China Cognition and Aging Study
(China COAST)
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1. Study glossary

Academic committee	AC
Alzheimer's disease	AD
Autosomal dominant Alzheimer disease	ADAD
Alzheimer's disease international	ADI
Activity of daily living	ADL
Amnestic mild cognitive impairment	a-MCI
Apolipoprotein	APOE
Boston naming test	BNT
Clinical dementia rating	CDR
Cognition and aging study	COAST
Case report form	CRF
Cerebrospinal fluid	CSF
Data management committee	DMC
Diagnostic and Statistical Manual-Fourth Edition, Text Revision	DSM-IV-R
Digit span test	DST
End diastolic velocity	EDV
Familial Alzheimer's disease	FAD
[^{18}F]Fluorodeoxyglucose	FDG
Geriatric depression scale	GDS
Genome-wide association studies	GWAS
Intima-media thickness	IMT
Mild cognitive impairment	MCI
Modified Hachinski ischemic score	m-HIS
Mini-mental state examination	MMSE
Montreal cognitive assessment	MoCA
Magnetic resonance imaging	MRI
Medial temporal lobe atrophy	MTA
National Institute on Aging-Alzheimer’s Association	NIA-AA
National institute of neurological and communicative disorders and stroke-AD and related disorders association	NINCDS-ADRDA
Neuropsychiatric inventory	NPI
Positron emission tomography	PET
Principle investigator	PI
Pittsburgh compound B	PIB
Peak systolic velocity	PSV
Quality control committee	QCC
Sporadic Alzheimer's disease	SAD
Subcortical ischemic vascular disease	SIVD
Cerebral small vessel disease	SVD
Trail making test	TMT
Vascular dementia	VaD
Vascular cognitive impairment	VCI

Vascular cognitive impairment with no dementia,	VCIND
World Health Organization-University of California Los Angeles, Auditory Verbal Learning Test	WHO-UCLA AVLT
White matter lesion	WML

2. Introduction

2.1 Background and significance

Dementia is a major cause of disability in the elderly. In the late stage, patients lose their ability to live independently and rely on other people's care. The main subtype of dementia is Alzheimer's disease (AD), followed by vascular dementia (VaD). Other subtypes include mixed dementia, frontotemporal dementia, Lewy body dementia, Parkinson's disease with dementia, alcoholic dementia, hydrocephalus dementia, post-traumatic dementia, etc. The number of dementia in China accounts for a quarter of the total number of dementia in the world, and the annual economic cost of AD alone has exceeded 1100 billion Chinese yuan, which brings heavy burden to the sustainable development of the country (1).

A study reported that the prevalence of AD people over 65 years old in 1997 was 3.50%, and that of VaD was 1.10% (2). After that, studies have reported that the prevalence of dementia in people over 65 years old is 2.0-13.0% (3-7). In 2014 and 2019, two large-scale multicenter cross-sectional studies were carried out, respectively. The results showed that the prevalence of dementia ($\geqslant$ 65 years old) was 5.14% and 5.60%, respectively, that of AD was 3.21%, and that of VaD was 1.50% (8, 9). For the first time, the team reported the regional differences in dementia prevalence in China (the highest in the West, the lowest in the South, the Central and the North are in the middle), urban-rural differences (rural areas are higher than urban areas, possibly due to low education), and the impact of age and gender. Only a few studies have reported the prevalence of other subtypes of dementia. The prevalence of mixed dementia is 1.5%, Parkinson's disease dementia 0.4%, and Lewy body dementia 0.2% (10, 11). The studies of incidence of dementia before 2010 were mostly single center. In 2016, a multicenter study reported that the incidence rate of dementia, AD and VaD in people aged 65 and above were 12.14, 8.15 and 3.13/1000 person year, respectively (12). The research on the prevalence and incidence rate of dementia were mostly based on single center and small sample. The research methods are not consistent, and there is lack of epidemiological data on other subtypes of dementia. Periodic large-scale, multicenter, consistent methods and standards are needed for updating data in a timely manner.

The risk factors of dementia are mainly divided into genetics, comorbidity, lifestyle and other factors. Genetic factors include: carrying the ε 4 allele of apolipoprotein E (ApoE) gene (13), triggering receptor expressed on myeloid cells 2 (TREM2) gene(14), clusterin (CLU) gene (15), vascular endothelial growth factor (VEGF) gene (16), beta-secretase 1 (BACE1)(17), insulin degrading enzyme (IDE) gene (18), etc. Comorbidity factors include tension-type headache (19), migraine (20), sensory impairment (21), stroke (22), hypertension (23), hyperlipidemia (24), chronic nephropathy (25), insomnia (26), diabetes (24), hearing disorder (27), etc. Lifestyle factors include: smoking (24), secondhand smoke (28), sedentary behavior (29), bad drinking history (24), less physical exercise and cognitive activities (30), etc. Other risk factors include: living in the rural area (31), old age, low education level (22), sex (AD: female (24); VaD: male (32)), loneliness (33), weakness (34), zoster (35), high dose benzodiazepines (36), pesticides (37), exposure to trace elements (38), low folic acid and vitamin B12 and high homocysteine (39), high body mass index (BMI) (40) or unexpected reduction (41), etc. Protective factors are mainly divided into genetic factors, lifestyle and other factors. Genetic factors include: APOEε2 allele, Toll like receptor 9 (TLR9) gene (42), LDL receptor related protein 1 (LRP1) gene (43), etc. Lifestyle factors include: sports, outdoor activities, labor, social activities, intellectual activities, quitting smoking (44), healthy diet (45), supplement folic acid and vitamin B12 (46), etc. Other protective factors include: living in the urban area (31), high education level (44), high level of thiamine diphosphate (47), cantoness/mandarin bilingualism (48), Tai Chi (49), etc. At present, the research on dementia risk and protective factors is lack of quantitative and objective evaluation indicators, and through certain interventions to further clarify the impact of these factors in dementia. By further defining the risk and protective factors of dementia and regulating them on this basis, it is expected to prevent the onset or delay the progress of dementia.

Genetics plays an important role in the pathogenesis of dementia. Take AD for example, AD can be divided into sporadic AD (SAD) and familial AD (FAD). The single gene association study of SAD has been conducted for more than 30 years, but the only recognized genetic susceptibility gene is *APOE* ε 4 allele (50). Other susceptibility genes, such as *ACT*, *IDE*, *BACE1*, *MAPT*, *LRP1*, were only confirmed in some populations (17, 51). At precent, many new AD susceptibility genes have been found in Europe and America through

genome wide association (GWAS), such as *GAB2*, *CLU*, *PICALM*, *CD2AP*, *CD33*, *EPHA1*, and *ABCA7* (52-54). In 2018, also through GWAS, Japan found that *SORL1* gene was related to the risk of AD (55). However, there is no report on the whole genome association of AD in China. The functional study of susceptible gene variation is of great significance to clarify the mechanism of related genes in the pathogenesis of AD. Most of these variation sites are located in gene regulatory regions, including promoter region and 3' untranslated region (3'UTR) (56, 57). FAD are mostly autosomal dominant. About 30% - 40% of FAD families are caused by *PSEN1*, *PSEN2* and *APP* gene mutations. At present, more than 350 pathogenic mutations have been found in these three genes, including 289 *PSEN1* mutations, 48 *PSEN2* mutations, and 58 *APP* mutations. New mutations are reported in AD mutation database every year (https://www.alzforum.org/mutations). At present, the genetic research of dementia and its main subtypes in the world is mostly based on Caucasian population, so further studies are needed to verify them in China's dementia population, and to explore the genetic etiology with Chinese characteristics. In addition, at present, the functional research on the pathogenic and susceptible genes of dementia is not comprehensive enough, and most of them focus on AD. There are few studies on the genetic mechanism of VaD and other subtypes of dementia. Therefore, it is of great significance to further explore the genetic variation, mutation and polymorphism of genes in dementia, and understand their distribution and mechanism of action in the pathogenesis.

The studies of diagnostic markers of dementia mainly include biofluid, genetic and imaging markers. In the biofluid markers, some can reflect the typical pathophysiological changes of AD, such as amyloid β (Aβ) (58, 59), tau protein (T-tau, P-tau), others such as neurogranin (Ng) (60, 61), neurofilament light (NfL) (62, 63), visinin-like protein-1 (VLP-1) (64), chitinase-3-like protein-1 (YKL-40), tumor necrosis factors-α (TNF-α), soluble TNF receptors-1 (sTNFRs-1), TNF-α converting enzyme (TACE), interleukin 6 (IL-6) (65, 66). Genetic markers include pathogenic genes and risk genes, and mutations of pathogenic genes such as *APP*, *PSEN1* and *PSEN2* (67-73). Risk genes such as carrying *APOEε4* (50). In imaging markers, MRI suggests that the atrophy of temporal olfactory area and hippocampus has important diagnostic value in AD (74). PET tracing technology can detect the levels of Aβ and tau in brain (75-77). These results are mainly based on Caucasian population, many of which have not been verified in Chinese population, and there is no clear cut-off value. The sensitivity and specificity of using single marker for early diagnosis of dementia is not enough, so it is necessary to explore the diagnostic efficacy of the combination of several markers in different stages of dementia in China. Meanwhile, developing early diagnosis system risk prediction model of MCI, AD (sporadic and familial) and VaD that are suitable for Chinese people, and promoting the application in clinical field, can reach the effective identification of high-risk or even asymptomatic population. Therefore, the population with disease tendency can receive early intervention, so as to prevent the occurrence of dementia.

At present, the commonly used diagnostic criteria for AD are the National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) standard in 1984, the National Institute of Aging and Alzheimer's Association (NIA-AA) standard in 2011, and the International Working Group-2 (IWG-2) standard in 2014. The international diagnostic standards of VaD include: Diagnostic and Statistical Manual of Mental Disorders, fourth edition standard (DSM-Ⅳ), the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10) standard, American Alzheimer's Disease Diagnosis and Treatment Center (ADDTC) standard, American National Institute of Neurological Disorders and Stroke National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) standard, American Stroke Association / American Heart Association (ASA / AHA) standard in 2011, American Psychiatric Association (APA) standard in 2013, and the International Society of Vascular Behavioural and Cognitive Disorders (Vas-Cog) standard in 2014 (78). The diagnostic standard of MCI was first proposed by Petersen in 1999. In 2003, the IWG revised the MCI diagnostic standard, which has become a widely used MCI diagnostic standard (79). The subtypes of frontotemporal dementia (FTD), dementia of Lewy body (DLB), Parkinson's disease dementia (PDD) also have international diagnostic standards. However, due to the difference of sensitivity and specificity of the standards, as well as the influence of region and culture, their application in Chinese population is limited. In addition，whether there is memory clinic or dementia specialist greatly affects the diagnosis level of dementia in different hospitals (1)，and this calls for a promotion of health system in the whole country..

The evaluation of dementia patients usually includes cognitive function evaluation (including memory evaluation, attention / executive function evaluation, language function evaluation, visuospatial and structural ability, application, calculation), non-cognitive evaluation (mental behavior change), and daily function evaluation (personal living ability, social ability, work ability), etc. The main scale used in cognitive function assessment is Mini-mental State Examination (MMSE) (80), Montreal Cognitive Assessment test (MoCA)

(81), Alzheimer's Disease Assessment Scale, cognitive component (ADAS-cog) (common scale of drug clinical trials), Vascular Dementia Assessment Scale, cognitive component (VaDAS-cog) (82), Clinical Dementia Rating scale (CDR) (83), World Health Organization University of California-Los Angeles, Auditory Verbal Learning Test (WHO-UCLA AVLT) (84), Rey auditory verb learning test (RAVLT) (85), trail making test (TMT) A and B (86), digital spaning test, forward and backward (DST) (87), verbal fluency test (VFT) (88), Boston naming test (BNT) (88), Rey-Osterriche complex figure test (ROCF) (89), clock drawing test (CDT) (90), etc. Non-cognitive evaluation scales include neuropsychiatric inventory questionnaire (NPI-Q) (91), geriatric depression scale (GDS) (92), etc. Daily function evaluation scales include ability of daily living scale (ADL) (93), functional activities questionnaire (FAQ) (94), etc. In addition, there is the modified Hachinski ischemic index scale (m-HIS) used to distinguish AD from VaD (95). At present, most of the psychological assessment scales are translated from foreign versions or modified by domestic scholars according to the different characteristics of Chinese language and culture. However, the current modified version of the scales still cannot completely overcome the shortcomings in assessing the cognitive status of Chinese people, and there is no unified cut-off value, which is not beneficial to the diagnosis of the disease progression of dementia. Therefore, it is of great significance to develop psychological assessment scales with high sensitivity and specificity, in line with the Chinese people characteristics, through large-scale multi-center survey of the representative elderly population in the whole country, based on the changes brought about by China's society, culture and materials in recent years.

As one of the early interventions of AD and dementia, non-pharmacologic treatment (NPT) has been studied more and more in recent years. At present, the NPT research on dementia mainly focuses on improving the lifestyle, physical exercise, music, cognitive training, risk factor control and so on. Lifestyle interventions are potential NPT methods for AD and other dementia, including diet and sleep habits, smoking, drinking and social interaction (96-99). Physical exercise as a common NPT method can improve the cognitive function of MCI patients and slow down the progression of AD (100-102). Physical exercise may improve cognitive function through oxidative stress, inflammation, metabolism and other mechanisms (103), and affect the brain structure related to dementia, such as hippocampus/parahippocampal area, anterior cingulate gyrus and prefrontal cortex (104). Music therapy can improve some cognitive functions of mild AD patients, especially episodic memory, executive function and general cognition, and also has a positive impact on mental and psychological health (105-107). Cognitive training can delay the onset of symptoms and improve the Aβ related memory deficit by preventing oxidative stress and changing the plasticity of white matter in the brain (108-110). At present, most of the NPT studies have a single sample, lack of quantitative and objective evaluation criteria, do not exclude other influencing factors (other comorbid diseases, gender, etc.). Furthermore, their neurobiological mechanism is not clear. It is necessary to explore the efficacy and potential neurobiological mechanism of NPT in AD and dementia through well-designed randomized controlled trials, and systematic and effective intervention programs (111).

To popularize the basic concept of dementia, improve the public awareness and attention to dementia, and understand the symptoms in the pre-dementia stage, can make patients get timely diagnosis and effective intervention, which is conducive to the prevention of dementia. At present, the public awareness of dementia is not enough, especially for people over 60 years old, with low level of education and living in rural areas. Carry out relevant propaganda and education is needed (112). In addition, through psychological care, environmental care, rehabilitation training, cognitive training, physical training, scientific diet, reasonable living and other nursing knowledge education for dementia patients and caregivers, the quality of life of dementia patients can be improved to a certain extent, and the psychological stress and mental burden of caregivers can be reduced (113-115).

Through the establishment and improvement of the Chinese cognitive and aging research cohort, this study can clarify and regularly update the data of the prevalence and incidence of dementia and its subtypes in China, and understand the risk and protective factors of dementia in China, explore its genetic characteristics and pathogenesis. Furthermore, by studying markers, assessment scales, diagnostic criteria and intervention methods, finally achieve early diagnosis and treatment of dementia, improve the diagnosis and treatment level, and provide basis for developing dementia prevention and control strategy.

2.2 Specific aims

The aim of this study is to establish and perfect the China Cognition and Aging Study (China COAST) cohort, to clarify the epidemiology, influencing factors, genetic characteristics, pathogenesis, disease characteristics and diagnosis and treatment status of

dementia and its subtypes in China. It is of great significance to establish a relatively comprehensive national database of cognitive disorders, improve the clinical diagnosis and treatment level of cognitive disorders, and formulate prevention and treatment strategies for dementia. The primary aims of China COAST are as follows:

1. To use the prospective cohort to establish a large database research platform, so as to provide comprehensive epidemiological data, clinical and neuropsychological evaluation data, biological samples, and laboratory tests and imaging data.

2. To update the prevalence and incidence rate of dementia and its subtypes every 2-3 years, and clarify the conversion pattern from normal elderly to MCI and from MCI to dementia.

3. To explore the known or unknown protective and risk factors of dementia and its major subtypes (AD, VaD, other dementia).

4. To discover new pathogenic genes and susceptible genes of dementia and its major subtypes (AD and VaD), as well as new mutation sites of known pathogenic genes. To study the genetic variation, mutation and polymorphism of *PSEN1*, *PSEN2*, *APP* and *APOE* genes in dementia patients, and to understand their distribution and roles in the pathogenesis.

5. To study the biomarkers (body fluid, genetics, imaging) with diagnostic value of MCI, AD (sporadic and familial) and VaD, to define their cut-off values, and to establish prediction models.

6. To study the diagnostic criteria of cognitive normal, MCI, dementia and their subtypes (clinical and molecular subtypes) in the cohort, and to make psychological assessment scales with high sensitivity and specificity, and in line with the characteristics of Chinese people.

7. To find potentially modifiable risk factors for dementia and to study the prevention and intervention effect of non-pharmacological treatment on APOE ε4 carriers, MCI and AD or other dementia patients，which included improvements in education, nutrition, health care, and lifestyle changes. This needs a long time follow-up.8. To explore the relationship between dementia as well as its major subtype AD and cerebral and systemetic circulatory disorders (for example, mixed dmentia), as well as potential therapeutic strategies.

9. To carry out investigation and researches about dementia related education, improve the awareness of dementia, and strengthen the management of dementia.

3. Study design

3.1 Research content

1. Through the collection of basic demographic information and clinical data from the multi-center cohort, we will calculate the prevalence and incidence rate of AD, VaD, other dementia (mixed dementia, FTD, DLB, PDD, alcohol dementia, hydrocephalus dementia, post-traumatic dementia, etc.), and update the numbers every 1-2 years.

2. To clarify the conversion pattern from normal elderly to MCI and from MCI to dementia. Through the collection and analysis of current medical history, past history, family history, living habits, drug use, physical examination and other information, we will explore the protective and risk factors of dementia and its main subtypes (AD, VaD, Other dementia), including age, gender, education level, rural/urban, marital status, parental dementia history, dietary habbit, blood pressure, drinking, smoking, diabetes, hyperlipidemia, cerebrovascular disease, heart disease, depression, hearing impairment, exercise habits (Tai chi, etc.), dementia specialist influence on patients, occupation, BMI, lifestyle changes, air pollution, head injury , social contact, low-income, and other unknown protective or risk factors. To investigate the role of *ApoE* gene, especially *Ap*oEε4 in the disease onset and development, and to explore the non-pharmacological interventions For the study purpose we do follow-up every 2or 3 years.

3. By using exome sequencing, GWAS, WGS and other methods, we will search for new mutations of known pathogenic genes (*APP*, *PSEN1*, *PSEN2*) of AD in China, find new pathogenic genes and susceptible genes of dementia and its main subtypes (AD and VaD), and understand their distribution. We will explore the independent and combined effect of susceptibility gene variation on the risk of illness in Chinese AD population, and to obtain the key mutation sites that have a clear relationship with the incidence of AD. We will do regular follow up visits for the FAD members with new mutations of pathogenic genes, and clarify the important role of new mutations of pathogenic genes during the onset and progression of AD.

4. We will collect the biofluids (blood, cerebrospinal fluid, urine, etc.) and ^{18}F-FDG / ^{11}C-PIB PET/MR multimodal imaging data from people with normal cognition, MCI, AD (sporadic and familial) and VaD, and conduct regular follow up. Discover and verify the

SAD related susceptible gene and FAD related pathogenic gene mutation. Through analyzing the imaging data (such as MRI brain regional volume, ^{18}F-FDG PET and cortical Aβ load), cerebrospinal fluid and plasma markers (such as Aβ, T-tau and P-tau) and clinical features (such as psychiatric symptoms and age of onset), we will develop gene chip with high sensitivity and high specificity for early screening of dementia; develop diagnostic kits for biofluid markers (blood and cerebrospinal fluid); determine imaging cut-off values at all stages of dementia in Chinese people. We will do correlation analysis to establish early diagnosis and risk prediction model for dementia, and verify the newly developed instruments that can detect the peripheral markers of dementia patients and predict the disease progression in national large sample.

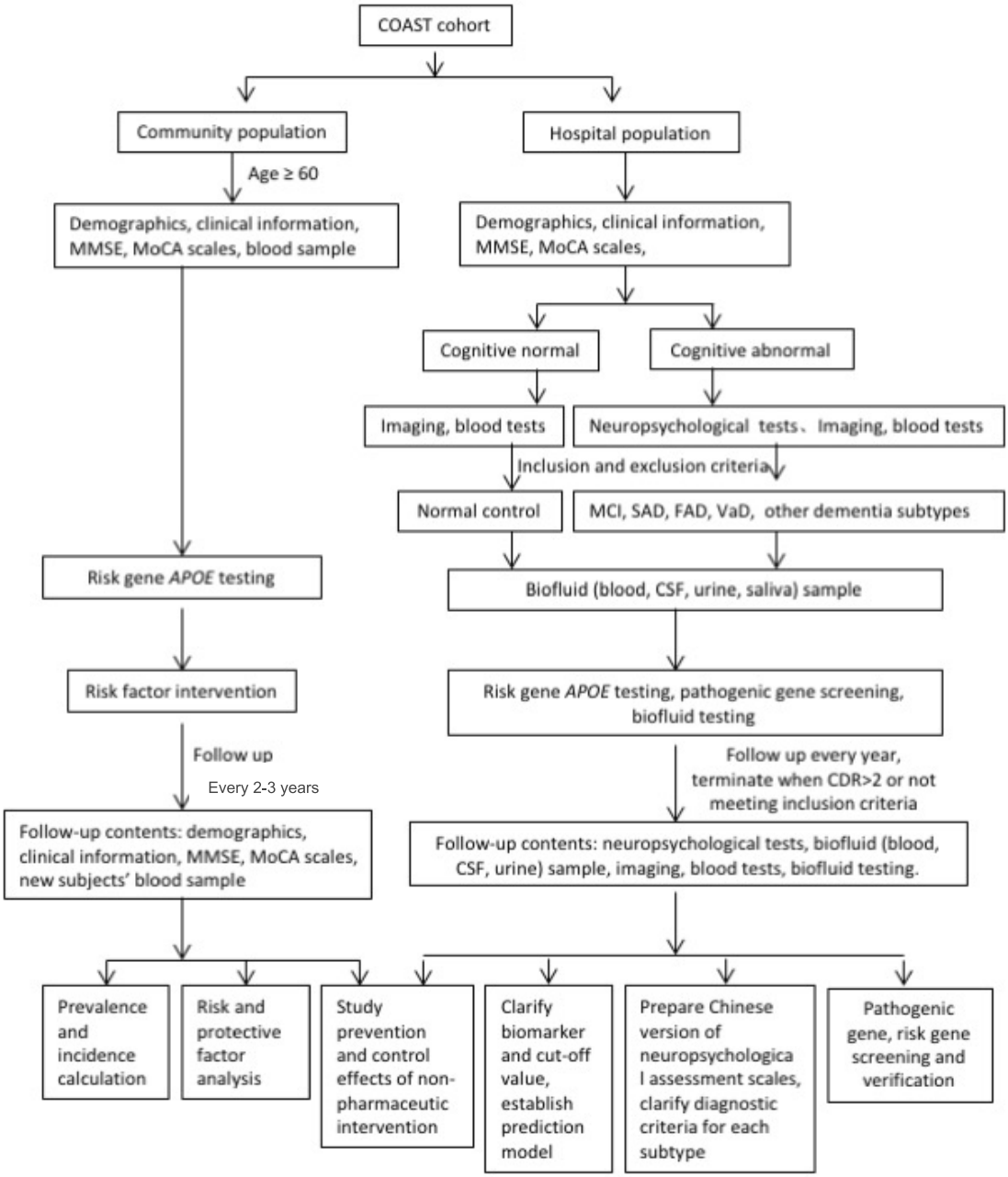
5. Through the unified and standardized neuropsychological scales, including MMSE, MoCA, CDR, NPI, ADL, etc, we will conduct investigation to subjects in baseline and follow-up period, and analyze the changes of cognitive function, ability of daily life and mental behavior symptoms in different cognitive disorders. According to the social, cultural and material changes in China in recent years, we will develop psychological assessment scales with high sensitivity and specificity, and in line with the characteristics of Chinese people. Meanwhile, on the basis of the international diagnostic standards of various subtypes of dementia, combined with the etiology, clinical manifestations, scale classification, imaging characteristics, biofluid examination, etc., we will study the novel typing method and diagnostic standards of cognitive normal, MCI, dementia and its subtypes (clinical and molecular subtypes) in Chinese population.

6. Through designing randomized controlled trials, we will study the systematic and effective NPT intervention program, including lifestyle (diet and sleep habits, smoking, drinking and social networking), health products, exercise habits, cognitive training, risk factor control, etc. We will explore the quantitative and objective evaluation criteria of NPT in AD and dementia, clarify its prevention and control efficacy on *APOE ε4* carriers, MCI and dementia patients, and potential neurobiological mechanism. At the same time, we will carry out dementia related education in the community, improve the public knowledge, attention and awareness of dementia, so that patients can get early detection, early diagnosis and early intervention.

7. To explore the relationship between dementia as well as its major subtype AD and cerebral circulatory disorders (cerebral ischemic and hemorrhage diseases, cerebral arteriosclerosis and stenosis, cerebral venous diseases, etc.), especially clarify the relationship between chronic cerebral ischemia and AD, as well as its effect on AD onset, and whether or not it's risk factor for AD. Whether the therapeutic strategies for cerebral circulatory disorders should be included in the treatment of AD.

3.2 Research methods

Through the establishment of a national multi-center cognition and aging cohort, this study will collect relevant demographic information and clinical data, biofluid samples, neuropsychological evaluation, imaging examination, blood examination and other comprehensive evaluation of study subjects, so as to study the epidemiology, influence factors, genetics and pathogenesis, diagnostic standards, prevention and control strategies of dementia and its subtypes. The study flow chart is as follows (figure 1):



3.2.1 Inclusion and exclusion criteria:

Community population: age ≥ 55 years, male or female, with consent to participant the study.

Hospital population: subjects are all over 18 years old. Through clinical evaluation, neuropsychological test, imaging examination, blood and cerebrospinal fluid examination, etc, we will comprehensively evaluate the cognitive function and various test measures.

(1) MCI and its subtypes

Inclusion criteria:

1) Diagnosis according to 2004 Peterson's MCI criteria.

2) CDR = 0.5.

3) Memory loss is prominent, and may also be with other cognitive domain dysfunction.

4) Insidious onset, slow progress.

5) Not reaching the level of dementia.

Exclusion criteria:

1) With history of stroke and a neurological focal sign, the imaging findings are consistent with cerebral small vessal disease (Fazekas score ≥ 2 points).

2) Other neurological diseases that can cause brain dysfunction (such as depression, brain tumor, Parkinson's disease, metabolic encephalopathy, encephalitis, multiple sclerosis, epilepsy, brain trauma, normal intracranial pressure hydrocephalus, etc.).

3) Other systemic diseases that can cause cognitive impairment (such as liver, renal and thyroid insufficiency, severe anemia, folic acid or vitamin B12 deficiency, syphilis, HIV infection, alcohol and drug abuse, etc.).

4) Mental and neurodevelopmental retardation.

5) Contraindications to MRI.

6) Suffering from a disease that cannot be combined with cognitive examination.

7) Refuse to draw blood.

8) Refuse to sign the informed consent at baseline

(2) Sporadic Alzheimer's disease (SAD)

Inclusion criteria:

1) Dementia is diagnosed according to the criteria described by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-R). The diagnosis of AD is made using the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) or National Institute on Aging and the Alzheimer's Association (NIA-AA) criteria.

2) Subjects and their informed persons can complete relevant and follow- up examinations.

3) Subjects or their authorized legal guardians sign the informed consent.

Exclusion criteria:

1) With a family history of dementia.

2) Other neurological diseases that can cause brain dysfunction (such as depression, brain tumor, Parkinson's disease, metabolic encephalopathy, encephalitis, multiple sclerosis, epilepsy, brain trauma, normal intracranial pressure hydrocephalus, etc.).

3) Other systemic diseases that can cause cognitive impairment (such as liver, renal and thyroid insufficiency, severe anemia, folic acid or vitamin B12 deficiency, syphilis, HIV infection, alcohol and drug abuse, etc.).

4) Mental and neurodevelopmental retardation.

5) Contraindications to MRI.

6) Suffering from a disease that cannot be combined with cognitive examination.

7) Refuse to draw blood.

8) Refuse to sign the informed consent at baseline

(3) Familial Alzheimer's disease (FAD)

Inclusion criteria:

1) Written informed consent obtained from participant or legal guardian prior to any study-related procedures.

2) Members in FAD pedigree (FAD is defined as at least two first- degree relatives suffer from AD).

3) Aged 18 (inclusive) or older.

4) At least two persons who can provide reliable information for the study.

Note: Dementia is diagnosed according to the criteria described by DSM-IV-R. The diagnosis of AD is made using NINCDS-ADRDA or NIA-AA criteria. A diagnosis of MCI is assigned according to Petersen criteria.

Exclusion criteria:

1) Dementia caused by other factors such as depression, other psychiatric illnesses, thyroid dysfunction, encephalitis, multiple sclerosis, brain trauma, brain tumor, syphilis, acquired immunodeficiency syndrome (AIDS), Creutzfeldt-Jakob disease and other types of dementias such as vascular dementia (VaD), frontotemporal dementia (FTD), dementia with Lewy bodies (DLB), and Parkinson's

disease dementia (PDD).

2) MRI and laboratory tests do not support or rule out a diagnosis of AD.

3) Severe circulatory, respiratory, urinary, digestive, hematopoietic diseases (such as unstable angina, uncontrollable asthma, active gastric bleeding) and cancer.

4) Participant has severe psychiatric illness or severe dementia that would interfere in completing initial and follow-up clinical assessments.

5) With history of alcohol or drug abuse.

6) Pregnant or lactating women.

7) No reliable insiders.

8) Refuse to sign the informed consent at baseline.

(4) Vascular dementia (VaD)

Inclusion criteria:

Diagnosis for probable VaD according to NINDS-AIREN diagnostic criteria.

MRI inclusion criteria:

All patients who meet clinical inclusion criteria should accept MRI scans which include an assessment of hippocampal volume.

a. multiple (≥3) supratentorial subcortical small infarcts (3-20 mm in diameter) with or without any degree of white matter lesion (WML); or moderate to severe WML (Fazekas score ≥ 2), with or without small infarction; or ≥ 1 subcortical small infarct in key regions, such as caudate nucleus, globus pallidus, or thalamus.

b. no cortical and watershed infarction, hemorrhage, hydrocephalus, or WML with specific causes (such as multiple sclerosis).

c. no hippocampus or entorhinal cortex atrophy (MTA score = 0 point).

Exclusion criteria:

1) Other neurological diseases that can cause brain dysfunction (such as depression, brain tumor, Parkinson's disease, metabolic encephalopathy, encephalitis, multiple sclerosis, epilepsy, brain trauma, normal intracranial pressure hydrocephalus, etc.).

2) Other systemic diseases that can cause cognitive impairment (such as liver insufficiency, renal insufficiency, thyroid insufficiency, severe anemia, folic acid or vitamin B12 deficiency, syphilis, HIV infection, alcohol and drug abuse, etc.).

3) With a history of mental illness or those with congenital mental retardation.

4) Suffering from a disease that cannot be combined with a cognitive examination.

5) Contraindications to MRI.

6) Refuse to draw blood.

7) Refuse to sign informed consent.

(5) Normal control

Inclusion criteria:

1) Aged 18 (inclusive) or above.

2) Normal MMSE and MoCA evaluations. MMSE>19 points for illiteracy, >24 points for those educated less than 7 years, >27 points for those educated equal to or more than 7 years. MoCA>13 points for illiteracy, >19 points for those educated less than 7 years, >24 points for those educated equal to or more than 7 years.

Exclusion criteria:

1) Subjects with abnormal MMSE or MoCA scores.

2) Subjects with a history of cerebral infarction, traumatic brain injury or related manifestations in MRI.

3) Other neurological diseases that can cause brain dysfunction (such as depression, brain tumor, Parkinson's disease, metabolic encephalopathy, encephalitis, multiple sclerosis, epilepsy, brain trauma, normal intracranial pressure hydrocephalus, etc.).

4) Other systemic diseases that can cause cognitive impairment (such as liver, renal and thyroid insufficiency, severe anemia, folic acid or vitamin B12 deficiency, syphilis, HIV infection, alcohol and drug abuse, etc.).

5) Mental and neurodevelopmental retardation.

6) Suffering from a disease that cannot be combined with a cognitive examination.

7) Contraindications to MRI.

8) Refuse to draw blood.

9) Refuse to sign the informed consent at baseline.

3.2.2 Subject interview

(1) Baseline and follow-up interview items

During the follow-up of the subjects, the research supervisors were responsible for uploading data. Based on population, subjects were divided into community population and hospital population. Hospital population was further divided into MCI, FAD, SAD, VaD, normal control subjects. The supervisors of the centers monitored follow-up visits at different follow-up intervals in different population. The contents of the survey are shown in **Table 1**.

Among them, the community population and normal control cohort only completed MMSE and MoCA for the baseline cognitive assessment part. If the MMSE and MoCA scores did not meet the normal population criteria at the time of follow-up visit, the subject should complete all the assessment scales. The investigator should judge whether the subject meets the criteria for inclusion in other groups in the cohort based on the assessment scores.

Table 1. List of items during baseline and follow-up

Items	Baseline	Follow-up
Informed consent	✔	
Personal information	✔	✔
Current medical history	✔	✔
habits and customs	✔	
Family history	✔	
Past history	✔	✔
Medication for cognitive impairment	✔	✔
Physical examination	✔	✔
Hachinski ischemic score	✔	✔
Cognitive assessment	✔	✔
Mental behavior assessment	✔	✔
Daily and overall functional assessment	✔	✔
Image examination	✔	✔
Laboratory examination	✔	✔
Clinical diagnoses	✔	✔

(2) Follow-up period

The follow-up period was 1-3 years, with an average of 1 year, depending on the subject. Among them, the follow-up period of FAD patients was performed according to the CFAN study protocol standard.

(3) Telephone follow-up

Subjects who were unable to face-to-face follow-up due to geographic reason or severe disease were evaluated by telephone follow-up. The main purpose of telephone follow-up is to keep in touch with the subject, to grasp the subject's changes in cognitive function, learning ability, activities of daily living, social ability, and to collect information on adverse reactions (116).

(4) Consistency of the examination time

All subjects were required to complete all examinations within a 4-week time window, including personal information, clinical assessment, neuropsychological scale testing, biomarker collection, and imaging examination.

(5) Study termination

The main reasons for termination of the study are as follows:

1. Violation of the research protocol, no longer meet the inclusion criteria.
2. The subject is unwilling or unable to participate.
3. Withdraw informed consent.
4. The study is terminated by the project leader or the coordination management center.
5. Safety risks, subjects may withdraw according to their wishes at any time during the clinical trial if safety risks arise.
6. Death.
7. Other.

3.2.3 Study duration

This study is from February, 2008 to January, 2038, or longer.

3.2.4 Sample size

This study is planned to recruit 100 thousand subjects, from all participant centers that cover the North, South, East and Western parts of China.

3.2.5 Study centers

There are 68 participating research centers for this study, including 26 provinces, cities or autonomous regions. Detailed information can be found in Appendix 12.

4. Evaluation criteria

4.1 Clinical evaluation

4.1.1 Demographic data

The demographic data at baseline should be filled in as completely as possible, including: date of birth, age, family address, contact information, education level. At follow-up period(s), if information is changed, they will be updated.

4.1.2 Current medical history

The detailed and objective current medical history must be filled out by the physicians. If case report form (CRF) cannot describe the symptoms and characteristics of the subject in detail, fill in the blanks.

Describe the specific manifestations of cognitive impairment, such as the specific manifestations of memory impairment (nearly/distant/ semantic forgetting); the specific manifestations of language barriers (difficulty in finding words, understanding, expressing, naming, writing, etc.); specific manifestations of disorientation (time, place, people, etc.); specific manifestations of personality and mental behavior (apathy, withdrawal, depression, agitation, wandering, abnormal sleep, antisocial behavior such as theft, etc.; the specific forms of hallucinations such as visual hallucinations, auditory hallucinations, etc.); manifestations of dyskinesia (such as ataxia, Parkinson-like dyskinesia, involuntary movements, etc.); implementation of dysfunction; spatial skills decline and other specific performance.

Physicians should describe the extent of decline in each cognitive domain, whether cognitive impairment affects the patient's daily ability and social function, and how it behaves.

4.1.3 Past history

According to the current internationally recognized diagnostic criteria, the previous illness of the subject is diagnosed or confirmed, and the presence or absence of the relevant disease, the time of diagnosis and the course of the disease are recorded in detail. Try to let the subject or family provide the hospital's medical record/diagnostic certificate, etc., or the investigator will retrieve the patient's past medical records for inspection and confirmation.

4.1.4 Medication situation

The subject's medication needs to be documented in detail, including the name of the medication for the treatment of cognitive impairment and other diseases, the frequency of administration, and the adherence of the medication. Try to have the subject present a

medical record, drug package or prescription.

4.1.5 Family history and family diagram drawing

For subjects with a family history, the investigator should investigate in detail the incidence of each member of the family, and generally investigate the three generations of relatives of the patient. For cognitive impairment and suspected cognitive impairment in the family, the disease should be recorded in detail (e.g. age of onset, first symptom, progression of disease, involvement of each cognitive domain, age of dementia, diagnosis and treatment, clinical consistency with the proband, etc.).

4.1.6 Physical examination

Physical examinations include general medical examinations and neurological examinations performed by senior neurologists.

4.2 Neuropsychological assessment (See Appendix 1-11 for details)

Investigators should strictly follow the guidelines and scoring criteria, be consistent with different subjects and avoid inducing subjects. Patience is encouraged to complete the subject and, if needed, a short break. Check as far as possible in an independent, quiet space, try to be one-on-one with the subject to avoid outside interference.

4.2.1 Mini-Mental State Examinations (MMSE) (80)

The MMSE is a brief, frequently used screening instrument for dementia. The MMSE scale evaluates the following seven aspects: time orientation, location orientation, immediate memory, attention and computation, delayed memory, language, and visual space. There are a total of 30 topics. The total score ranges from 0 to 30. The test scores are closely related to the educational level. Higher scores indicate better cognitive function.

4.2.2 Montreal Cognitive Assessment (MoCA) (81)

The MoCA is, similar to the MMSE, a brief cognitive assessment designed to detect cognitive dysfunction at the MCI stage. This scale has been shown to have adequate sensitivity and specificity in clinical settings to detect suspected MCI. The MoCA evaluates a variety of cognitive domains including attention, executive function, memory, language, visual space, orientation, and computational capacity. The total score is 30 points.

4.2.3 Neuropsychiatric Inventory Questionnaire (NPI-Q) (91)

NPI-Q is a well-validated evaluation tool. It evaluates neuropsychiatric symptoms in AD based on interviews with informed individuals, with relatively short visit time (<15 minutes). It assesses the presence and severity of 12 neuropsychiatric features, including delusions, hallucinations, agitation/aggression, depression/bad mood, anxiety, euphoria, apathy, disinhibition, irritability/emotional instability, abnormal motor behavior, sleep/nighttime behavior, appetite and eating disorders. At the same time, the severity of the symptoms (1-3 points), frequency (1-4 points), and the degree of distress of the caregiver (0-5 points) are evaluated.

4.2.4 Geriatric Depression Scale (GDS) (92)

The GDS is a self-report scale designed to screen for symptoms of depression in the elderly and to measure the self feeling of the elderly within a week. The scale has a total of 30 items, including the following symptoms: low mood, reduced activity, irritability, withdrawal of painful thoughts, negative scores of the past, present and future. The total score is 0-10 points, which is normal; 11-20 points, mild depression; 21-30 points, moderate to severe depression.

4.2.5 Modified Hachinski Ischemic Scale (m-HIS) (95)

The m-HIS can be used to identify VaD through clinical findings. It has a total of 8 items, and 12 points. The items include stepwise aggravation, complain of physical symptoms, emotional loss of control, hypertension history, which are scored 1 point each; acute onset, stroke history, neurological focal symptoms, nervous system focal signs, which are scored 2 points each. The total score is 0-12 points. The higher the evaluation score, the greater the possibility of VaD: those with a score of 4 or less are AD; those with a score of 7 or more are VaD.

4.2.6 World Health Organization University of California-Los Angeles, Auditory Verbal Learning Test (WHO-UCLA AVLT) (84)

AVLT is a list learning task for evaluating multiple cognitive parameters related to learning and memory. In each of the three learning trials, 15 unrelated nouns are spoken out by the tester at the speed of one word per second, and the subjects immediately recall the words freely, which is called the immediate recall test. In addition, after 30-minutes delay of completing the unrelated test, the subject again freely recall the original 15-words list, which is to test delayed recall. Then the tester reads 30 words (including 15 learned words and 15

interference options), and asks the subject to judge whether it is a learned word, and records the number of correct words, which is a delayed recognition test. The results are expressed as the number of nouns that are correctly recalled in each trial. The scale examines the ability to enter, store, extract, pay attention, and vocabulary of memory, and the score increases with increasing educational level.

4.2.7 Trail Making Test (TMT) A and B (86)

Part A of TMT consists of 25 circles, numbered 1 to 25, and the tester instructs the subject to draw lines as fast as possible in increasing numerical order. Part B is also composed of 25 circles, but these circles are white circles (1-12) and black circles (1-13). Subjects need to alternately connect circles of different colors in numerical order. The completion performance of the subject is determined based on the number of correctly completed lines and the time required to complete. Although both the part A and part B rely on visual motion and perceptual scanning skills, part B requires considerable cognitive flexibility to complete the black and white transition connection under time pressure.

4.2.8 Digit Span Test (Forward and Backward) (DST) (87)

The DST requires the subject to repeat a sequence of numbers that are read aloud by the examiner. In the forward test, the subjects must repeat the numbers in the same order; in the backward test, the numbers are repeated in opposite order. The length of the digits gradually increases from 3 to 10 digits in the forward test, and gradually increases from 2 to 8 digits in the backward test, and each digit length includes two tests. The test is terminated when both tests are incorrect. The maximum score of the forward test is 10 points and that of the reverse test is 8 points.

4.2.9 Boston Naming Test (BNT) (88)

This visual naming based scale shows 30 items. The objects in the picture are presented to the subject in a pattern of easily identifiable first and then not easily identifiable. If the subject encounters difficulties in naming the object, the examiner will provide a clue prompt or an option prompt. Record respectively the correct number of independent initial naming, clue naming, and option naming.

4.2.10 Activities of daily living (ADL) (93)

The ADL scale can evaluate the daily activities of the subject comprehensively, accurately and quickly. It consists of the physical life self-care scale and the instrumental ADL. There are 14 items, including two parts: first, the physical life self-care scale has a total of 6 items, including toilet, eating, dressing, grooming, walking and bathing; second, instrumental ADL has a total of 8 items, including call, shop, prepare meals, do housework, laundry, use transportation, take medicine and financing abilities. The higher the subject scores, the worse the ability of daily living.

4.2.11 Clinical Dementia Rating Scale (CDR) (83)

The CDR is a refinement of information that the doctor obtains through conversations with the patient and his/her family, and to assess the degree of impairment of the patient's cognitive function, and then to quickly assess the severity of the patient's condition. The assessment of cognitive domains consists of six items: memory, orientation, judgment and problem solving, work and social ability, family life and hobbies, and independent living ability. The judgment is in five levels, "normal CDR=0, suspected dementia CDR=0.5, mild dementia CDR=1, moderate dementia CDR=2, severe dementia CDR = 3". The CDR-SOB (CDR sum of box) total score is a simple sum of the scores of the six items. CDR sum of boxes adds up the 6 items, and the total score ranges from 0 to 18. As long as the score is greater than 0, the subject has at least one cognitive impairment. Generally, the change value of CDR sum of boxes can be used in clinical trials to obtain more accurate cognitive evaluation (117). CDR is a widely used measure of the severity of dementia.

5. Imaging examination

At each assessment, subjects will receive MRI, PET, and carotid ultrasound. PET imaging includes FDG-PET and amyloid PET scans.

5.1 Imaging equipment and qualifications

Xuanwu Hospital and each sub-center have advanced imaging equipment. Most centers have Siemens or GE full-body MRI scanner, and some centers have PET/MR integrated whole body scanner or PET scanner. Each center has the license for the use of radioactive drugs by the National Food and Drug Administration (fourth category) and has the qualification to prepare new drugs (tracers) for research and development.

5.2 MRI

MRI should be performed within 1 month before or after neuropsychological testing (with no new vascular disease events). All subjects should be checked for MRI contraindications before MRI scanning, such as the presence of metal implants in vivo. Remove active metal objects from the body before examination. After the subjects lie down, his right temple is used as a stereotactic marker, and the scan follows given directions. Three dimensional T1 weighted images of the whole brain were obtained. All subjects will undergo regular scan (T1WI, T2WI, FLAIR, DWI, MRA) and hippocampal phase scan (coronal T1-FLAIR sequence). Image acquisition is completed by radiology department of each center, stored and transmitted in DICOM format, and then image processing is carried out to obtain brain volume, cortex thickness and other indicators. Fazekas score and MTA score were obtained and used as location and quantitative indicators of white matter lesions and gray matter atrophy.

5.3 PET

5.3.1 FDG-PET

FDG-PET can detect abnormal brain metabolism in patients with dementia, and should be performed within 1 month before or after neuropsychological examination (with no new vascular disease event). Fasting for at least 6 hours before examination, and fasting blood glucose was measured. Blood glucose levels should be <140 mg / dL (7.8 mmol/L). Image acquisition is completed by radiology department of each center, stored and transmitted in DICOM format, and then image processing is carried out to obtain whole brain and regional standard uptake value ratio (SUVR), and used as location and quantitative indicators of brain metabolic function.

5.3.2 ^{11}C-PIB PET

Amyloid tracer [N-methyl-^{11}C]2-[4'-(methylamino) phenyl]-6-hydroxybenzothiazole (^{11}C-PIB) is the mostly studied and relatively mature Phenothiazine Aβ imaging agent, which is a ^{11}C-labeled derivatives of Thioflavin-T. It can specifically bind to Aβ plaques in the brain of AD patients and is used for positioning and quantitative analysis of Aβ in brain. ^{11}C-PIB PET can differentiate AD and normal patients in the early and middle stages of the disease, reflect the pathological changes of brain tissue, provide more objective data for early diagnosis. Further combined with clinical history, laboratory tests, neuropsychology scale and structural imaging results, it can help improve the accuracy of the diagnosis to guide early treatment. Image acquisition is completed by radiology department of each center, stored and transmitted in DICOM format, and then image processing is carried out to obtain whole brain and regional standard uptake value ratio (SUVR), and used as location and quantitative indicators of Aβ deposition.

5.4 Carotid ultrasound

Carotid ultrasound can clearly demonstrate the vascular intima-media thickness, the location and size of plaque, the degree of vascular stenosis, and analyze hemodynamics. It plays a key role in the assessment and diagnosis of vascular-related diseases caused by atherosclerosis. Carotid ultrasound examination should be performed within 1 month before or after neuropsychological examination (with no new vascular disease event). An experienced ultrasound physician is required to perform the operation according to "Guidelines for Carotid Ultrasound Examination". Longitudinal and transverse section scanning are performed from frontal and lateral directions. Observe and record the peak systolic velocity (PSV), end diastolic velocity (EDV), intima-media thickness (IMT) and plaque (diameter, number, acoustic properties) of internal carotid artery, common carotid artery and carotid bifurcation.

6. Laboratory examination

6.1 Laboratory testing items

6.1.1 Genetic gene detection

PS1, PS2, APP, APOE and other genetic gene tests are performed on cognitive normal and dementia individuals in ADAD cohort and unknown mutation cohort. Collect the genetic information and biological materials of familiar dementia pedigree to help the basic and clinical research for the pathogenesis of dementia.

6.1.2 Risk gene locus detection

Conduct whole-exon analysis, genome-wide analysis, whole genome association analysis for each enrolled participant, using case-control methods to detect, study and analyze novel risk gene loci that are disease relevant. Explore new pathogenic genes, mechanisms, and risk pathways to provide genetic basis for disease prevention and control.

6.1.3 Body fluid biomarkers detection

Conduct biomarkers detection in cerebrospinal fluid, blood, urine and saliva for each enrolled group, including blood and urine

routine tests, biochemistry, electrolytes and coagulation function tests, cerebrospinal fluid routine and biochemistry tests, etc. Special items include Aβ40, Aβ42, t-tau, p-tau and neurogranin in cerebrospinal fluid and blood to study and explore early diagnostic biomarkers and risk predictors of disease progression.

6.2 Collection and storage of biological specimens

6.2.1 Blood sample

Each participant requires fasting blood collection in the morning and 8ml of peripheral blood is drawn. 5ml is injected into purple head anticoagulation tube, and 3ml is injected into red head non-anticoagulated tube. Name and number are signed on each blood collection tube. Centrifuge within 2 hours. After the purple head anticoagulation tube is centrifuged at 2000 rpm for 10 minutes, aspirate upper layer plasma by pipette and retain the remaining blood sample in the tube. After the red head non-anticoagulation tube is centrifuged at 2000 rpm for 10 minutes, the serum is pipetted and distributed into two of 1.5ml centrifugal tubes, about 500μl per tube. Name, number and the type of specimen are signed on each centrifugal tube (serum is labeled Q, while plasma is J). Centrifugal tubes are immediately stored at -80°C, while the anticoagulation tubes are stored at -20°C fridge.

6.2.2 Cerebrospinal fluid sample

Lumbar puncture should be done in the morning. To eliminate the impact of puncture bleeding on the quality of cerebrospinal fluid specimens, the first 1-2 ml of CSF should be discarded. 10ml CSF for biomarker analysis should be collected. Centrifuge within 2 hours after collection (2000 rpm for 10 minutes), then pipette and distribute the supernatant into ten of 1.5ml centrifugal tubes, 1 ml per tube. Centrifugal tubes are immediately stored at a -80°C fridge.

7. Informed consent

In this study, a series of memory and intelligence tests will be performed on participants, and if necessary, auxiliary examination will be arranged to confirm the diagnosis. After that, regular follow-up will be arranged for each person to tract the change of disease status. Participants and their families should be informed that they should sign an informed consent form after fully understanding the research, and should be reminded that participation in the study is voluntary.

According to the current edition of the Declaration of Helsinki, the principle of informed consent will be implemented before protocol procedures are carried out. Information about the research content should be provided in both oral and written form and reviewed by an ethics committee. Subjects, relatives and guardians must have ample opportunity to inquire about details of the study. The informed consent should be in the language and script that subjects or legal representative can fully understand. During the clinical study, subjects can keep abreast of their research information.

Informed consent will be recorded by using a written document approved by the Ethics Committee and signed by the subject and/or legally authorized representative. The written informed consent document will embody the elements of informed consent as stated in the Helsinki Declaration and will comply with local regulations. Informed consent should mainly include the following contents:

7.1 Inform benefits and risks

7.1.1 Benefits

This study can help clinicians understand patient's disease and enable participants to obtain good and free medical services, such as free neuropsychological assessment, neurology physical examination, as well as follow-up observation and consultation.

7.1.2 Risk

The entire research process may occupy a certain period of time of the participants, but will not cause any physical harm.

7.2 Inform rights and obligations

7.2.1 Rights

Research clinicians introduce research process to participants and their families, and emphasize that participation in the study is voluntary. All participant-related events during the study are informed in time so that participants can decide whether to continue or not. Participants and their families can refuse to participate or withdraw at any time during the study without affecting the participants' own medical care or causing other benefit loss.

7.2.2 Obligations

Insist the principle of voluntary and sign the informed consent form before the study begins. Obey the arrangement of research and

cooperate with the research clinicians. Do not use other drugs without authorization during the study period. If must, please consult the research clinicians before usage and inform after usage.

7.3 Study termination:

If continuing to participate in the study is no longer in the best interests of the participants, the research clinicians will recommend participants to withdraw from the study. If there is a potential risk to the health of participants, the research institution or research clinician can terminate the study after informing the participants and their families.

7.4 Confidentiality

The records of participants will be kept properly in strict confidence, and only those who obtain authorization can preview the records. The ethics committee and the National Food and Drug Administration inspectors are allowed to review records, but the name, contact information and identification certificates of participants will not appear in the review report.

8. Safety and risk to the participant

8.1 Neuropsychological testing

Participants and caregivers may feel tired, boring or embarrassing about neuropsychological testing. If they still cannot cooperate after being persuaded by the research clinician, they can choose to rest for a while before starting again. any problems of the participants detected by the research clinicians through neuropsychological tests (such as cognitive decline, depression, etc.) might expose the participants to unemployment, loss of medical insurance or other discrimination. Therefore, research clinicians should pay attention to the method of notification and avoid these events.

8.2 Lumbar puncture

The participants may have local discomfort at the lumbar puncture site, as well as back pain, neck stiffness and shoulder pain. The puncture site may appear bruising, swelling or rash, and the dizziness or headache may occur for the participants after lumbar puncture. The risk of other related complications is very rare, including the infections of puncture site, allergies to local anesthetics or disinfectants, and the injury of spinal nerve.

8.3 Blood collection

Slight discomfort, bruising, bleeding or infection at the venipuncture site. Very few participants may faint during or after the puncture.

8.4 Imaging

Participants may be allergic to the contrast agent or have radioactive substance radiation exposure risk during the MRI or PET inspection. Participants with metal implants may experience implant displacement during exposure to magnetic fields. Claustrophobia and anxiety may occur on the participants for lying in enclosed spaces.

9. Ethics

9.1 Setting up internal related committees

Both main unit and sub units are required to pass ethical review. China COAST consists of several committees that work together to conduct research. Details are as follows:

9.1.1 Academic committee

China COAST study is mainly managed by an academic committee consisting of the principle investigator (PI) of main unit, all core members, and the PI of each participating unit. The Academic committee will work with the data management committee and the quality control committee to ensure that the China COAST program is conducted in accordance with the prescribed research design and methodology and will be responsible for the review of research protocol that is related to article writing.

9.1.2 Data management committee

China COAST data can be used by qualified academic or research staff to maximize the value of research data. The data management committee is responsible for managing the storage of data, periodically generating data sets, and accepting supervion by the quality control committee to ensure the completion and accuracy of data. To acquire the China COAST research data, an application must be submitted to the academic committee. After the research application is approved, the data management committee is responsible for extracting and distributing data and data statistics.

9.1.3 Quality control committee

Quality control must be performed in real-time during the data collection phase to ensure that enrolled subjects meet the inclusion and exclusion criteria of the study, identify missing or abnormal items, assess the consistency of longitudinal follow-up, and clarify the status of the subject (continue follow-up or termination). The quality control committee is responsible for reviewing the standardization of collection, transportation, storage and analysis of biological samples; whether the imaging data and clinical information provided by each sub-center meet the requirements of the research program, and if there is any inconsistency, the quality control committee will request the research unit to provide missing or clarify contradictory information. The quality control committee is also responsible for the training of researchers to facilitate the consistency and labeling of the entire study.

9.1.4 Internal ethics committee

Internal ethics committee reviews and approves the written informed consent statements of each participating unit, and provide written statements to the subjects and/or their authorized representatives. The research ethics committee is responsible for reviewing the overall research protocol. If any accident or issue that affects the safety of the subject occurs during the research process, the research unit must immediately report to the research ethics committee. The committee organizes an internal meeting to deal with various issues in a timely manner and keeps records in written form.

9.2 Informed consent

The principle of informed consent will be implemented before protocol procedures are carried out. Information about the research content should be provided in both oral and written form and reviewed by a research ethics committee.

Participants, their relatives, guardians or authorized representatives and study partners must be given ample opportunity to inquire about details of the study. The consent form generated by the investigator must be approved, along with the protocol. Consent forms must be in a language fully comprehensible to the prospective participants and/or their authorized representatives. Informed consent will be documented by the use of a written consent form approved by the REB and signed by the participant and/or an authorized representative. The written consent document will embody the elements of informed consent as stated in the Helsinki Declaration and will comply with local regulations. In any case, participants and their legal representatives should sign an informed consent form after fully understanding the research information. Informed consent signed by each participant must be kept on file by the investigator for possible review by regulatory authorities and/or monitors. The informed consent will cover consent for the study including the genetic research as well. Consent forms will specify that DNA and other biomarker samples including imaging are for research purposes only; the research tests are not diagnostic in nature and participants will not be informed of their test results. The informed consent will specify that Xuan Wu Hospital, Capital Medical Unversity will receive and store research data, MRI data and samples.

10. Quality control

The sponsors and research units of the research should adopt the standard operating procedures established by the quality control committee to ensure the implementation of quality control and quality assurance system of clinical research. The quality control committee verifies all observations and findings in clinical trials to ensure data reliability and to ensure that conclusions from clinical trials are derived from raw data. Quality control must be used at every stage of data processing to ensure that all data is reliable and processed correctly.

10.1 Preparing researcher's case report form

The CRF is prepared by the lead investigator. The main contents include informed consent, personal information of subjects, current medical history, living habits, family history, past history, medication for cognitive impairment, physical examination, Hachinski ischemic score, cognitive assessment, psychobehavioral assessment, daily and overall functional assessment, imaging examination, laboratory test, and clinical diagnosis.

10.2 Researcher training

Before the start of clinical research, the quality control committee convenes the researchers of each test center to conduct centralized and unified training, so that researchers can understand and be familiar with the research protocol, the researcher's manual, the CRF, and understand the various scales.

The evaluators of clinical evaluation include physicians, nurses, and caregivers. The preparation, implementation, score evaluation,

and interpretation of the test results are standard and uniform, and through the centralized training, the evaluators achieve the consistency standard in the classification of the scales, and are required to be consistent for the test environment and test sequence of the subjects, so as to reduce the impact of human or environmental factors. After the training is completed, an exam is organized to test whether the evaluators have reliable testing skills.

10.3 Subject compliance

Sign the informed consent form.

The investigator should carefully implement informed consent so that the subject fully understands the test requirements and cooperates with the test. The sponsor provides free trial medication, laboratory examination fees, etc.

10.4 The researcher fills in the data requirements

The investigator should ensure that the data is true, accurate, complete, and timely loaded into the CRF and uploaded.

For all subjects who have filled in the informed consent form and are screened to be qualified for entering the test, the investigator must record the observed information in the CRF carefully and in detail, without empty entries or missing items.

All data in the CRF needs to be checked against the subject's original medical record data.

CRF can only be crossed when making any corrections, and modified by the side, with the signature and date of the researcher.

The original test sheet (or copy) and imaging report form (or copy) are pasted on the test sheet paste place in the study medical record.

Data that are significantly higher or lower or outside the clinical acceptance range should be verified or reexamined and made necessary instructions by the investigators.

11. Data management

All demographic, clinical, neuropsychological and imaging laboratory data are first registered in the CRF form by the researchers in each participating unit. Relevant personnel enter the data into the China COAST data network management platform after initial review and verification, and manage and share the multi-center entry data through a multi-center network management platform. The data management committee completes the monitoring, review and entry of data from each research center, including computer automatic verification and manual quality control by website data monitoring personnel.

The data management committee discusses and decides that the main research unit has access to the data of all research units, and each participating unit only has access to the data of its own unit. After the portal site entry, there is a simple custom search engine that can be used to query data types and specific data. The data will be provided to China COAST inspectors in a phased manner, and virtually “isolated” until the quality control process is completed, and only the data management committee members and those responsible for completing the quality control procedures can access them. After the quality control is completed, the data will be released from the quarantine area and accessible to authorized users. The MRI and PET imaging data are stored as an image data file (file extension .dcm) conforming to the DICOM 3.0 standard, and the imaging materials are sent to the imaging center platform.

12. Statistical analysis

To ensure data quality, the data management committee will periodically review the data to determine if they meet the original statistical expectations. The statistical department of the data management committee will implement China COAST data statistics quality control, mainly for abnormal and missing data monitoring, and compare between research centers. The data management committee will generate relevant data sets and distribute them to researchers. The statistical department will then participate in statistical analysis and article writing, and use professional statistical software such as SAS and SPSS in consultation with the author. The statistics department will be responsible for writing the analysis statistics section of the article. If the researchers choose to do their own analysis, the statistical department will make statistical comments on the manuscript that they submit.

13. Data sharing

The principle of data sharing is cooperation, and data sharing is coordinated by academic committee and data management committee. The data management committee generates data sets every six months through data freezing for quality control and research personnel

to use. For data access rights, sub-center researchers can independently use the data they collect themselves, and based on the amount and completeness of the household data they provide, they can be co-authored in articles published by China COAST or apply for more complete data for independent analysis and article writing. Researchers writing articles using China COAST data should indicate in the article that the data is from the China COAST or China COAST study group.

Investigators are required to submit an application to the academic committee by e-mail, including the research protocol and the type, quantity and format of the application data. The academic committee assesses the scientificity and feasibility of the research protocol. If the research proposal lacks scientificity or the information submitted is incomplete, the application will not be approved. The academic committee will also give amendment suggestions for the research proposal. After repeated communications and consultations with the applicant to determine the final version of the research protocol, the statistical department will organize the data and send it to the sub-centers or independent non-China COAST researchers. All researchers are committed to protect the privacy of the subject and need to ensure that the data will not be reassigned to other researchers or institutions.

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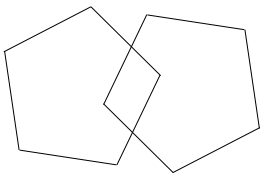
14. Appendix

Appendix 1 Mini-mental state examination (MMSE) (80)

Activity	Score
ORIENTATION – one point for each answer	
Ask: "What is the: (year)(season)(date)(day)(month)?"	_____
Ask: "Where are we: (state)(county)(town)(hospital)(floor)?"	_____
REGISTRATION – score 1,2,3 points according to how many are repeated	
Name three objects: Give the patient one second to say each.	
Ask the patient to: repeat all three after you have said them.	
Repeat them until the patient learns all three.	_____
ATTENTION AND CALCULATION – one point for each correct subtraction	
Ask the patient to: begin from 100 and count backwards by 7.	
Stop after 5 answers. (93, 86, 79, 72, 65)	_____
RECALL – one point for each correct answer	
Ask the patient to: name the three objects from above.	_____
LANGUAGE	
Ask the patient to: identify and name a pencil and a watch. (2 points)	_____
Ask the patient to: repeat the phrase "No ifs, ands, or buts." (1 point)	_____
Ask the patient to: "Take a paper in your right hand, fold it in half, and put it on the floor " (1 point for each task completed properly)	_____
Ask the patient to: read and obey the following: "Close your eyes." (1 point)	_____
Ask the patient to: write a sentence. (1 point)	_____
Ask the patient to: copy a complex diagram of two interlocking pentagons. (1 point)	_____

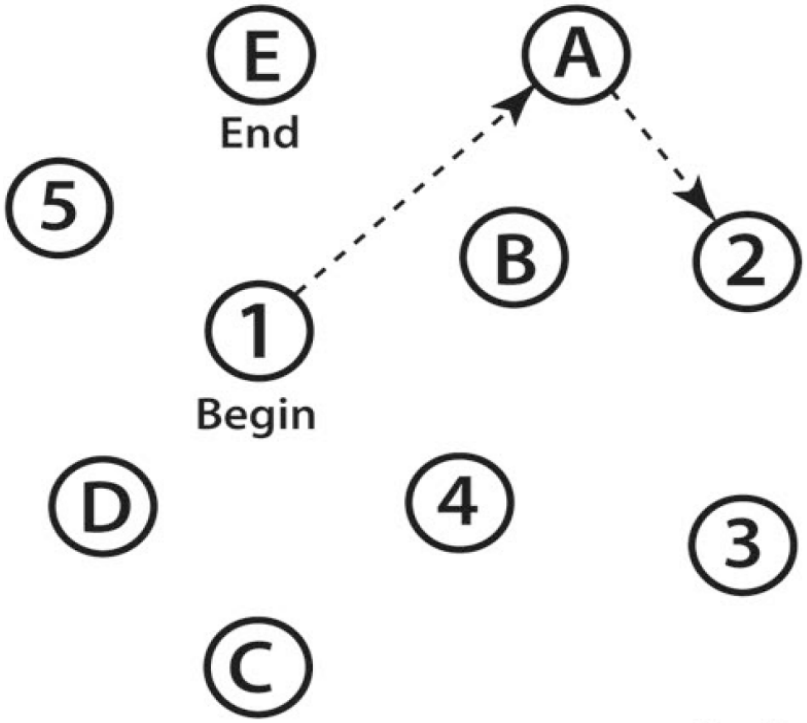


TOTAL (0-30): _____

Appendix 2 Montreal cognitive assessment(MoCA) (81)

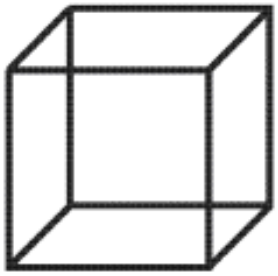
Montreal Cognitive Assessment (MoCA) was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal.

	contents	Administration and Scoring Instructions	score
2.1	Alternating Trail Making	Administration: The examiner instructs the subject: "Please draw a line, going from a number to a letter in ascending order. Begin here [point to (1)] and draw a line from 1 then to A then to 2 and so on. End here [point to (E)]." Scoring: Allocate one point if the subject successfully draws the following pattern: 1 −A- 2- B- 3- C- 4- D- 5- E, without drawing any lines that cross. Any error that is not immediately self-corrected earns a score of 0.	



2.1 score☐

2.2	Visuoconstructional Skills (Cube)	Administration: The examiner gives the following instructions, pointing to the cube: “Copy this drawing as accurately as you can, in the space below”. Scoring: One point is allocated for a correctly executed drawing. • Drawing must be three-dimensional • All lines are drawn • No line is added • Lines are relatively parallel and their length is similar (rectangular prisms are accepted) A point is not assigned if any of the above-criteria are not met.	



2.2 score☐

2.3	Visuoconstructional Skills (Clock)	Administration: Indicate the right third of the space and give the following instructions: “Draw a clock. Put in all the numbers and set the time to 10 past 11”. Scoring: One point is allocated for each of the following three criteria:	

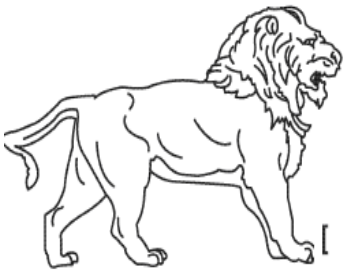
• Contour (1 pt.): the clock face must be a circle with only minor distortion acceptable (e.g., slight imperfection on closing the circle);
• Numbers (1 pt.): all clock numbers must be present with no additional numbers; numbers must be in the correct order and placed in the approximate quadrants on the clock face; Roman numerals are acceptable; numbers can be placed outside the circle contour;
• Hands (1 pt.): there must be two hands jointly indicating the correct time; the hour hand must be clearly shorter than the minute hand; hands must be centered within the clock face with their junction close to the clock center.
A point is not assigned for a given element if any of the above-criteria are not met.
At the same time, the score is given by the 15-point method (see table below), not counting the total score.

	Contents	Yes	No	score
1	Shape similar to the clock	1	0	
2	Round circumference	1	0	
3	Diameter >2.5 cm (if the first painting is small, encourage it to draw larger)	1	0	
4	All the numbers are inside the circle	1	0	
5	First locate 12,6,3,9	1	0	
6	The numbers are arranged at regular intervals (symmetrically arranged on a 12-6 axis). If it is so, skip the 7th question	2	0	
7	If there is a spatial alignment error, it can be corrected (with traces of alteration)	1	0	
8	Only Arabic numerals	1	0	
9	Only the Arabic numerals 1-12 appear	1	0	
10	1-12 appears in sequence, no omission or misalignment	1	0	
11	Only 2 pointers	1	0	
12	The pointer is like an arrow	1	0	
13	The hour hand is between 11 and 12	1	0	
14	The minute hand is longer than the hour hand	1	0	
15	There is no problem under the column	1	0	
	1)The minute hand points to 10 o'clock			
	2)Write the words 11:10			
	3)Extra pointer or circle			
	4)Any letters, words or diagrams appear			
	5)Any extra lines appear below the circle			

2.3 score ☐——3-point method

2.3.1 score☐☐——15-point method

2.4	Naming	Administration: Beginning on the left, point to each figure and say: “Tell me the name of this animal”. Scoring: One point each is given for the following responses: (1) lion (2) giraffe (3) camel or dromedary.	2.4 score☐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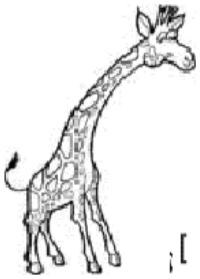
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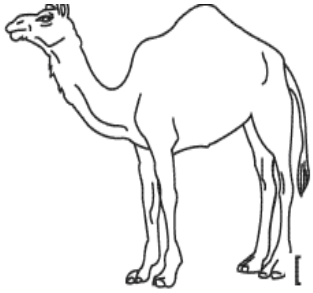

[ ]

2.5	Memory	Administration: The examiner reads a list of 5 words at a rate of one per second, giving the following instructions: "This is a memory test. I am going to read a list of words that you will have to remember now and later on. Listen carefully. When I am through, tell me as many words as you can remember. It doesn't matter in what order you say them". Mark a check in the allocated space for each word the subject produces on this first trial. When the subject indicates that (s) he has finished (has recalled all words), or can recall no more words, read the list a second time with the following instructions: "I am going to read the same list for a second time. Try to remember and tell me as many words as you can, including words you said the first time." Put a check in the allocated space for each word the subject recalls after the second trial. At the end of the second trial, inform the subject that (s)he will be asked to recall these words Again by saying, "I will ask you to recall those words again at the end of the test." Scoring: No points are given for Trials One and Two.	

	Face	Velvet	School	Daisy	Red
First					
Second					

2.6	Forward Digit Span	Give the following instruction: "I am going to say some numbers and when I am through, repeat them to me exactly as I said them". Read the five number sequence at a rate of one digit per second. Scoring: Allocate one point for each sequence correctly repeated. **21854** [ ]	2.6 score☐
2.7	Backward Digit Span	Administration: Give the following instruction: "Now I am going to say some more numbers, but when I am through you must repeat them to me in the backwards order." Read the three number sequence at a rate of one digit per second. Scoring: Allocate one point for each sequence correctly repeated, (N.B.: the correct response for the backwards trial is 2-4-7). **742** [ ]	2.7 score☐
2.8	Vigilance	Administration: The examiner reads the list of numbers at a rate of one per second, after giving the following instruction: "I am going to read a sequence of numbers. Every time I say the number 1, knock the table once. If I say a different letter, do not knock the table". Scoring: Give one point if there is zero to one errors (an error is a knock on a wrong number or a failure to knock on number 1). **5213941180621519451114190511 2** [ ]	2.8 score☐

2.9	Serial 7s (Refer to the MMSE result score)	Administration: The examiner gives the following instruction: “Now, I will ask you to count by subtracting seven from 100, and then, keep subtracting seven from your answer until I tell you to stop.” Give this instruction twice if necessary. Scoring: This item is scored out of 3 points. Give no (0) points for no correct subtractions, 1 point for one correction subtraction, 2 points for two-to-three correct subtractions, and 3 points if the participant successfully makes four or five correct subtractions. Count each correct subtraction of 7 beginning at 100. Each subtraction is evaluated independently; that is, if the participant responds with an incorrect number but continues to correctly subtract 7 from it, give a point for each correct subtraction. For example, a participant may respond “92 – 85 – 78 – 71 – 64” where the “92” is incorrect, but all subsequent numbers are subtracted correctly. This is one error and the item would be given a score of 3. [ ]**93** [ ]**86** [ ]**79** [ ]**72** [ ]**65**	2.9 score☐
2.10	Sentence repetition	Administration: The examiner gives the following instructions: “I am going to read you a sentence. Repeat it after me, exactly as I say it [pause]: I only know that John is the one to help today.” Following the response, say: “Now I am going to read you another sentence. Repeat it after me, exactly as I say it [pause]: The cat always hid under the couch when dogs were in the room.” Scoring: Allocate 1 point for each sentence correctly repeated. Repetition must be exact. Be alert for errors that are omissions (e.g., omitting "only", "always") and substitutions/additions (e.g., "John is the one who helped today;" substituting "hides" for "hid", altering plurals, etc.). I only know that John is the one to help today. [ ] The cat always hid under the couch when dogs were in the room. [ ]	2.10score☐
2.11	Verbal fluency	Administration: "Please tell as many animals as you can, as soon as possible. The time is 1 minute, are you ready? Start." Stop after one minute. Scoring: If the subject names ≥11 within 1 minute, score 1 point. At the same time, record the examiner's answer as much as possible. Deified animals such as dragons, phoenixes, and unicorns are also correct. please record : 2.11.1(0-15 s)_____ 2.11.2(16-30 s)_____ 2.11.3(31-45 s)_____ 2.11.4(46-60 s)_____ [ ]_____(N≥11 words)	2.11score☐
2.12	Abstraction	Administration: The examiner asks the subject to explain what each pair of words has in common, starting with the example: “Tell me how an orange and a banana are alike”. If the subject answers in a concrete manner, then say only one additional time: “Tell me another way in which those items are alike”. If the subject does not give the appropriate response (fruit), say, “Yes, and they are also both fruit.” Do not give any additional instructions or clarification. After the practice trial, say: “Now, tell me how a train and a bicycle are alike”. Following the response, administer the second trial, saying: “Now tell me how a ruler and a watch are alike”. Do not give any additional instructions or prompts. Scoring: Only the last two item pairs are scored. Give 1 point to each item pair	2.12score☐

correctly answered. The following responses are acceptable:

[ ] Train-bicycle： Means of transportation, means of travelling, you take trips in both;

[ ] Ruler-watch ： Measuring instruments, used to measure.

The following responses are not acceptable: Train-bicycle = they have wheels; Ruler-watch = they have numbers.

2.13 Delayed recall

Administration: The examiner gives the following instruction: "I read some words to you earlier, which I asked you to remember. Tell me as many of those words as you can remember." Make a check mark (√) for each of the words correctly recalled spontaneously without any cues, in the allocated space.
Scoring: Allocate 1 point for each word recalled freely without any cues.
Following the delayed free recall trial, prompt the subject with the semantic category cue provided below for any word not recalled. Make a check mark (√) in the allocated space if the subject remembered the word with the help of a category or multiple-choice cue. Prompt all non-recalled words in this manner. If the subject does not recall the word after the category cue, give him/her a multiple choice trial, using the following example instruction, "Which of the following words do you think it was, NOSE, FACE, or HAND?"
Use the following category and/or multiple-choice cues for each word, when appropriate:

	Face	Velvet	School	Daisy	Red
No prompt					
category cue	part of the body	type of fabric	type of building	type of flower	a colour
multiple choice	nose, face, hand	denim, cotton, velvet	church, school, hospital	rose, daisy, tulip	red, blue, green

Scoring: No points are allocated for words recalled with a cue. A cue is used for clinical information purposes only and can give the test interpreter additional information about the type of memory disorder. For memory deficits due to retrieval failures, performance can be improved with a cue. For memory deficits due to encoding failures, performance does not improve with a cue.

2.13score☐

2.14 Orientation

Administration: The examiner gives the following instructions: "Tell me the date today". If the subject does not give a complete answer, then prompt accordingly by saying: "Tell me the [year, month, exact date, and day of the week]." Then say: "Now, tell me the name of this place, and which city it is in."
Scoring: Give one point for each item correctly answered. The subject must tell the exact date and the exact place (name of hospital, clinic, office). No points are allocated if subject makes an error of one day for the day and date.
[ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

2.14score☐

2.15 Total score

2.15score☐

☐

TOTAL SCORE: Sum all sub scores listed on the right-hand side. Add one point for an individual who has 12 years or fewer of formal education, for a possible maximum of 30 points.
A final total score of 26 and above is considered normal.

Appendix 3 Neuropsychiatric Inventory (NPI-Q) (91)

Scoring levels with example definitions for the NPI-Q

Frequency of occurrence (1~4)

1. Occasionally: less than once per week
2. Often: about once per week
3. Frequently: several times per week but less than every day
4. Very frequently: once or more per day

Severity of behavior (1~3)

1. Mild: mildly distressing to the patient and not a major problem
2. Moderate: distressing to the patient but easily overcome by reassurance
3. Marked: distressing to the patient and difficult to redirect or deal with

Distress to you (0~5)

0. Not at all
1. Minimally: rarely distressing and easily tolerated
2. Mildly: occasionally distressing, but not a significant problem
3. Moderately: somewhat distressing and problematic, but usually tolerable
4. Severely: very distressing and difficult to cope with
5. Very severely or extremely: markedly distressing and extremely difficult to cope with

The score for each item is calculated by multiplying the frequency by the intensity; and the total score for the NPI is calculated by adding the scores of all symptoms.

Thus, scores may range from 0 to a maximum of 144, where the higher the score, the more severe the psychopathology.

Summary table for NPI-Q scores.

Symptom		Frequency	Severity	Total (frequency × severity)	Distress to you
3.1 Delirium	Does the patient have a false idea, such as thinking that someone else has stolen his/her things? Do you suspect that someone is harming him?				
3.2 Hallucinations	Does the patient have hallucinations such as visual hallucinations or auditory hallucinations? See or hear something or sound that doesn't exist? Talking to someone who doesn't actually exist?				
3.3 Agitation/aggression	Does the patient often refuse help from others? Unmanageable? Stubborn? Shouting at others? Snoring others?				
3.4 Depression/dysphoria	Does the patient show grief or express a depression?				
3.5 Anxiety	Is it uncomfortable after the patient is separated from the caregiver? Does the patient have mental stress such as shortness of breath, sigh, can't relax or feel nervous?				
3.6 Joy/euphoria	Is the patient too happy and feeling too good? Feeling humorous and laughing at things that others are not interesting about? Joy that doesn't match the situation?				
3.7 Apathy	Did the patient lose interest in activities that were previously of interest? Indifferent to other people's activities and plans?				
3.8 Disinhibition	Does the patient lose self-control, such as talking to strangers like an acquaintance? Or talk regardless of the feelings of others?				
3.9 Irritability/lability	Does the patient show impatience or crazy behavior? Can't bear the delay? Can't wait patiently for the planned activities?				
3.10 Abnormal motor behaviour	Does the patient repeat nonsense activities, such as turning around a house, playing with buttons, bandaging with a rope, etc.? Or other repetitive activities?				
3.11 Sleep disorders	Does the patient wake others up at night? Get up early in the morning? Frequent snoring during the day?				
3.12 Eating disorders	Does the patient's weight decrease or increase? Do you like the taste of food changes?				

3.13 Total score		

Appendix 4 Geriatric Depression Scale (GDS) (92)

Please answer “yes” or “no” to the following questions in regards to how you have been feeling recently.

	Yes	No
4.1 Are you basically satisfied with your life?		
4.2 Have you dropped many of your activities and interests?		
4.3 Do you feel that your life is empty?		
4.4 Do you often get bored?		
4.5 Are you hopeful about the future?		
4.6 Are you bothered by thoughts you can’t get out of your head?		
4.7 Are you in good spirits most of the time?		
4.8 Are you afraid that something bad is going to happen to you?		
4.9 Do you feel happy most of the time?		
4.10 Do you often feel helpless?		
4.11 Do you often get restless and fidgety?		
4.12 Do you prefer to stay at home, rather than going out and doing new things?		
4.13 Do you frequently worry about the future?		
4.14 Do you feel you have more problems with memory than most?		
4.15 Do you think it is wonderful to be alive now?		
4.16 Do you often feel downhearted and blue?		
4.17 Do you feel pretty worthless the way you are now?		
4.18 Do you worry a lot about the past?		
4.19 Do you find life very exciting?		
4.20 Is it hard for you to get started on new projects?		
4.21 Do you feel full of energy?		
4.22 Do you feel that your situation is hopeless?		
4.23 Do you think that most people are better off than you are?		
4.24 Do you frequently get upset over little things?		
4.25 Do you frequently feel like crying?		
4.26 Do you have trouble concentrating?		
4.27 Do you enjoy getting up in the morning?		
4.28 Do you prefer to avoid social gatherings?		
4.29 Is it easy for you to make decisions?		
4.30 Is your mind as clear as it used to be?		

Appendix 5: Modified Hachinski ischemic scale (m-HIS) (95)

	Feature	Yes	No
H1	Abrupt onset	□2	□0
H2	Stepwise deterioration	□1	□0
H3	Somatic complaint	□1	□0
H4	Emotional incontinence	□1	□0
H5	History or presence of hypertension	□1	□0
H6	History of strokes	□2	□0
H7	Focal neurological symptoms	□2	□0
H8	Focal neurological signs	□2	□0
H9	Total (attention：score ≥4 can be chosen)	|___|.|___|	

Appendix 6: World Health Organization University of California-Los Angeles, Auditory Verbal Learning Test (WHO-UCLA AVLT (84)

On each of 3 learning trials, 15 unrelated words (all nouns) are presented orally at the rate of one word per second and immediate free recall of the words is elicited. The number of correctly recalled words on each trial is recorded. Following a 30-minute delay filled with unrelated testing, free recall of the original 15 word list is elicited. In cued recall, the experimenter prompts the subjects with the word category. Finally, a yes/no recognition test is administered which consists of the original 15 words and 15 randomly interspersed distracter words. The number of target "hits" and false positive responses are recorded.

	Text 1	Text 2	Text 3		Delay recall
arm				arm	
cat				cat	
axe				axe	
bed				bed	
airplane				airplane	
ear				ear	
dog				dog	
hammer				hammer	
chair				chair	
car				car	
eyes				eyes	
horse				horse	
knife				knife	
clock				clock	
bicycle				bicycle	

Item category	**Record**		
a body part	☐ arm	☐ ear	☐ eyes
animal	☐ cat	☐ dog	☐ horse
tools	☐ axe	☐ hammer	☐ knife
furniture	☐ bed	☐ chair	☐ clock
vehicle	☐ airplane	☐ car	☐ bicycle

	Yes	No		Yes	No
mirror			mouse		
hammer			tree		

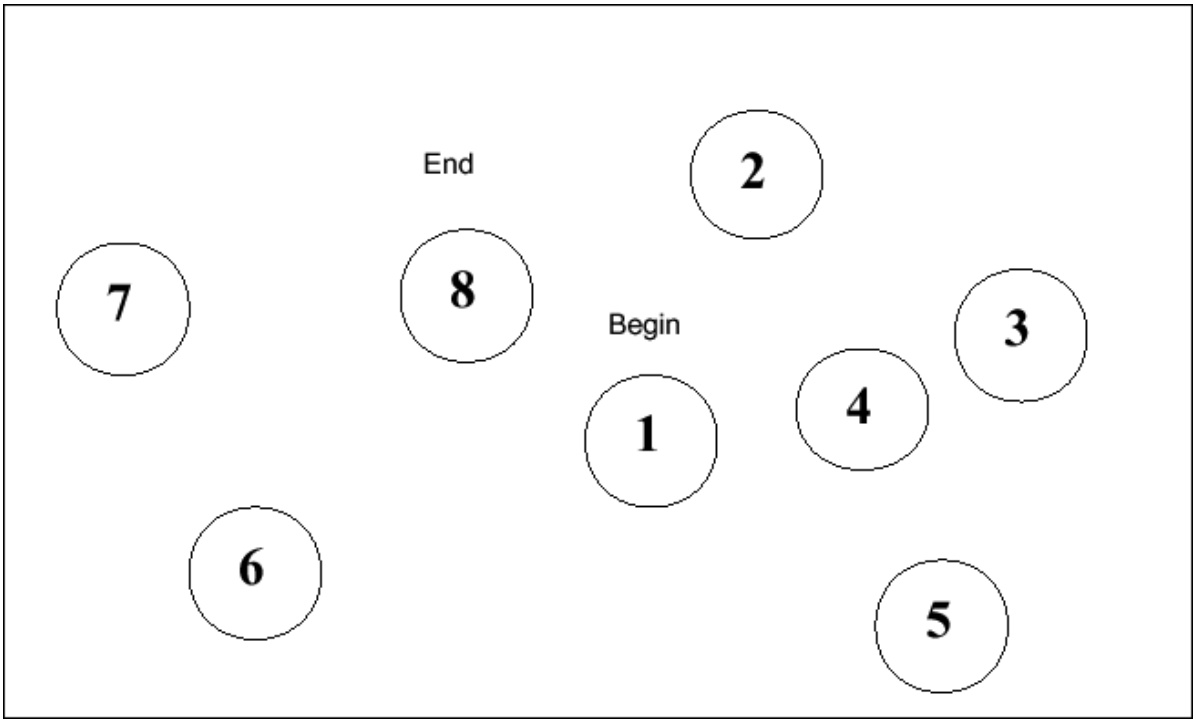
knife			arm		
candle			nose		
motorbike			sun		
axe			truck		
clock			eyes		
chair			fish		
airplane			ear		
tortoise			bicycle		
horse			snake		
thigh			bench		
dog			bus		
table			bed		
cat			car		

Appendix 7: Trail making test (TMT) (86)

Part A

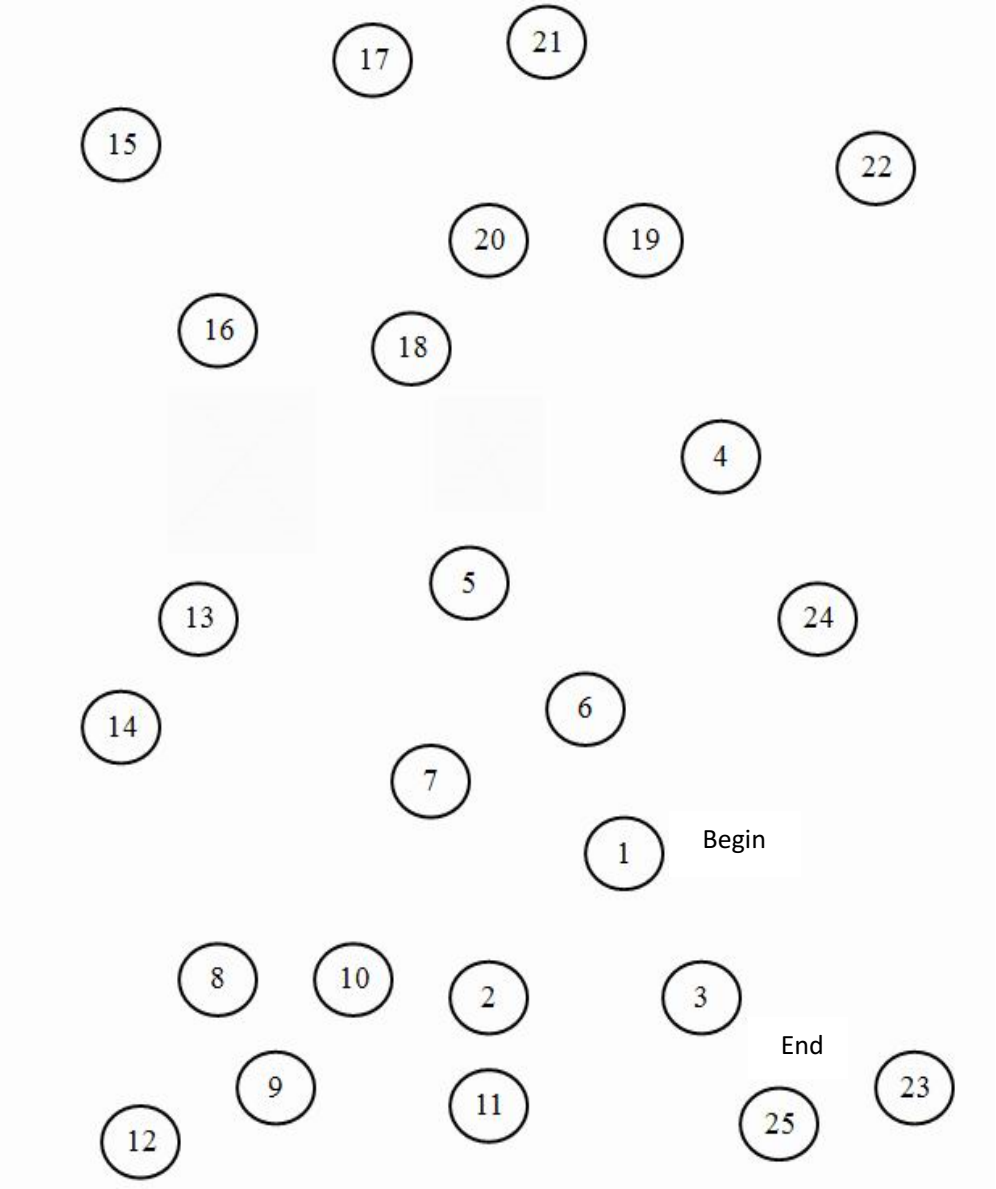
Practice test

Administration: The following are some circles with numbers in the circle. I would like to ask you to connect in the order of 1-2-3... with a pen. Note: Do not leave the pen tip away from the paper and the line drawn must pass through the graphic. If I am wrong, I will point out that you need to go back and paint again. Let us give it a try now. The sooner you paint, the better. Are you ready? Start! Note: The following is a practice test, not scored. Correct every time you make a mistake, and tell the correct connection method, while actively encouraging.



Actual test

Administration: There is a similar circle diagram here, please connect it again as above. Please note that the faster you draw, the better. Do not leave the pen tip and the lines drawn must pass through the graphic. Start here (pointing to the starting point) until here (pointing to the end). Ready? Start. (time)

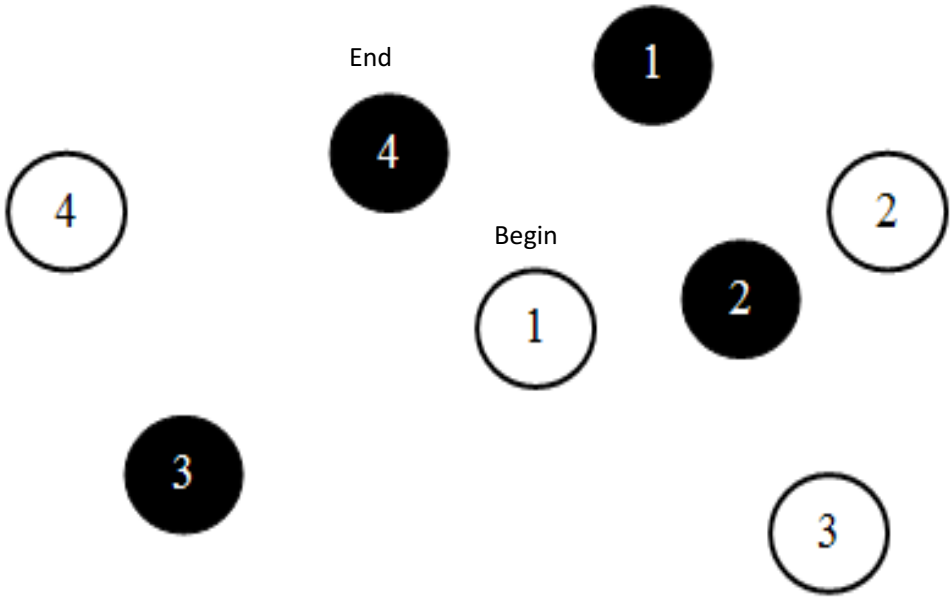


7.1.1 All digital completion time (0-150) seconds (if 150 seconds is not completed, record 150)
7.1.2 Number of errors(0-25; 88=Not applicable)
7.1.3 Correct number (0-25; 88=Not applicable)

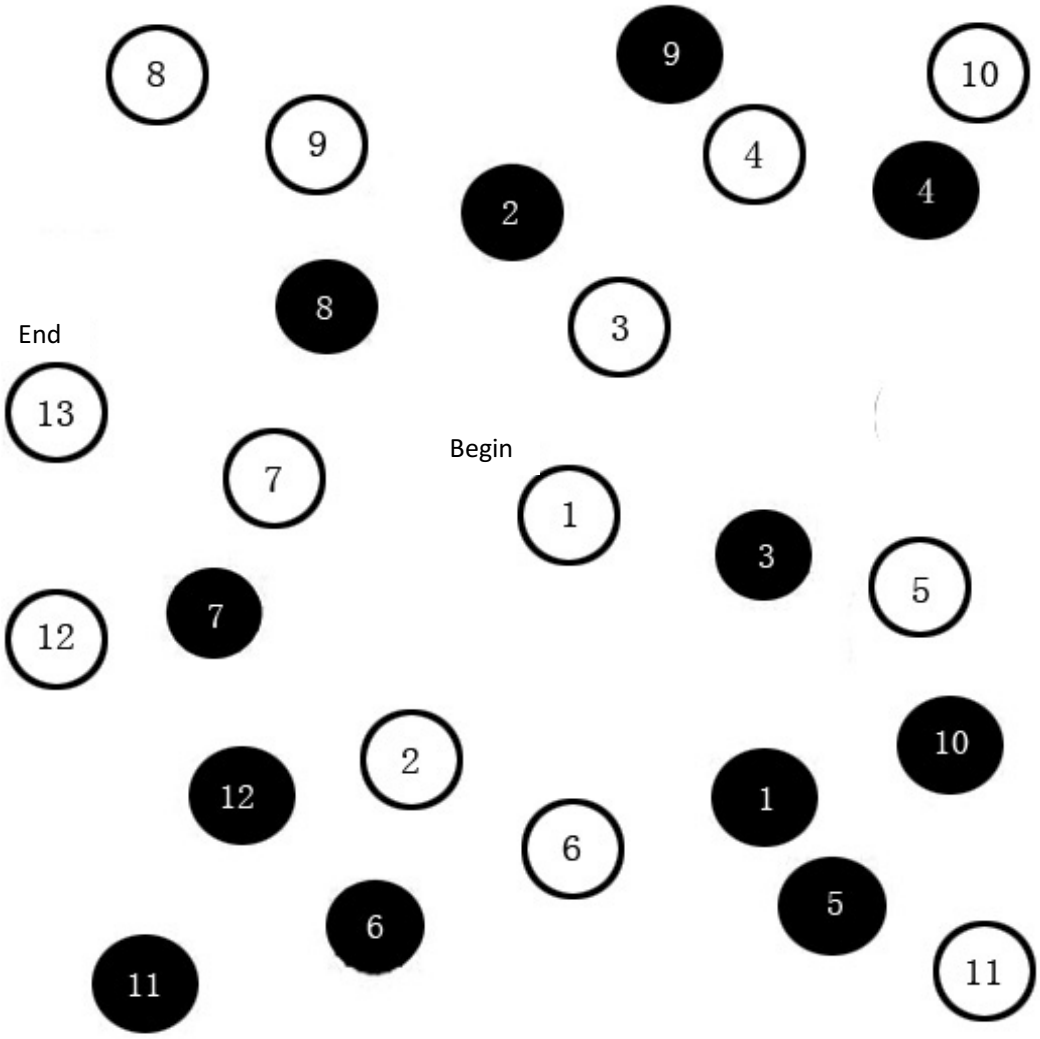
Part B

Administration: The following are 1-13 white circle numbers and 1-12 black circle numbers. They are also scattered. Please connect them in order, i.e. white circle 1 - black circle 1 - white circle 2 - black circle 2... Note: Do not leave the pen tip away from the paper and the line drawn must pass through the graphic. If I am wrong, I will point out that you need to go back and paint again. Let us give it a try now. The sooner you paint, the better. Are you ready? Start!

Practice test



Actual test



7.2.1 All digital completion time (0-300) seconds (if 300 seconds is not completed, record 300)
7.2.2 Number Sequence Error Number (0-25; 88=Not applicable)
7.2.3 Correct number of lines (0-24; 88=Not applicable)

Appendix 8: Digit span test (DST) (87)

This task consists of two parts. Digits forward is administered first and requires the repetition of digits in the same order presented, while in digits backwards participants must repeat digits in an inverse or backwards order. Text 2 is administered even if the participant fails in Text 1.

	Text 1		Text 2
3	5-8-2	3	6-9-4
4	6-4-3-9	4	7-2-8-6
5	4-2-7-3-1	5	7-5-8-3-6
6	6-1-9-4-7-3	6	3-9-2-4-8-7
7	5-9-1-7-4-2-8	7	4-1-7-9-3-8-6
8	5-8-1-9-2-6-4-7	8	3-8-2-9-5-1-7-4
9	2-7-5-8-6-2-5-8-4	9	7-1-3-9-4-2-5-6-8
10	5-2-7-4-9-1-3-7-4-6	10	4-7-2-5-9-1-6-2-5-3
			Digit span

	Text 1		Text 2
2	2-4	2	5-8
3	6-2-9	3	4-1-5
4	3-2-7-9	4	4-9-6-8
5	1-5-2-8-6	5	6-1-8-4-3
6	5-3-9-4-1-8	6	7-2-4-8-5-6
7	8-1-2-9-3-6-5	7	4-7-3-9-1-2-8
8	9-4-3-7-6-2-5-8	8	7-2-8-1-9-6-5-3
			Backwards digit span

Appendix 9: Boston naming test (BNT) (88)

Administration: "I will show you some pictures now, please tell me what these pictures are."

If the tester fails to answer the answer, he is prompted: For example, "This is (plant), is there another name?"

If you still can't answer, then three answers are given in order to let the tester choose. Remember to record every answer of the testier, whether correct or not (only calculate the score of spontaneous naming: correct = 1, answer = 0).

	Picture	Answer (yes = 1; wrong = 0)	If wrong, specific record	If the answer is wrong, prompt	Answer (yes = 1; wrong = 0)	If wrong, specific record	If the prompt still answers the error, please select (circle the specific choice)		
9.1	2. Tree			plant			Peach blossom	Tree	Fireworks
9.2	3. Pen			Used for writing			straw	Original ball pen	pen
9.3	6. Scissors			tool			Scissors	clamp	Spoon
9.4	8. Flowers			plant			Vegetables	straw hat	flower
9.5	9. Saw			Woodworking equipment			Machine gun	Saw	Knife
9.6	12. Broom			Used for cleaning			Mop	Writing brush	Broom
9.7	*14. Mushroom			food			Mushroom	Cauliflower	umbrella
9.8	15. Hangers			Inside the wardrobe			roof	hanger	hook
9.9	16. Wheelchair			Patient use			Executive chair	trolley	wheelchair
9.10	17. Camel			animal			camel	mountain	Cattle
9.11	21 racquet			Sporting goods			Ping pong paddle	racquet	mirror
9.12	22. Snail			animal			snails	Squid	scallop
9.13	24. Seahorse			Marine life			hook	abalone	Seahorse
9.14	25. Darts			Used to throw			Target	Darts	rocket
9.15	30. Harmonica			Musical instrument			Harmonica	Air conditioner	box
9.16	31. Rhinoceros			animal			Canned knife	hippo	rhinoceros
9.17	33. Igloo			Used to live			Ice house	Grass house	grave
9.18	36. Cactus			plant			Iron tree	cactus	cross
9.19	37 escalator			Use up and down			Sliced bread	Slide	escalator
9.20	38. Harp			Musical instrument			harp	floor lamp	piano
9.21	42. Stethoscope			Doctor			Earphone	Stethoscope	sphygmomanometer
9.22	43. Pyramid			In Egypt			Zongzi	Sphinx	pyramid
9.23	46. Funnel			Pour water			Funnel	Ice cream cones	Pump
9.24	47. Accordion			Musical instrument			Harmonica	accordion	Blinds
9.25	50. Compass			painting			Cotton pliers	ruler	Compasses
9.26	52. Tripod			For photography			tripod	Mechanical arm	easel
9.27	54. tongs			Appliance			Spatula	tongs	canoe
9.28	57. Flower shed/ trellis			Park has			Flower shed/ trellis	trash can	network
9.29	59. Protractor			stationery			Pound scale	Triangle ruler	Protractor
9.30	60. Abacus			Counting			Calculator	Abacus	Curtain
Total	9.31			9.32			9.33		

Appendix 10: Activities of daily living (ADL) (93)

Ask the insider to rate the following functions of the patient based on the information provided (assessed according to the level of intelligence).

Rating	Instrumental Daily Living Ability Scale (LADH) Scoring Project
1	Ability to use the phone
	☐1、take the initiative to operate the phone - check the number, dial, etc.
	☐2、can dial a few familiar numbers
	☐3、can answer the phone but not dial the phone
	☐4、cannot use the telephone
2	Shopping
	☐1、independently handle all shopping needs
	☐2、a small amount of shopping independently
	☐3、need to accompany on any purchase
	☐4、completely unable to shopping
3	Cooking
	☐1、independently plan, prepare and make the right amount of meal
	☐2、if the raw materials can be prepared to prepare enough meal
	☐3、heating, serving or cooking, or cooking but not keeping the right amount
	☐4、Need to prepare the meal and do it well
4	Hosting housework
	☐1、independently host housework or occasionally need help (such as heavy work needs family help)
	☐2、do daily light physical housework such as washing dishes, making beds
	☐3、do daily light physical housework but cannot maintain an acceptable level of cleanliness
	☐4、all housework needs help
	☐5、do not participate in any housework
5	Washing

	□1、can complete a personal bath
	□2、wash small pieces of clothing - wash socks, etc.
	□3、all washing must be done by others
6	Transportation
	□1、independent public transport or driving a car
	□2、travel by taxi, but no bus
	□3、take the bus when accompanied by others
	□4、can only travel by taxi or car with the help of others
	□5、no travel at all
7	Responsibility for the medical care
	□1、can take medicine seriously according to the correct time and dose
	□2、if you prepare for each dose, you can take medicine
	□3、you can't prepare your own medicine
8	Financial ability
	□1、independently handle finance (budget, write checks, pay rent, bills, go to the bank), collect and maintain income channels
	□2、manage daily shopping, but need help in banking affairs and big shopping, etc.
	□3、can't handle finance

9 IADL total score

Rating	Somatic Self-care Ability Scale (PSUS) Scoring Project
10	Bowel and bladder function at the toilet,
	□1、in the bathroom can be completely self-care, no incontinence
	□2、need to be reminded of self-cleaning, or need help, or a small number of accidents (at least once a week)
	□3、dirty or wet during sleep, more than once a week
	□4、dirty or wet when awake, more than once a week
	□5、incontinence

11	Eating
	☐1、no need to help when eating
	☐2、eating a small amount of time to eat and/or need to prepare special food, or need help after cleaning after meals
	☐3、need moderate help for meal, and it is not neat
	☐4、all meals need a lot of help
	☐5、can't eat at all, and resist feeding by others
12	Dressing
	☐1、wear clothes, undress, and choose clothes from your wardrobe
	☐2、wearing clothes and undressing, need a small amount of help
	☐3、need moderate help in dressing and choosing clothes
	☐4、need more help in wearing clothes, but with the help of others
	☐5、can't wear clothes at all, and it is against the help of others
13	Carding (tidy, hair, nails, hands, face, clothes)
	☐1、always dressed neatly, properly decorated, no need to help
	☐2、can properly decorate themselves, occasionally need a small amount of help, such as repairing beard
	☐3、need moderate or reasonable help or guidance in combing
	☐4、all combing matters need help, but can be kept neat after others help
	☐5、actively oppose the efforts of others to help sort out
14	Walking
	☐1、walk to the venue or urban area
	☐2、Walk in the residential area or walk near a street
	☐3、walking needs help (choose 1) a() cane, b() walker, c() wheelchair
	☐1-In and out without help

	☐2-In and out need help
	☐4、don’t need to sit in a chair or a wheelchair, but you can’t push it yourself without help
	☐5、more than half of the time bedridden
15	Bathing
	☐1、take a bath (bath, shower, bath), no need to help
	☐2、need help when getting in and out of the tub
	☐3、only wash your face and hands, cannot wash other parts of the body
	☐4、cannot take a bath, but with others to bathe him
	☐5、cannot take a bath, and resist efforts to keep him clean

16 BADL total score

17 ADL total score (IADL+BADL)

The total score below 16 is completely normal, and greater than 16 points have different degrees of functional decline, up to 64 points. The single item is divided into 1 normal, 2 to 4 is divided into functional decline, where there are 2 or more than ≥ 3 points, or the total score is ≥ 22 points, there are obvious obstacles to function

Appendix 11: Clinical Dementia Rating (CDR) (83)

This is a semi-structured interview. Please ask all of these questions. Ask any additional questions necessary to determine the subject's CDR. Please note information from the additional questions.

Memory Questions for Informant:

1. Does he/she have a problem with his/her memory or thinking? 1a. If yes, is this a consistent problem (as opposed to inconsistent)?
   Yes No
   Yes No
2. Can he/she recall recent events? Usually Sometimes Rarely
3. Can he/she remember a short list of items (shopping)? Usually Sometimes Rarely
4. Has there been some decline in memory during the past year? Yes No
5. Is his/her memory impaired to such a degree that it would have interfered with his/her activities of daily life a few years ago (or pre-retirement activities)? (collateral sources opinion) Yes No
6. Does he/she completely forget a major event (e.g., trip, party, family wedding) within a few weeks of the event? Usually Sometimes Rarely
7. Does he/she forget pertinent details of the major event? Usually Sometimes Rarely
8. Does he/she completely forget important information of the distant past (e.g., birthdate, wedding date, place of employment)? Usually Sometimes Rarely

9. Tell me about some recent event in his/her life that he/she should remember. (For later testing, obtain details such as location of the event, time of day, participants, how long the event was, when it ended and how the subject or other participants got there).

   Within 1 week:

   Within 1 month:

10. When was he/she born?
11. Where was he/she born?
12. What was the last school he/she attended?
    Name _____
    Place _____
    Grade _____
13. What was his/her main occupation/job (or spouse's job if subject was not employed)?
14. What was his/her last major job (or spouse's job if subject was not employed)?
15. When did he/she (or spouse) retire and why?

Orientation Questions for Informant:

How often does he/she know of the exact:

1. <u>Date of the Month?</u>

Usually Sometimes Rarely Don't Know

2. Month?

Usually Sometimes Rarely Don't Know

3. Year?

Usually Sometimes Rarely Don't Know

4. Day of the Week?

Usually Sometimes Rarely Don't Know

5. Does he/she have difficulty with time relationships (when events happened in relation to each other)?

Usually Sometimes Rarely Don't Know

6. Can he/she find his/her way about familiar streets?

Usually Sometimes Rarely Don't Know

7. How often does he/she know how to get from one place to another outside his/her neighborhood?

Usually Sometimes Rarely Don't Know

8. How often can he/she find his/her way about indoors?

Usually Sometimes Rarely Don't Know

Judgment and Problem Solving Questions for Informant:

1. In general, if you had to rate his/her abilities to solve problems at the present time, would you consider them: As good as they have ever been

   Good, but not as good as before

   Fair

   Poor

   No ability at all

2. Rate his/her ability to cope with small sums of money (e.g., make change, leave a small tip):

   No loss

   Some loss

   Severe loss

3. Rate his/her ability to handle complicated financial or business transactions (e.g., balance check-book, pay bills):

   No loss

Some loss

Severe loss

4. Can he/she handle a household emergency (e.g., plumbing leak, small fire)?

   As well as before

   Worse than before because of trouble thinking

   Worse than before, another reason (why) _____

5. Can he/she understand situations or explanations?

   Usually Sometimes Rarely Don't Know

6. Does he/she behave* appropriately [i.e., in his/her usual (premorbid) manner] in social situations and interactions with other people?

   Usually Sometimes Rarely Don't Know

*This item rates behavior, not appearance.

Community Affairs Questions for Informant:

Occupational

1. Is the subject still working? Yes No N/A
   If not applicable, proceed to item 4 If yes, proceed to item 3
   If no, proceed to item 2

2. Did memory or thinking problems contribute to the subject's decision to retire? (Question 4 is next) Yes No D/K

3. Does the subject have significant difficulty in his/her job because of problems with memory or thinking?

   Rarely or Never Sometimes Usually Don't Know

Social

4. Did he/she ever drive a car? Yes No

5. Does the subject drive a car now? Yes No

6. If no, is this because of memory or thinking problems? Yes No

7. If he/she is still driving, are there problems or risks because of poor thinking? Yes No

*8. Is he/she able to independently shop for needs?

   Rarely or Never (Needs to be accompanied on any shopping trip) Sometimes (Shops for limited number of items; buys duplicate items or forgets needed items) Usually Don't Know

9. Is he/she able to independently carry out activities outside the home?

   Rarely or Never (Generally unable perform activities Sometimes (Limited and/or routine, e.g., Usually (Meaningful participation Don't Know

without help) participation in or meetings; trips to beauty parlor) activities, voting)

10. Is he/she taken to social functions outside a family home? Yes No
If no, why not? _____

11. Would a casual observer of the subject's behavior think the subject was ill? Yes No

12. If in nursing home, does he/she participate well in social functions (thinking)? Yes No

*Is there enough information available to rate the subject's level of impairment in community affairs? Yes No
If not, please probe further.

Community Affairs: Such as going to church, visiting with friends or family, political activities, professional organizations such as bar association, other professional groups, social clubs, service organizations, educational programs.

*Please add notes if needed to clarify subject's level of functioning in this area:

Home and Hobbies Questions for Informant:

1a. What changes have occurred in his/her abilities to perform household chores? _____

1b. What can he/she still do well?

2a. What changes have occurred in his/her abilities to perform hobbies?

2b. What can he/she still do well?

3. If in nursing home, what can he/she no longer do well (H and H)?

Everyday Activities (Blessed):

	No loss		Severe loss
4. Ability to perform household tasks	0	0.5	1

Please describe: _____

5. Is he/she able to perform household chores at the level of: (Pick one. Informant does not need to be asked directly).

No meaningful function.
(Performs simple activities, such as making a bed, only with much supervision)

Functions in limited activities only.
(With some supervision, washes dishes with acceptable cleanliness; sets table)

Functions independently in some activities.
(Operates appliances, such as a vacuum cleaner; prepares simple meals)

Functions in usual activities but not at usual level.

Normal function in usual activities.

IMPORTANT:
Is there enough information available to rate the subject's level of impairment in HOME & HOBBIES?

If not, please probe further.
Homemaking Tasks: Such as cooking, laundry, cleaning, grocery shopping, taking out garbage, yard work, simple care maintenance, and basic home repair.

Hobbies: Sewing, painting, handicrafts, reading, entertaining, photography, gardening, going to theater or symphony, woodworking, participation in sports.

Personal Care Questions for Informant:

*What is your estimate of his/her mental ability in the following areas:

A.Dressing(Blessed)	Unaided	Occasionally misplaced buttons, etc.	Wrong sequence commonly forgotten items	Unable todress
	0	1	2	3
B.Washing,grooming	Unaided	Needs Prompting	Sometimes needs help	Always or nearly always needs
	0	1	2	3
C.Eating habits	Cleanly proper utensils	Messily; spoon	Simple solids	Has to be fed completely
	0	1	2	3
D.Sphincter control (Blessed)	Normal complete control	Occasionally wets bed	Frequently wets bed	Doubly incontinent
	0	1	2	3

*

A box-score of 1 can be considered if the subject's personal care is impaired from a previous level, even if they do not receive prompting.

Memory Questions for Subject:

1. Do you have problems with memory or thinking? Yes
   No

2. A few moments ago your (spouse, etc.) told me a few recent experiences you had. Will you tell me something about those? (Prompt for details, if needed such as location of the event, time of day, participants, how long the event was, when it ended and how the subject or other participants got there).

Within 1 week

1.0 – Largely correct _

_____ 0.5

0.0 – Largely incorrect

Within 1 month

1.0 – Largely correct _

_____ 0.5

0.0 – Largely incorrect

3. I will give you a name and address to remember for a few minutes. Repeat this name and address after me: (Repeat until the phrase is correctly repeated or to a maximum of three trials).

Elements	1	2	3	4	5
	John	Brown,	42	Market Street,	Chicago
	John	Brown,	42	Market Street,	Chicago
	John	Brown,	42	Market Street,	Chicago

(Underline elements repeated correctly in each trial).

4. When were you born? _

_____

5. Where were you born? _

_____

6. What was the last school you attended?
   Name _____
   Place _____ Grade _

7. What was your main occupation job (or spouse if not employed)? _

_____

8. What was your last major job (or spouse if not employed)? _

_____

9. When did you (or spouse) retire and why? _

10. Repeat the name and address I asked you to remember (underline elements repeated correctly):

Elements	1	2	3	4	5
	John	Brown,	42	Market Street,	Chicago

Orientation Questions for Subject:

Record the subject's answer verbatim for each question

1. What is the date today? Correct / Incorrect

2. What day of the week is it? Correct / Incorrect

3. What is the month? Correct / Incorrect

4. What is the year? Correct / Incorrect

5. What is the name of this place? Correct / Incorrect

6. What town or city are we in? Correct / Incorrect

7. What time is it? Correct
Incorrect

8. Does the subject know who the informant is (in your judgment)? Correct
Incorrect

Judgment and Problem Solving Questions for Subject:

Instructions: If initial response by subject does not merit a grade 0, press the matter to identify the subject's best understanding of the problem. Circle nearest response.

Similarities:

Example: "How are a pencil and pen alike? (writing

instruments) How are these things alike?"

Subject's Response

1. turnip……cauliflower _____

(0 = vegetables)
(1 = edible foods, living things, can be cooked,etc.)
(2 = answers not pertinent; differences; buy them)

2. desk……bookcase
(0 = furniture, office furniture; both hold books)
(1 = wooden, legs)
(2 = not pertinent, differences)

Differences:

Example: "What is the difference between sugar and vinegar?

(sweet vs sour) What is the difference between these things?"

3. lie……mistake

_____

(0 = one deliberate, one unintentional)

(1 = one bad the other good – or explains only one)

(2 = anything else, similarities)

4. river……canal

_____

_____

(0 = natural - artificial)

(2 = anything else)

Calculations:

5.How many nickels in a dollar?	Correct	Incorrect
6.How many quarters in $6.75?	Correct	Incorrect
7.Subtract 3 from 20 and keep subtracting 3 from each new number all the way down.	Correct	Incorrect

Judgment:

8. Upon arriving in a strange city, how would you locate a friend that you wished to see?

(0 = try the telephone book, go to the courthouse for a directory; call a mutual friend)

(1 = call the police, call operator (usually will not give address)

(2 = no clear response)

9. Subject's assessment of disability and station in life and understanding of why he/she is present at the examination (may have covered, but rate here):

Good Insight Partial Insight Little Insight

CDR global

Use all the information you get to make the most appropriate judgments. Evaluate the six functional areas respectively, fill in the scores in the corresponding "_", and note that only when the decline of ability is caused by cognitive impairment can the score be scored. If the severity of dysfunction is between two levels, in principle, it shall be evaluated as the severity level. Finally, based on the scores of six functional areas, the global CDR is summarized according to the following principles:

1. Memory (M) is the main item, the other 5 items are the secondary items;
2. When M=0.5, CDR≠0, only =0.5or 1;
3. CDR=M (memory score):

1）When at least 3 secondary items are the same as the memory score;

2）When only 1 or 2 minor item scores = M, no more than 2 minor item scores are on either side of M;

3）When the scores of 3 secondary items are on one side of the memory score and the scores of the other 2 secondary items are on the other side of the memory score;

4）When at least 3 minor items are all 0, if M = 0.5, CDR = 0.5;

5）Only when 1 minor item ≥ 0.5, if M = 0, CDR = 0.

4. CDR≠M (memory score):

1）When 3 or more minor item scores are greater than or less than M, CDR = most minor item scores;

2）When M = 0.5 and at least 3 minor items score ≥ 1, CDR = 1;

3）When M = 0, 2 or more minor items ≥ 0.5, CDR = 0.5;

4）When M≥1, CDR≠0, at this time, if most of the other minor items = 0, CDR=0.5.

5. Principle of near association: when the above principle is not met, CDR = M score of the closest secondary item (e.g., M and a secondary item score =3, 2 secondary item score =2, 2 secondary item score =1, CDR=2).

CDR (sum of boxes)

It refers to the sum of the scores of all six functional areas.

CDR (supplementary part)

The assessment shall be made according to the test conditions and shall not be included in the total score.

CLINICAL DEMENTIA RATING (CDR)

CLINICAL DEMENTIA RATING (CDR):	**0**	**0.5**	**1**	**2**	**3**

	Impairment				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe
11.1 Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; Partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
11.2 Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
11.3 Judgment &Problem Solving	Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
11.4 Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside a family home

11.5 Home and Hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
11.6 Personal Care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Appendix12: Participating unit and participant number

A total of 8 digits: the number of each unit (3) + the number of the participant (5), with a horizontal bar in the middle. For example, the number of eighth participant in Xuanwu Hospital is 001-00008. The number of each participating unit is shown in the table below.

NO.	Unit name	NO.	Unit name
001	Xuanwu Hospital, Capital Medical University	035	Jiangxi Provincial People's Hospital
002	Beijing Tian Tan Hospital, Capital Medical University	036	Anshanshi Changda the Hospital
003	Beijing Chao-Yang Hospital, Capital Medical University	037	Affiliated Zhongshan Hospital of Dalian University
004	Fu Xing Hospital, Capital Medical University	038	The First Hospital of China medical University
005	Peking Union Medical College Hospital	039	Baotou Central Hospital
006	Peking University First Hospital	040	General Hospital of Ningxia Medical University
007	Peking University Third Hospital	041	People’s Hospital of Ningxia Hui Autonomous Region
008	Chinese PLA General Hospital	042	The Affiliated Hospital of Qingdao University
009	China-Japan Friendship Hospital	043	78th Hospital of the People's Liberation Army
010	Beijing Geriatric Hospital	044	Qilu Hospital of Shandong University
011	Dalian Municipal Hospital Affiliated of Dalian Medical University	045	Qilu Hospital of Shandong University (Qingdao)
012	Fujian Medical University Union Hospital	046	Shangdong Provincial Hospital
013	Guangzhou Brain Hospital	047	QingDao Municipal Hospital
014	Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University	048	First Hospital of Shanxi Medical University
015	The first Affiliated Hospital of Guangxi Medical University	049	Tangdu Hospital, Fourth Military Medical University
016	The Affiliated Hospital of Guizhou Medical University	050	The first Affiliated Hospital of Xi’ an Jiao Tong University

017	HanDan Central Hospital	051	Rui Jin Hospital Shanghai Jiao Tong University School of Medicine
018	Heibei General Hospital	052	Renji Hospital Shanghai Jiao Tong University School of Medicine
019	Shijiazhuang First Hospital	053	Shanghai Changzheng Hospital
020	Tangshan Workers Hospital	054	Affiliated Hospital of North Sichuan Medical University
021	Hennan Provincial People's Hospital	055	Tianjin Huanhu Hospital
022	KaiFeng Central Hospital	056	General Hospita of Tianjin Medical University
023	People's Hospital of Zhengzhou	057	Xinjiang Autonomous Region Chinese Medicine Hospital
024	The First Affiliated Hospital of Harbin Medical University	058	Ningbo City Medical Treatment Center Lihuili Hospital
025	Tongji Hospital, Huazhong University of Science and Technology	059	The First Affiliated Hospital of Wenzhou Medical University
026	People's Hospital Affiliated Hubei University of Medicine	060	The First Affiliated Hospital, Zhejiang University
027	Zhongnan Hospital of Wuhan University	061	Shao Yifu Hospital, Zhejiang University of Medicine
028	The Third Xiangya Hospital of Central South University	062	Zhejiang Provincial People's Hospital
029	Xiangya Hospital, Central South University	063	Daping Hospital of the Third Military Medical University
030	The First Hospital of Jilin University	064	The Second Affiliated Hospital of Chongqing Medical University
031	China-Japan Friendship Hospital of Jilin University	065	The First Hospital Affiliated Anhui Medical University
032	Subei People's Hospital	066	Chongqing General Hospital
033	Affiliated Hospital of Nantong University	067	Dongfang Hospital, Beijing University of Chinese Medicine

034	Xuzhou Mine General Hospital	068	Zigong First People's Hospital