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Postprint: Association Between Subjective Cognitive Decline and Chronic Disease Multimorbidity in Older Adults

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Date: 2022-11-23T00:00:00+00:00

Abstract

Background Subjective cognitive decline (SCD) represents a target stage for early prevention of Alzheimer' s disease. Investigating its associated influencing factors and controlling modifiable factors can help slow the progression of Alzheimer's disease. Multimorbidity is known to be an important modifiable risk factor for objective cognitive impairment, yet research on its correlation with subjective cognitive decline remains limited and inconclusive. Objective To explore the correlation between SCD and multimorbidity in elderly individuals, providing a theoretical basis for early prevention and intervention of Alzheimer' s disease. Methods From January 2021 to June 2022, 612 elderly individuals aged $ $60 years were selected from communities and nursing institutions in Guangzhou using convenience sampling. General information questionnaires were used to collect sociodemographic and health-related data. Objective cognitive function was assessed using the Basic version of the Montreal Cognitive Assessment (MoCA-B), Clinical Dementia Rating (CDR), Hachinski Ischemic Scale (HIS), and Activities of Daily Living (ADL) scale. SCD was evaluated using the SCD standard diagnostic framework and the Subjective Cognitive Decline Questionnaire (SCD-Q9). Sleep quality, depressive symptoms, and anxiety symptoms were assessed using the Pittsburgh Sleep Quality Index (PSQI), Patient Health Questionnaire-9 (PHQ-9), and Generalized Anxiety Disorder-7 (GAD-7), respectively. Binary logistic regression analysis was employed to explore the correlation between SCD and multimorbidity in elderly individuals. Results SCD was detected in 250 elderly individuals (40.8%). Multimorbidity was detected in 475 cases (77.6%), including 352 cases (57.5%) with low comorbidity level and 123 cases (20.1%) with high comorbidity level. Logistic regression analysis revealed that advanced age, poor activities of daily living, poor sleep quality, presence of anxiety symptoms, and high comorbidity level were risk factors for SCD, while years of education was a protective factor (all

P<0.05). Specifically, the risk of SCD in individuals with high comorbidity level was 1.8 times that of those without high comorbidity level (OR=1.826, 95%CI=1.037-3.216, P<0.05). Conclusion High comorbidity level is associated with SCD and constitutes an independent risk factor for SCD. Healthcare professionals in communities and nursing institutions may incorporate multimorbidity as an assessment indicator for cognitive decline, collaboratively implement management of multimorbidity and related factors, actively identify and intervene in SCD, thereby delaying the onset and progression of Alzheimer' s disease in elderly individuals and promoting healthy aging.

Full Text

Correlation Between Subjective Cognitive Decline and Multimorbidity Among the Elderly

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Abstract

Background: Subjective cognitive decline (SCD) represents a target stage for early prevention of Alzheimer' s disease (AD). Investigating its influencing factors and modulating modifiable factors can help slow AD progression. While multimorbidity is recognized as a crucial modifiable risk factor for objective cognitive impairment, research on its correlation with SCD remains limited and inconclusive.

Objective: To explore the correlation between SCD and multimorbidity among elderly individuals, providing a theoretical basis for early prevention and intervention of AD.

Methods: From January 2021 to June 2022, 612 elderly adults aged $ $60 years were selected from communities and nursing homes in Guangzhou using convenience sampling. A general information questionnaire collected sociodemographic and health-related data. Objective cognitive function was assessed using the Montreal Cognitive Assessment Basic (MoCA-B), Clinical Dementia Rating Scale (CDR), Hachinski Ischemic Scale (HIS), and Activities of Daily

Living Scale (ADL). SCD was evaluated using the standard diagnostic framework for SCD and the Subjective Cognitive Decline Questionnaire (SCD-Q9). Sleep quality, depression, and anxiety symptoms were assessed using the Pittsburgh Sleep Quality Index (PSQI), Patient Health Questionnaire-9 (PHQ-9), and Generalized Anxiety Disorder Scale (GAD-7), respectively. Binary logistic regression analysis was employed to examine the correlation between SCD and multimorbidity.

Results: Among participants, 250 (40.8%) were identified with SCD. Multimorbidity was detected in 475 cases (77.6%), including 352 (57.5%) with low multimorbidity level and 123 (20.1%) with high multimorbidity level. Logistic regression analysis revealed that advanced age, poor ADL, poor sleep quality, anxiety symptoms, and high multimorbidity level were risk factors for SCD, while years of education served as a protective factor (all $P<0.05$). Specifically, the risk of SCD among those with high multimorbidity level was 1.8 times that of those without high multimorbidity level (OR=1.826, 95%CI=1.037-3.216, $P<0.05$).

Conclusion: High multimorbidity level is associated with SCD and represents an independent risk factor for its occurrence. Healthcare professionals in communities and nursing facilities should incorporate multimorbidity as an assessment indicator for cognitive decline, collaboratively implement management of multimorbidity and related factors, and actively identify and intervene in SCD to delay AD onset and progression, thereby promoting healthy aging.

Keywords: Alzheimer’ s disease; subjective cognitive decline; multimorbidity; elderly; early prevention

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Introduction

As population aging intensifies, dementia has become a major issue affecting quality of life among older adults. China now has the world’ s largest number of dementia patients, accounting for approximately 25% of the global total [1]. Alzheimer’ s disease (AD) is the most common type of dementia. Currently, there is no effective treatment for AD, prompting most research to focus on its prodromal symptoms and modifiable risk factors. Accumulating evidence confirms that subjective cognitive decline (SCD) represents the earliest manifestation of AD and a pre-stage of mild cognitive impairment (MCI) [2]. SCD, also known as subjective memory impairment (SMI), subjective memory complaints (SMC), subjective memory decline (SMD), subjective cognitive impairment (SCI), or subjective cognitive complaints (SCC), refers to an individual’ s subjective perception of cognitive decline compared to their previous normal state, while objective neuropsychological tests remain within normal ranges and the decline is not associated with acute events [3]. A systematic review by Pike et al. [4] based on 46 longitudinal studies indicated that older adults with SCD have 2.48 times higher risk of developing dementia and 1.83 times higher risk of

developing MCI compared to cognitively normal individuals. Researchers have found that SCD can emerge up to ten years before AD diagnosis [5], leading the academic community to identify SCD as a critical gateway for early AD prevention and treatment.

Multimorbidity refers to the coexistence of two or more chronic diseases in the same patient [6], with prevalence reaching 76.5% among Chinese older adults [7]. As one of the important modifiable risk factors for AD, multimorbidity significantly increases the risk of objective cognitive impairment [8]. SCD represents a target population for early AD prevention, making it crucial to understand the correlation between SCD and multimorbidity for early prevention of AD and control of chronic diseases among older adults. However, no consensus has been reached regarding the impact of multimorbidity on the ultra-early stage of AD, namely SCD. Previous research has primarily focused on the correlation between objective cognitive impairment and multimorbidity, with fewer studies examining SCD and multimorbidity, yielding controversial results [9-15]. Most studies have not employed the SCD diagnostic framework from the Subjective Cognitive Decline Initiative (SCD-I) to screen SCD populations, have included individuals with objective cognitive impairment, have not focused specifically on older adults, and have been limited to memory clinics or community settings. Therefore, this study, using Guangzhou older adults as an example and employing the standard SCD diagnostic framework, investigates the correlation between SCD and multimorbidity among Chinese elderly to provide evidence for improving SCD and multimorbidity status and for preventing and delaying AD progression, thereby promoting healthy aging.

Methods

1.1 Study Subjects

From January 2021 to June 2022, 734 elderly adults aged $ $60 years were initially selected from communities and nursing homes in Guangzhou through face-to-face, one-on-one surveys. Inclusion criteria were: (1) residence in a nursing home for $ $1 month or in the community for $ $6 months; (2) voluntary participation. Exclusion criteria included: (1) diagnosis of MCI or dementia; (2) possible mild or greater cognitive impairment detected through objective cognitive screening in this study; (3) history of cerebrovascular disease or recent traumatic brain injury; (4) other neurological diseases affecting objective cognitive function, such as brain tumors, Parkinson' s disease, encephalitis, epilepsy, carbon monoxide poisoning, etc.; (5) other diseases affecting objective cognitive function, such as severe metabolic diseases or severe cardiopulmonary diseases; (6) severe psychiatric disorders such as schizophrenia, bipolar disorder, major depression, or severe anxiety; (7) severe visual or hearing impairment preventing assessment participation; and (8) current participation in cognitive rehabilitation or intervention studies. After strict application of inclusion and exclusion criteria, the final effective sample size was 612 cases. This study was approved by the university ethics committee (approval number: Ethics [2021] No. 27),

and all participants provided informed consent.

1.2 Assessment Tools

1.2.1 General Data Collection A self-designed general information questionnaire was used, covering two aspects: (1) Sociodemographic data including gender, age, residence, years of education, marital status, pre-retirement occupation type, and monthly income; and (2) Health-related data including body mass index (BMI), waist circumference, smoking habits, alcohol consumption, tea drinking habits, exercise frequency, napping habits and average duration, sleep quality, depression and anxiety symptoms, and ADL. BMI was calculated from participants' weight and height measurements ($\text{BMI} = \text{weight[kg]}/(\text{height[m]})^2$). Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), which evaluates sleep patterns over the past month with total scores ranging from 0-21; scores $ $7 indicate poor sleep quality [16]. The PSQI has a split-half reliability of 0.87, with sensitivity and specificity of 98.3% and 90.2%, respectively. Depression and anxiety symptoms were assessed using the Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder Scale (GAD-7), respectively. The PHQ-9 was developed by Spitzer et al. [17] and validated in Chinese by Jin Tao et al. [18], with a Cronbach' s α coefficient of 0.767; total scores range from 0-27, with scores $ $5 indicating depressive symptoms. The GAD-7 Chinese version was translated by He Xiaoyan et al. [19], with a Cronbach' s α coefficient of 0.842; total scores range from 0-21, with scores $ $5 indicating anxiety symptoms. ADL was assessed using the version revised and sinicized by He Yanling et al. [20], comprising basic activities of daily living (BADL) and instrumental activities of daily living (IADL) with 20 items rated on a 4-point Likert scale, yielding scores from 20-80; lower scores indicate better daily functioning, with total ADL scores $ $26 representing essentially normal daily living ability.

1.2.2 Objective Cognitive Screening Objective cognitive function was assessed using the Montreal Cognitive Assessment Basic (MoCA-B), Clinical Dementia Rating Scale (CDR), and Hachinski Ischemic Scale (HIS), with ADL as a supplementary measure to exclude older adults with abnormal objective cognitive function, MCI, and dementia. (1) The MoCA-B was developed by Thai scholar Julayanont [21] based on the original MoCA and sinicized by Guo Qihao et al. [22]. Suitable for individuals with low education levels, it contains 30 items with a total score of 30. Normal objective cognition score ranges: >19 for education $ $6 years; >22 for education 7-12 years; >24 for education >12 years. The MoCA-B demonstrates reliable internal consistency with a Cronbach' s α coefficient of 0.807. (2) The CDR assesses severity of cognitive impairment: 0 = no dementia, 0.5 = questionable dementia, 1 = mild dementia, 2 = moderate dementia, and 3 = severe dementia [23]. (3) The HIS evaluates cerebral blood flow and can differentiate vascular dementia, AD, and mixed dementia. The scale totals 18 points; for individuals with dementia, scores <4 indicate AD-type dementia, 4-7 indicate mixed dementia, and $ $7 indicate vascular de-

mentia; for non-demented older adults, scores <4 represent good cerebral blood flow [16].

1.2.3 Subjective Cognitive Decline Assessment Referencing the diagnostic criteria and additional criteria from the Subjective Cognitive Decline Initiative (SCD-I) and SCD-plus framework [24]: (1) self-perceived persistent cognitive decline compared to previous normal state, unrelated to acute events; (2) normal performance on standardized cognitive tests after adjusting for age, gender, and education, not meeting MCI diagnostic criteria; (3) persistent memory decline complaints within the past 5 years; (4) age $ $60 years; and (5) subjective memory decline (not other cognitive domains) with associated worry. The Subjective Cognitive Decline Questionnaire (SCD-Q9) was used to assess persistent memory decline. Developed by Gifford et al. [25] and sinicized by Hao Lixiao et al. [26], this questionnaire distinguishes SCD from normal older adults. It comprises two dimensions: overall memory ability and temporal comparison (4 items) and daily activity ability (5 items), totaling 9 items. The Cronbach' s α coefficient ranges from 0.870-0.881, with total scores from 0-9; higher scores indicate more severe subjective cognitive decline. Based on objective cognitive screening and SCD assessment results [27-30], older adults with normal overall objective cognition, meeting SCD diagnostic framework criteria, and SCD-Q9 scores $ $5 were classified as the SCD group (n=250), while those with normal objective cognitive function and SCD-Q9 scores <5 formed the cognitively normal (CN) group (n=362).

1.2.4 Multimorbidity Status Assessment Referencing the definition of multimorbidity [6] and average disease burden among Chinese older adults [31, 32], participants were categorized by disease count into: non-multimorbidity level (0-1 diseases), low multimorbidity level (2-4 diseases), and high multimorbidity level ($ $5 diseases). A dichotomous question collected chronic disease history: "In the past year, have you been told by a doctor or other healthcare professional that you have any of the following chronic conditions?" The chronic disease checklist was designed according to the International Classification of Diseases, 10th Revision (ICD-10). Based on previous epidemiological studies and prevalence rates, the following chronic conditions were selected for analysis of their relationship with SCD: hypertension, diabetes, coronary heart disease, chronic obstructive pulmonary disease/emphysema/chronic bronchitis, hyperlipidemia, arthritis, chronic neck/lumbar spine disease, chronic nephritis, prostate hyperplasia, chronic gastritis/enteritis, cataract/glaucoma, gout, osteoporosis, and other diseases such as chronic hepatitis.

1.2.5 Sample Size Calculation Sample size was calculated using the formula for cross-sectional surveys: $n = \frac{u^2 \times P(1-P)}{\delta^2}$. Assuming α=0.05 (two-sided), and referencing previous domestic research [33], P represents SCD prevalence (P=18.8%), δ indicates maximum allowable error (δ=0.035), and u is the statistic corresponding to the test level α. The calculated minimum sample size

was 479 cases. Considering a 15% non-response rate, the minimum sample size should be 564 cases.

1.3 Quality Control

During the study period, any identified problems were promptly communicated and resolved with expert team members. Before data collection, thorough preparations were made and three graduate students were uniformly trained as investigators. During surveys, the research protocol was strictly followed, with investigators using standardized instructions to explain the study' s purpose, significance, and main content to participants. After obtaining informed consent, one-on-one, face-to-face questionnaires were conducted. Following each survey, completeness and quality were immediately checked, and any missing items were promptly clarified and completed with participants. Final SCD classification was determined by licensed physicians from Guangdong Mental Health Center and neurologists from Guangzhou Geriatric Hospital (all with $ $3 years of experience in geriatric cognitive impairment). After excluding unqualified questionnaires, qualified questionnaires were coded and entered using Epidata 3.1 with double real-time entry to ensure data accuracy.

1.4 Statistical Methods

Data analysis was performed using IBM SPSS 26.0 software. The Kolmogorov-Smirnov test or Q-Q plots were used to verify normality of continuous variables. Normally distributed continuous variables were expressed as mean ± standard deviation ($\bar{X} \pm S$), non-normally distributed continuous variables as median and interquartile range (M(P25,P75)), and categorical or ordinal variables as frequency and percentage (n,%). Comparisons of general data, chronic diseases, and multimorbidity levels between SCD and CN groups used independent t-tests for normally distributed continuous variables, Mann-Whitney U tests for non-normally distributed or ordinal variables, and chi-square tests for categorical variables. The correlation between SCD and multimorbidity was analyzed using binary logistic regression. The significance level was set at α=0.05 (two-sided).

Results

2.1 Basic Characteristics of Participants

Participants'ages ranged from 60-98 years, with a mean age of (76.54$\pm$8.73)$years$; 196(32.0$\pm$1.95).

2.2 Comparison of General Data Between SCD and CN Groups

Univariate analysis revealed statistically significant differences between SCD and CN groups in gender, age, years of education, pre-retirement occupation type, monthly income, tea drinking habits, ADL, sleep quality, and depression and anxiety symptoms (see Table 1 , all P<0.05).

2.3 Comparison of Chronic Diseases and Multimorbidity Levels Between SCD and CN Groups

Among the diseases examined, 574 participants (93.7%) had chronic diseases, with hypertension, chronic neck/lumbar spine disease, and cataracts being the three most prevalent conditions. Statistically significant differences between SCD and CN groups were found in multimorbidity status/level and the prevalence of diabetes, arthritis, and osteoporosis (all $P<0.05$), as detailed in Table 2 .

2.4 Correlation Between Subjective Cognitive Decline and Multimorbidity

To explore the independent effect of multimorbidity on SCD, binary logistic regression analysis was performed with SCD as the dependent variable and variables showing statistical significance in univariate analysis of general data plus multimorbidity level as independent variables (variable assignments shown in Table 3). Results showed that advanced age, poor ADL, poor sleep quality, anxiety symptoms, and high multimorbidity level were risk factors for SCD, while years of education was a protective factor (all $P<0.05$, see Table 4). Specifically, the risk of SCD among those with high multimorbidity level was 1.8 times that of those without high multimorbidity level (OR=1.826, 95%CI=1.037-3.216).

Discussion

3.1 Current Status of Subjective Cognitive Decline Among Older Adults

An international aging cohort study across 16 countries standardized SCD prevalence estimates by age and gender, reporting a range of 7.8%-52.7% [34]. Our findings fall within this range. The SCD detection rate of 40.8% in this study indicates a relatively high level among Guangzhou older adults, similar to results from Chen Wen et al. [35]. Hao et al. [33] reported an SCD prevalence of 18.8% in Shunyi District, Beijing in 2017. This discrepancy may be attributed to differences in population characteristics and SCD assessment methods. Our study participants were older (mean age 76 years) compared to Hao et al.' s study where 68.9% were aged 60-69 years, and advanced age increases SCD risk [33, 35]. Healthcare professionals in communities and nursing facilities should strengthen health education about SCD and its early prevention, improve awareness of SCD among older adults, and conduct early cognitive screening [36] to achieve early prevention, detection, and intervention.

3.2 Current Status of Multimorbidity Among Older Adults

Fortin et al. [37] suggested that including more than 12 chronic diseases provides more accurate multimorbidity prevalence estimates. Our study included

15 chronic conditions, meeting this requirement. A systematic review of multimorbidity prevalence among Chinese community-dwelling adults aged $ $60 years [7] reported a wide range (6.4%-76.5%). Our multimorbidity prevalence of 77.6% falls within this range but is higher than rates reported by Guo Dan et al. [38] (71.71%), Zhao et al. [39] (69.5%), and Zhang Ran et al. [40] (43.6%). The higher prevalence in our study may be due to different population characteristics and disease categories. Most of our participants were from nursing homes, many reporting poor health as the reason for institutionalization [41], and the population was older. The multimorbidity situation among older adults is severe, yet most chronic diseases are preventable and controllable. This suggests that primary healthcare institutions and nursing facilities should strengthen chronic disease management, focus on the large population of older adults with multimorbidity, establish health records and multimorbidity specialty clinics, continuously monitor multimorbidity status, conduct health education and comprehensive interventions targeting risk factors for chronic diseases, and reduce adverse outcomes such as disability or complications to improve quality of life in later years.

3.3 Influencing Factors of Subjective Cognitive Decline

3.3.1 Sociodemographic Aspects Our findings indicate that advanced age is a risk factor for SCD, while years of education is a protective factor, consistent with previous research [33, 35, 42, 43]. With increasing age, individuals inevitably experience brain aging, accelerating cognitive decline [44], thus increasing SCD risk. Older adults with more years of education typically have higher cognitive reserve and stronger brain network compensation or reserve functions, providing greater resistance to cognitive decline [45]. Additionally, those with higher education tend to have better health literacy [46], may possess more health knowledge and engage in health behaviors such as finger exercises and reading, thereby exercising cognitive function and reducing SCD risk. Therefore, healthcare workers in communities or nursing facilities should pay attention to older adults who are advanced in age and have lower education levels, strengthen training in health-related knowledge and skills, and encourage older adults themselves to maintain lifelong learning to enhance or preserve cognitive reserve and health literacy.

3.3.2 Health Status Aspects This study demonstrated that poor ADL and sleep quality, and presence of anxiety symptoms are risk factors for SCD, consistent with previous research [35, 36, 47-50]. Since ADL is associated with memory and executive function [51], and older adults with SCD experience self-perceived memory decline [24] and significant executive function impairment [52], those with poor ADL have higher SCD risk. Sleep promotes clearance of potentially neurotoxic waste from the central nervous system [53] and optimizes memory consolidation [54], providing protective effects on cognitive function. Conversely, poor sleep quality leads to production of AD pathology-related biomarkers such as increased amyloid-β and tau proteins [55, 56], thereby in-

creasing SCD risk. Research shows that anxiety symptoms in older adults cause impairment across multiple cognitive domains including language and executive function [57], while older adults with SCD score significantly lower than normal older adults in language and executive function [58]. Therefore, SCD and anxiety may share common neurobiological mechanisms, potentially increasing SCD risk by affecting language and executive function. This suggests that healthcare professionals and family members in communities and nursing facilities should emphasize training in ADL, particularly instrumental activities such as encouraging older adults to make phone calls and do housework independently, and should pay attention to sleep quality, subjective memory, and psychological mood to promptly identify high-risk SCD populations and reduce cognitive decline risk.

3.4 Correlation Between Subjective Cognitive Decline and Multimorbidity

Our study found that the prevalence of multimorbidity in the SCD group was higher than in the CN group, similar to findings from a study across 48 low- and middle-income countries and a large-sample cross-sectional study based on Spanish census data [9, 12]. Furthermore, after controlling for age, years of education, ADL, sleep quality, and anxiety symptoms, results indicated that high multimorbidity level is an independent risk factor for SCD, with SCD risk being 1.8 times higher in those with high multimorbidity level compared to those without, while low multimorbidity level was not associated with SCD risk. Fischer et al. [15], based on a Canadian memory clinic study of 85 adults aged \$ \$50 years, found no correlation between subjective cognitive function and multimorbidity, contradicting our findings. This discrepancy may be due to Fischer et al. including MCI and dementia populations (only 22% had normal objective cognition), small sample size, and different SCD and multimorbidity assessment tools. The reasons for the correlation between SCD and multimorbidity remain unclear but may be speculated from biological mechanisms and individual characteristics. Biologically [9], multimorbidity may affect cognition through atherosclerosis, microvascular changes, and inflammatory processes [59], or by increasing polypharmacy risk [60]; multiple medications and drug interactions may cause cognitive decline [11, 61], while cognitive impairment may affect multimorbidity severity and burden through reduced responsiveness (e.g., lower adherence), potentially creating a vicious cycle. Regarding individual characteristics, older adults with multimorbidity may tend to overestimate health-related risks, leading to more memory complaints and worries [14]; alternatively, multimorbidity may reduce functional independence, thereby decreasing leisure and social activities [13] that are protective factors against cognitive decline [62]. Since SCD risk may increase with multimorbidity level, and multimorbidity assessment is simple and rapid, this suggests that communities and nursing facilities should incorporate multimorbidity into cognitive decline assessment and develop multimorbidity management care plans to reduce cognitive decline risk.

3.5 Limitations

First, as a cross-sectional study, the causal relationship between SCD and multimorbidity cannot be determined. Future prospective cohort or basic research is needed to explore the correlation between multimorbidity and SCD. Second, this study did not examine correlations between different multimorbidity patterns and SCD, whereas specific diseases may have different impacts on cognitive function. Future research should investigate correlations between SCD and different multimorbidity patterns.

Conclusion

This study focused on the early stage of AD and its important modifiable risk factor, examining the relationship between SCD and multimorbidity. The results revealed concerning situations regarding both SCD and multimorbidity among older adults, with higher multimorbidity prevalence in the SCD group than the CN group. Advanced age, poor ADL, poor sleep quality, anxiety symptoms, and high multimorbidity level were identified as risk factors for SCD, while years of education served as a protective factor. Healthcare professionals in communities and nursing facilities should emphasize health education about SCD, incorporate multimorbidity as an assessment indicator for cognitive decline, implement management of multimorbidity and related influencing factors, and actively identify and intervene in SCD to delay cognitive decline, improve quality of life, and reduce family and socioeconomic burden.

Author Contributions: Song Yinhua was responsible for data analysis and manuscript writing; Liu Yushuang and Wang Shibin provided resources, research supervision, and quality control; Song Yinhua, Yang Qing, and Hu Qing were responsible for questionnaire quality control, field investigation, quality control, and data organization; Zheng Chunchan participated in questionnaire surveys and data organization; Zhang Ping was responsible for research supervision, manuscript revision, and overall accountability.

Conflict of Interest: The authors declare no conflicts of interest.

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Note: References 6 (report) and 16 (monograph) have no DOI; references 20 and 45 have no DOI available.

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