms, seam thickness=5.0 mm, lamellar spacing=1.5 mm, field of view (FOV)=230 mm, Matrix=320; FLAIR weighted imaging: TR/TE=8500/94 ms, seam thickness=5.0 mm, lamellar spacing=1.5 mm, FOV=230 mm, Matrix=256.

2.2.2 WHM lesion classification

According to T2WI and FLAIR sequential visual scale evaluation, we chose the Fazekas scale to evaluate WHM lesion level. This scale has been shown to be reliable and valid in studies published both in China and abroad. It has also been applied for clinical use.[9] The Fazekas scale divides Periventricular white matter hyperintensity (PWMH) scores and Deep white matter hyperintensity (DWMH) scores. Score standards are the following: PWMH scores: (a) no lesion: 0 points, (b) cap or pencil like layer lesions: 1 point, (c) smooth halo like lesions: 2 points, (d) erose lesions PWMH to DWMH: 3 points. DWMP scores: (a) no lesion: 0 points, (b) point like lesions: 1 point, (c) a few fusion lesions: 2 points, (d) more fusion lesions: 3 points. Fazekas scores are the following: Level 0: none or 1 WHM lesion point; Level 1: multiple lesion points; Level 2: fusion lesions (bridge like); Level 3: fused as large focus. Many studies have shown that Level 2 or 3 Fazekas scores are pathological and carry the risk of disability. According to other WHM studies[9], Fazekas scores of 0-1 were normal, but 2-3 indicated WHM.

2.2.3 Medial temporal lobes atrophy classification

According to T1WI layer scales, we used medial temporal lobes atrophy (MTA-scale)[10] as the temporal lobes atrophy evaluation method: choosing a layer through the hippocampus coronal plane in front of the pons. Score standards were the following: Level 0: no lesion; Level 1: only choroid fissure broadness; Level 2: accompanied with cornu temporale ventriculi lateralista enlargement; Level 3: decreased hippocampus height; Level 4: hippocampus volume reduced dramatically.

2.2.4 Depression evaluation and investigation of related factors

We used the HAMD scale to evaluate depression in the two groups.[11] In addition, we also investigated depression related factors: daily life styles (smoking or drinking), religion, incomes, family harmony, and so on. The investigation was applied with standard questionnaires, including gender (male, female), age (years), education (years), occupation (physical labor, mental labor), religion (yes, no), marriage (married, divorced, widowed), personality style (introversion, extroversion, mixed), smoking (yes, no), drinking (yes, no), fixed income (yes, no), place of residence (rural, urban), and family harmony (yes, no)

2.3 Statistical analysis

We used descriptive analysis methods. Continuous variables were shown by mean (SD) and categorical variables were shown by percentage. We used SPSS 20 to analyze data. T-test was applied to analyze continuous variables in 2 groups, while chi squared or Fisher's test was used to analyze categorical variables. We set statistical significance at $p<0.05$. After significant data was screened, HAMD total points were regard as the dependent variable to analyze depression related factors by linear regression, with $p<0.05$ indicating statistical significance.

3. Results

There was no statistical difference between the two groups in sex, age, career, marriage, personality before illness, smoking, drinking, income and residence. Compared with LOD, the control group was more religious (Fisher: $p=0.002$) and had more harmonious families (Fisher: $p=0.050$). Meanwhile, control HAMD scores was significantly lower than the LOD group ($t=17.381$, $p<0.001$). Statistical results were shown on Table 1.

As Table 2 shows, PWMH and WHM scores had significant differences (Fisher: $p=0.031$; $X^2=7.817$, $p=0.008$), but DWMH and MTA had none (Fisher: $p=0.265$; 0.253). Classic cases Fazekas scores in the two groups are shown in Figures 2 and 3. For further study, we used Pearson analysis to figure out the PWMH and WMH in the LOD group with age of onset of illness, however no significance was found. ($t=-0.035$, $p=0.881$; $t=-0.342$, $p=0.129$) See Table 3.

In Table 4, linear regression results (HAMD scores as the dependent variable; religion, family harmony and white matter total scores as independent variables) showed religion, family harmony and white matter scores were significantly related to depression ($t=3.347$, $p=0.002$; $t=3.164$, $p=0.003$; $t=3.404$, $p=0.001$).

4. Discussion

4.1 Main findings

LOD and EOD have some common pathogenic factors, but LOD also includes organic factors (brain degeneration and cerebrovascular lesions) and special psychosocial factors at these ages. Our study compared those with LOD with healthy controls and found more white matter impairment in LOD (79.2%). And linear

Table1. Comparison of demographic and sociological data between the two groups

Demographic factor	late-onset depression (*n*=24)	healthy control (*n*=23)	X^2 / *t*	*P*
Gender (*n*,%)				
Male	8(33.3%)	12(52.5%)	1.705	0.244
Female	16(66.7%)	11(47.8%)		
Age($\bar{x}$((SD),year)	71.25(6.60)	70.30(8.69)	0.419	0.678
Education($\bar{x}$(SD),year)	9.63(5.13)	11.65(4.21)	1.478	0.146
Profession(*n*,%)				
Mental labor	9 (37.5%)	13(56.5%)	1.707	0.248
Manual labor	15(62.5%)	10(43.5%)		
Religion(*n*,%)				
Yes	0	8(34.8%)	*Fisher's*	0.002*[a]
No	24(100%)	15(65.2%)		
Marital status (*n*,%)				
Married	19(79.2%)	21(91.3%)		
Divorced	2(8.3%)	0	*Fisher's*	0.581[a]
Widowed	3(12.5%)	2(8.7%)		
Personality type (*n*,%)				
Introversion	15(62.5%)	7(30.4%)		
Extroversion	7(29.2%)	10(43.5%)	*Fisher's*	0.076[a]
Mixed	2(8.3%)	6(26.1%)		
Smoker (*n*,%)				
Yes	22(91.7%)	22(95.7%)	*Fisher's*	1.000[a]
No	2(8.3%)	1(4.3%)		
Drinker (*n*,%)				
Never	22(91.7%)	20(87.0%)		
Once in a while	1(4.2%)	3(13.0%)	*Fisher's*	0.475[a]
Often	1(4.2%)	0		
Fixed-income (*n*,%)				
Yes	22(91.7%)	22(95.7%)	*Fisher's*	1.000[a]
No	2(8.3%)	1(4.3%)		
Residence (*n*,%)				
Urban	20(83.3%)	21(91.3%)	*Fisher's*	0.666[a]
Rural	4(16.7%)	2(8.7%)		
Family harmony (*n*,%)				
Yes	19(79.2%)	23(100%)	*Fisher's*	0.050*[a]
No	5(20.8%)	0		
HAMD	33.17(8.06)	4.00(1.60)	17.381	<0.001*

*$p<0.05$

[a] Fisher's exact test

Table 2. Comparison of visual scores of WMH and MTA between two groups

	late-onset depression (*n*=24)	Healthy contro (*n*=23)	X^2	*P*
PWMH score				
1	8(33.3%)	16(70.0%)		
2	8(33.3%)	5(21.7%)	*Fisher's*	0.031*[a]
3	8(33.3%)	2(8.7%)		
DWMH score				
0	3(12.5%)	4(17.4%)		
1	7(29.2%)	12(52.2%)	*Fisher's*	0.265[a]
2	10(41.7%)	6(26.1%)		
3	4(16.7%)	1(4.3%)		
WMH rating				
0-1	5(20.8%)	14(60.9%)	7.817	0.008*
2-3	19(79.2%)	9(39.1%)		
MTA score				
1	8(33.3%)	12(52.2%)		
2	14(58.3%)	11(47.8%)	*Fisher's*	0.253 [a]
3	2(8.3%)	0		

*$P<0.05$
[a] Fisher's exact test。
PWMH: Periventricular white matter hyperintensity; DWMH: Deep white matter hyperintensity; WMH: white matter hyperintensity; MTA: Medial temporal lobes Atrophy

Figure 2. A 71-year-old female healthy control subject with hypertension, Fazekas score: caps of hyperintensity surrounding ventricles (PWMH=1); punctate foci of high signal intensity in deep white matter (DWMH=1)

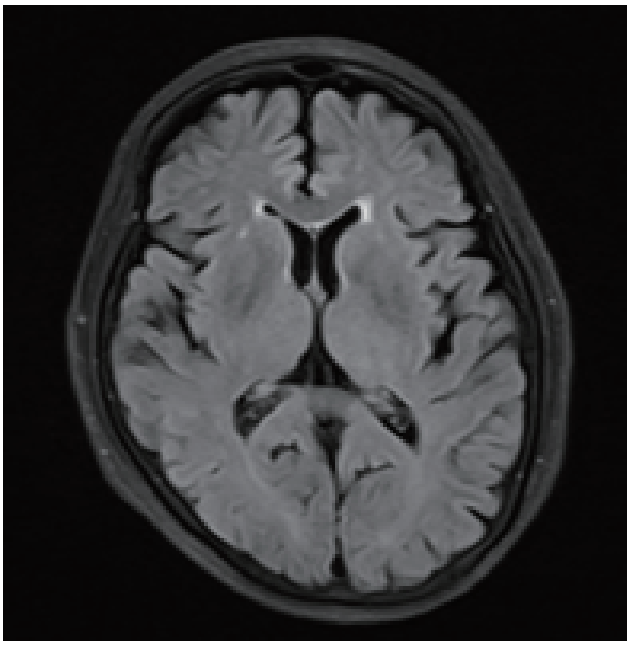


Figure3. A 70-year-old female with late-onset depression and hypertension, Fazekas score: irregular periventricular signal extending into the deep white matter(PWMH=3); beginning confluence of these punctate foci are noted in subcortical white matter (DWMH=2)

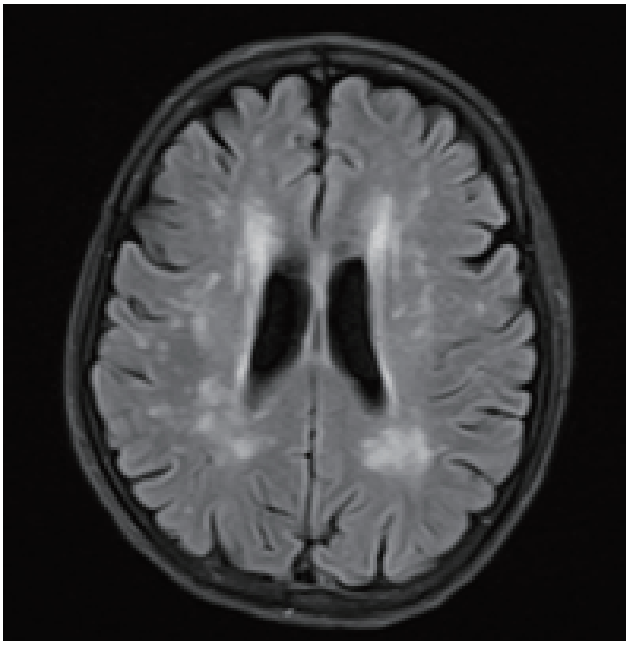


Table 3. Correlation analysis between PWMH score , WMH rating and age of onset

	PWMH score	WMH rating
Age of onset	-0.035	-0.342
Sig.(2-tail)	0.881	0.129
(n)	21	21

PWMH: Periventricular white matter hyperintensity;
WMH: white matter hyperintensity

Table 4. Possible factors associated with depression

Group	B	Standard error	Standard coefficient	T	*p*
Constant	-49.911	11.709		-4.263	<0.001
Religion	15.883	4.746	0.381	3.347	0.002
WMH score	12.219	3.590	0.383	3.404	0.001
Family harmony	18.297	5.782	0.360	3.164	0.003

Linear regression was used to analyze the depression related factors

regression results showed that WMH is significantly related to depression. Previous studies reported that WMH was related to LOD.[12] Even after adjusting age, hypertension, diabetes and ischemic heart disease, LOD white matter impairments were still more than those found in healthy controls.[13] Diffusion tensor imaging (DTI) also showed white matter impairments in the LOD frontal lobe, temporal lobe and midbrain, as well as impairment in the limbic orbital network. Abnormal white matter was more common and significant in LOD than EOD.[14] Maillard's study found[15] that WHM could also decrease cognition in those with LOD. He concluded that the accumulation of damage on small and microvascular vessels is a common neuropathological route in the elderly, leading to depression and cognitive decline, and deep white matter hyperintensity (DWMH) is an important risk factor for these episodes of LOD. These conclusions were not consistent with our findings in which the high signal of periventricular white matter hyperintensity (PWMH) was a factor affected by LOD. This could be related to the small sample size of our study. The mechanism of white matter impairment to depression may be the following 2 parts: 1) White matter lesion was mainly small vessel lesions. Lower blood supply inhibits axon functions (including some neurotransmitters production and releasing)[15]. 2) Many nerve fibers crossed white matter, and they can form neural circuits. Once white matter is impaired, these fibers could also be impaired, and then it can inhibit neural circuitry to promote depression.[16] In our study, although age and sex in the LOD group were matched with controls, we still found some significant white matter impairments in elders in the control group. Vonetta[17] posited that elders have a large variation in WMH. On the other hand, LOD had more relationship with white matter impairment caused by active ischemia, it was not only WMH accumulation. Meanwhile, the "vascular depression hypothesis" mechanism states that LOD only works together with age, physical disease and psychosocial factors to achieve mood and cognitive disorder, in addition to the key factors of cerebrovascular disease and WMH.[18] Thus, whether white matter impairment is the pathomechanism for LOD remains to be seen.

Comparing factors in LOD, including the effects of WMH, we concluded that psychosocial factors deserve more attention. For example religion and family harmony seemed to be correlated with lower incidence of LOD. Some reports indicated that religious beliefs can prevent depression relapse, with an effect rivaling anti-depressants. It may be because religious beliefs can increase brain DMN function.[19] We analyzed brain MRI data from participants in this study, which may shed light on the role religious belief has on DMN and other functions.[19] In addition family harmony was correlated with lower incidence of LOD. It can be shown that the elderly live somewhat socially restricted lives, with families generally being a key part of their social lives. Family problems can serious affect the elderly. Therefore conflict or stress within the family may be one of the important factors in geriatric depression. Some studies[20, 21] indicated that maintaining physical health and receiving family support can improve patients with LOD overall happiness, reduce drug usage and prevent depression relapse. Our findings seem to indicate the same as these studies.

4.2 Limitations

Our study considered only a few factors relevant to LOD. Because of time and space limitations in sample selection, fewer first onset LOD samples led to a small

sample size in this study, especially in the DWMH variation analysis in LOD and controls. And samples were only from patients in the hospital. Thus further studies require larger sample size with standardized inclusion criteria.

4.3 Implications

Our study found white matter was related with LOD, but it is not clear whether white matter impairment is a risk factor for LOD or a pathomechanism for LOD. However, religious belief and family support may be protective factors for depression. Therefore prevention of geriatric depression via psychosocial methods such as religious activities and improving family harmony deserves further support.

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Conflicts of interest statement

Authors report no conflict of interest related to this manuscript.

Informed consent

All subjects or their guardians provided written informed consent.

Ethical approval

This study was approved by the ethics committee of the Shanghai Mental Health Center.

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Authors' contributions

WANG Jing-hua: researcher;

LI Wei: data collection and analysis;

YUE Ling: researcher;

HONG Bo: data collection;

AN Na: data collection;

LI Guan-jun: researcher;

XIAO Shi-fu: supervision.

晚发型老年抑郁症发病相关因素分析

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背景： 老年抑郁症是老年人常见且危害性大的精神疾病之一，但目前对晚发型老年抑郁症与之相关的社会、心理学及脑结构因素之间的联系的研究较少。

目的：探讨晚发型老年抑郁症（LOD）的相关因素。

方法：共纳入 24 例首次发病年龄大于 60 岁的晚发型老年抑郁症患者（诊断符合 ICD-10 抑郁症的诊断标准）和 23 例健康老人作为研究的对象。通过视觉评估量表：Fazekas 量表评估脑白质高信号的严重程度，MTA 量表评估内侧颞叶萎缩程度，结合一般人口学资料及社会学资料，寻找晚发型老年抑郁症的影响因素。

结果：两组间的年龄 (t=0.419, p=0.678)、性别 (X^2=1.705, p=0.244)、教育程度 (t=1.478, p=0.146) 均无统计学差异。两组人群在脑白质高信号评分 (WMH)、脑室旁高信号评分（PWMH）、宗教信仰（有或无）和家庭和睦（是或否）亚项上存在差异（X^2=7.817, p=0.008；Fisher 精确检验：p=0.031；Fisher 精确检验：p=0.265；Fisher 精确检验：p=0.253），而逐步线性回归的结果显示，脑白质高信号评分、宗教信仰（有或无）和家庭和睦（是或否）是老年抑郁的相关因素。

结论：脑白质高信号是晚发型老年抑郁症的风险因素，而具有宗教信仰和 / 或家庭和睦是其保护性因素。

关键词：老年抑郁症；晚发型；MRI；脑白质高信号；宗教信仰；家庭和睦

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