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RESEARCH ARTICLE

Health status and risk profiles for brain aging of rural-dwelling older adults: Data from the interdisciplinary baseline assessments in MIND-China

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Abstract

Introduction: Multidomain intervention approaches have emerged as a potential strategy to reduce dementia risk. We sought to describe the baseline assessment approaches, health conditions, and risk profiles for brain aging of participants in the randomized controlled Multimodal INterventions to delay Dementia and disability in rural China (MIND-China).

Methods: MIND-China engaged residents who were ≥60 years of age and living in rural communities in the western Shandong province. In March to September 2018, all participants underwent the core module assessments via face-to-face interviews, clinical examinations, neuropsychological testings, and laboratory tests. Specific modules

of examination were performed for sub-samples, including brain magnetic resonance imaging scans, genetic and blood biochemical markers, actigraphy testing, cardiopulmonary coupling analysis for sleep quality and disturbances, audiometric testing, and optical coherence tomography examination. We performed descriptive analysis.

Results: In total, 5765 participants (74.9% of all eligible residents) undertook the baseline assessments. The mean age was 70.9 years (standard deviation, 5.9), 57.2% were women, 40.6% were illiterate, and 88.3% were farmers. The overall prevalence of common chronic diseases was 67.2% for hypertension, 23.4% for dyslipidemia, 23.5% for heart disease, 14.4% for diabetes mellitus, and 5.4% for dementia. The prevalence rates of hypertension, diabetes mellitus, dyslipidemia, obesity, heart disease, depressive symptoms, and dementia were higher in women than in men ($P < .05$). Overall, 87.1% of the participants had at least two of the 15 chronic diseases (89.3% in women vs 84.2% in men, $P < .001$). Participants examined for the specific modules were younger, more likely to be women, and more educated than those not examined.

Discussion: Comprehensive baseline assessments of participants in MIND-China provide extremely valuable data sources for interdisciplinary research into the complex relationships of aging, health, brain aging, and functional consequences among older adults living in the rural communities.

KEYWORDS
dementia, multimodal intervention, older adults, population-based study, rural area

Highlights

- MIND-China is a multimodal intervention study among rural residents ≥60 years of age.
- At baseline, 5765 participants undertook the interdisciplinary assessments.
- The baseline assessments consisted of core module and specific modules.
- Specific modules included brain magnetic resonance imaging (MRI), blood biomarkers, ActiGraph, cardiopulmonary coupling (CPC), pure-tone audiometry (PTA), and optical coherence tomography (OCT).

1 | INTRODUCTION

In 2019, dementia affected ≈50 million people worldwide, with global annual cost of care exceeding an estimated US$ 1 trillion.[1] In China, the overall prevalence of dementia among people ≥60 years of age was 5.3%, corresponding to ≈15 million people living with dementia.[2] Notably, the prevalence of dementia has increased steadily in China since the 1990s, and both prevalence and incidence of dementia are higher in rural than in urban populations.[3] It has been projected that the global economic and social burden of dementia would grow steadily in the coming decades,[4] where the one-child policy (1979 to 2015) and rapid urbanization in China will further exacerbate the difficulties for adequate care of individuals living with dementia.

In the past three decades, population-based cohort studies have identified major risk and protective factors for dementia, such as genetic factors (eg, the apolipoprotein E [*APOE*] ε4 allele in some pop-

ulations), low education, lifestyle factors (eg, smoking, unhealthy diet, and physical inactivity), and cardiometabolic risk factors (eg, obesity, hypertension, and diabetes).[5] Worldwide, around one-third of dementia cases might be attributable to seven modifiable risk factors (midlife hypertension, midlife obesity, diabetes, physical inactivity, smoking, depression, and low education).[6] Of note, data from the 10/66 Dementia Research surveys showed that the population attributable fractions of dementia due to modifiable risk factors were higher in low- and middle-income countries (LMICs) (eg, India and China) than in high-income countries (HICs), indicating a greater potential for dementia prevention in LMICs.[7] However, the majority of the community-based studies have targeted urban populations in HICs (eg, the Mayo Clinic Study of Aging and the Icelandic AGES-Reykjavik Study), with very few studies covering rural areas in LMICs.[8,9] Findings from studies in HICs may not be generalizable to populations in LMICs, especially in the rural populations, owing to differences in ethnicity, socioeconomic

status, and sociocultural background. In addition, it is feasible now to use advanced technology and portable devices in large-scale population-based studies, which can provide reliable and objective measures. Indeed, several new techniques have been utilized in epidemiological studies of brain aging and dementia, such as Acti-Graph accelerometer for sedentary behavior and physical activity, electrocardiography-based cardiopulmonary coupling (CPC) for sleep quality, pure-tone audiometry (PTA) for hearing loss, and optical coherence tomography (OCT) for retinal microstructure. These tools provide a unique opportunity to identify novel risk and protective factors as well as early biomarkers for dementia and Alzheimer's disease (AD), and thus will help shed light on the pathophysiological mechanisms linking various risk and protective factors to brain aging and dementia.

Multimodal intervention approaches have emerged as promising strategies to delay dementia onset.[10,11] In Europe, three multidomain intervention studies have yielded mixed results. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) study showed evidence that a 2-year intensive multidomain lifestyle intervention may help preserve cognitive function in at-risk older adults,[12] whereas the Prevention of Dementia by Intensive Vascular Care (PreDIVA) study in The Netherlands and the Multidomain Alzheimer Preventive Trial (MAPT) in France showed no convincing evidence that multidomain interventions could affect dementia risk.[13,14] Thus, additional multimodal intervention approaches that are socially and culturally sensitive need to be fully evaluated, especially in LMICs.

Therefore, we initiated the randomized controlled Multimodal INterventions to delay Dementia and disability in rural China (MIND-China) study that aimed to test whether multimodal intervention programs sensitive to Chinese lifestyle and sociocultural factors may help maintain cognitive and physical functioning among rural-dwelling older adults. In the current report, we seek to describe the baseline interdisciplinary assessment approaches as well as common health conditions and risk profiles for brain aging in the participants of MIND-China.

2 | METHODS

2.1 | Study population and basic design

MIND-China is an ongoing cluster-randomized, controlled multimodal intervention study that targets people who are ≥60 years of age and living in the rural communities. As part of the World-Wide FINGERS Network,[15] MIND-China is aimed primarily at testing whether vascular and multimodal intervention programs are effective in maintaining cognitive and physical functioning in older adults. In addition, data collected in MIND-China could be used to address a range of scientific questions related to health in aging, brain aging, and dementia in rural residents (Figure 1). MIND-China was designed as a three-arm intervention study: (1) the control group (standard of care) receives regular health care services provided by local town hospital; (2) the vascular intervention group receives health education, and if needed, medical treatment of hypertension, diabetes, and dyslipidemia that aimed

RESEARCH IN CONTEXT

1. Systematic Review: The authors reviewed the literature using traditional sources (eg, PubMed) on population-based studies of brain aging and multidomain interventions for prevention of dementia. The majority of the community-based studies have targeted urban populations in high-income countries (HICs) and previous multidomain intervention studies on dementia and cognitive aging have yielded mixed results.

2. Interpretation of Results: The MIND-China database is particularly unique and valuable in exploring a range of scientific questions related to aging and health, brain aging, and dementia.

3. Future Directions: In the future we will investigate: (1) the epidemiology of cognitive aging and dementias; (2) risk and protective factors for dementias; (3) clinical, biological, and neuroimaging markers for mild cognitive impairment and dementias; and (4) the natural history of cognitive aging and the potential mechanisms underlying any effects of multidomain interventions.

to improve control of these risk factors; and (3) the multimodal intervention group receives the same interventions as those in the vascular intervention group plus non-pharmacological multidomain interventions (lifestyle and dietary guidance, group exercise, personalized leisure activities, and cognitive training).

Prior to recruitment of participants for interventions, we performed interdisciplinary baseline assessments. Eligible participants included all registered residents (n = 7698) who were ≥60 years of age by the end of 2017 and living in the 52 villages of Yanlou Town, Yanggu County, western Shandong Province. Figure 2 shows the flowchart of the participants in the baseline assessments. In brief, the assessments were integrated with the annual health check-up program provided by local government for residents who reached 65 years of age. In addition, residents who were 60 to 64 years of age were specifically invited for the MIND-China study. Of the 6,528 eligible residents who were ≥65 years of age, 1282 (19.6%) were dropouts due to death prior to the examination (n = 123), severe mental illnesses (n = 23), refusal (n = 829), and not reachable (n = 307). Of the 1170 subjects who were 60 to 64 years of age, 651 (55.6%) were dropouts due to deceased (n = 5), severe mental illnesses (n = 13), refusal (n = 371), and not reachable (n = 262). Thus a total number of 5,765 residents (74.9% of all the eligible residents) participated in the baseline examination (Figure 2).

The MIND-China protocol was reviewed and approved by the ethics committee at Shandong Provincial Hospital in Jinan, Shandong, China. Written informed consent was obtained from all participants prior to the assessments, or in the case of cognitively impaired persons, from informants. In the case of illiterate participants, the written consent document that included all the informed consent elements was
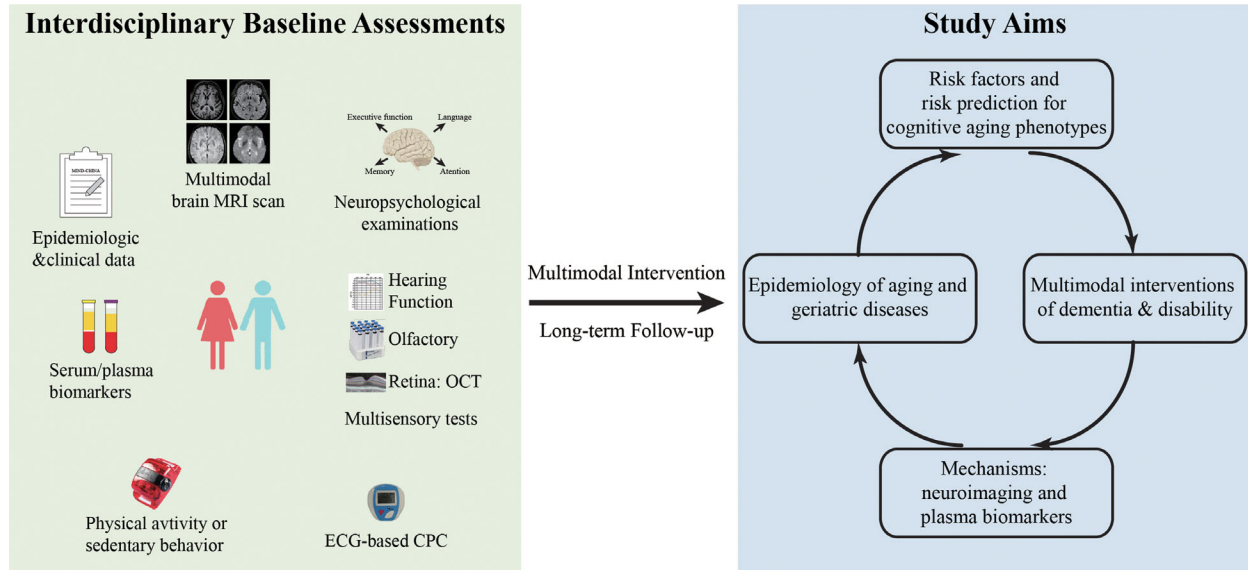
FIGURE 1 MIND-China is designed to address a range of crucially relevant scientific questions related to aging and heath, brain aging, and dementia. MIND-China, randomized controlled Multimodal INterventions to delay Dementia and disability in rural China; MRI, magnetic resonance imaging; OCT, optical coherence tomography; ECG, electrocardiogram; CPC, cardiopulmonary coupling
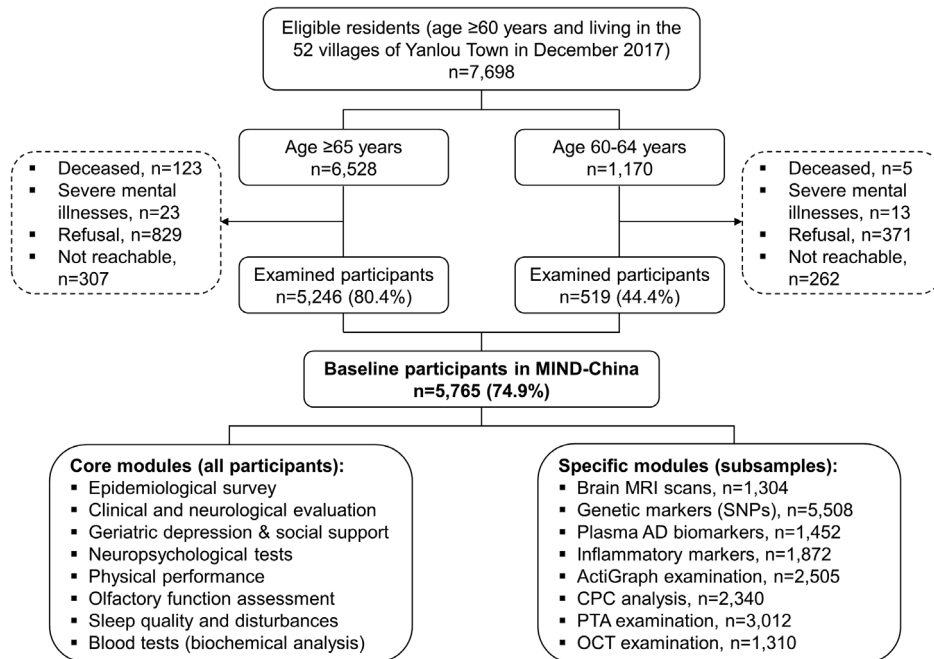
FIGURE 2 Flowchart of study participants and assessment modules at baseline. AD, Alzheimer's disease; MIND-China, randomized controlled Multimodal INterventions to delay Dementia and disability in rural China; CPC, cardiopulmonary coupling; MRI, magnetic resonance imaging; OCT, optical coherence tomography; PTA, pure-tone audiometry; SNP, single nucleotide polymorphism

first verbally presented to the participant or the legally authorized representative. The local village doctor or a neighbor of the participant was present as the witness to the oral presentation (verbal for the consent process). Then, a fingerprint was obtained from the participants. The protocol of MIND-China was registered in the Chinese Clinical Trial Registry (ChiCTR, www.chictr.org.cn; registration no.: ChiCTR1800017758).

2.2 | Core module of baseline assessments

The multidimensional baseline assessments of MIND-China included core module and specific modules. The core module assessments were performed by trained staff at the Yanlou Town Hospital in March to September 2018 through face-to-face interviews, clinical and neurological examinations, neuropsychological testing, and laboratory tests.

2.2.1 | Structured interviews

The interviews were performed following the structured questionnaires to collect data on[16]: (1) sociodemographic features: for example, age, birth date, sex, educational attainment, occupation, and living time per year in the local village; (2) medical and family history: for example, history of health conditions (eg, hypertension, diabetes, and heart disease), family history of chronic diseases, and current use of medications (names and dosages of drug use, and whenever possible, drug containers or prescriptions were inspected, and all medications were classified and coded according to the Anatomical Therapeutic Chemical [ATC] classification system);[17] (3) leisure activities: frequency (daily, weekly, or monthly) and time (minutes or hours) of participation in social, physical, and mental activities; and (4) lifestyle factors: for example, alcohol consumption, smoking, and dietary habits.

2.2.2 | Clinical and neurological examinations

All participants underwent routine geriatric and neurological examinations. Weight, height, and waist circumference were measured in light clothing without shoes. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2); obesity was defined as a BMI $\geq$28 kg/m^2. After a 5-minute rest, arterial blood pressure was measured on the right upper arm in a seated position using an electronic blood pressure monitor (HEM-7127J, Omron Corporation, Kyoto, Japan). Twelve-lead resting electrocardiography (ECG) was recorded (CM300, COMEN, Shenzhen, China) and a physician analyzed the ECG strips following the standard recommendations.[18] The neurological examination included evaluating motor and sensory function, testing tendon and pathological reflexes, and assessing the cranial nerves by the physicians.

Hypertension was defined as systolic pressure $\geq$140 mm Hg or diastolic pressure $\geq$90 mm Hg or current use of antihypertensive medication (ATC codes: C02, C03, and C07-09). Diabetes was defined by medical history as ascertained by a physician or fasting blood glucose (FBG) $\geq$7.0 mmol/L or use of blood glucose-lowering medication (ATC code: A10). Dyslipidemia was defined as total serum cholesterol $\geq$6.2 mmol/L or triglycerides $\geq$2.3 mmol/L or low-density lipoprotein cholesterol (LDL-C) $\geq$4.1 mmol/L or high-density lipoprotein cholesterol (HDL-C) <1.0 mmol/L or having received drug treatment for dyslipidemia (ATC code: C10).

2.2.3 | Depressive symptoms and social support

We assessed depressive symptoms using the 15-item Geriatric Depression Scale (GDS-15), which has been validated in the Chinese elderly population. The presence of depressive symptoms was defined as a GDS-15 score $\geq$5.[19] Social support was evaluated using the Social Support Rating Scale (SSRS), which consists of 10 items that measure three dimensions of subjective support (4 items, score range 8-32), objective support (3 items, score range 1-22), and support-seeking behavior (3 items, score range 3-12).[20]

2.2.4 | Neuropsychological assessments

A neuropsychological test battery was used to evaluate subjective cognitive decline (SCD), global cognitive function, and cognitive subdomains. SCD was assessed using three questions of memory problems, "Do you feel that in the past year you had difficulties in remembering things? ", "Do you feel that in the past year it was easier than before to forget things? ", and "Do you worry about your memory that has been getting worse in the past year? ".[21] Global cognitive function was assessed with the Chinese version of the Mini-Mental State Examination (MMSE).

Multiple cognitive domains were assessed using the neuropsychological test battery previously validated in Chinese older adults, which included memory, attention, executive function, and language. Specifically, memory was assessed using the Auditory Verbal Learning Test (AVLT) learning/immediate free recall, AVLT long delayed recall, and AVLT recognition recall.[22] Attention was assessed using the Trail Making Test-A (TMT-A) and Digit Span Forward (DSF).[23,24] Executive function was assessed with the Trail Making Test-B (TMT-B) and Digit Span Backward (DSB). Language was assessed with the Verbal Fluency Test (VFT), including animal, fruit, and vegetable categories.[25] The raw score for each cognitive test was standardized into z-score, and the composite z-score for a specific cognitive domain was calculated by averaging the z-scores of tests for this domain. The composite z-score for global cognitive function was estimated by averaging the composite z-scores of the four cognitive domains.

2.2.5 | Physical function and performance

The Chinese version of Activities of Daily Living (C-ADLs) and the Short Physical Performance Battery (SPPB) were used to assess physical function and physical performance.[26,27] The C-ADLs include 20 items: 8 items for assessing basic ADLs (ie, bathing, dressing, toileting, feeding, transferring, continence, and brushing teeth) and 12 items for assessing instrumental ADLs (ie, taking a bus, preparing meals, taking medicine, light housework, washing own clothes, cutting toenails, shopping, using the telephone, and managing personal money).

The SPPB consists of three subtests: a hierarchical test of balance, 4-meter walk at usual pace, and standing up five times from a seated position in a chair. Each subtest was scored from 0 (worst performance) to 4 (best performance). The total SPPB score ranges from 0 to 12, with a higher score indicating a better function.

2.2.6 | Clinical diagnosis of dementia, AD, and vascular dementia

Dementia was clinically diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), criteria,[28] in which a three-step diagnostic procedure was followed. In brief, the trained clinicians and interviewers first conducted routine clinical examination and assessments following structured

questionnaires to collect data on health-related factors, medical history, cognitive function, and C-ADLs. Then, neurologists specialized in dementia diagnosis and care reviewed all of the data documented in the first step, and made a preliminary diagnosis for participants who were suspected to have dementia. Finally, the neurologists conducted further face-to-face interviews with those who were suspected to have dementia or who had insufficient data for making a diagnosis of dementia status (n = 926), and reassessed their medical history, cognitive status, C-ADLs, and whenever available, neuroimaging data. In the case of uncertainty, a senior neurologist was consulted and discussed and a consensus diagnosis of dementia was reached. The diagnosis of dementia was further categorized into subtypes according to respective diagnostic criteria. AD was diagnosed according to the National Institute on Aging-Alzheimer's Association (NIA-AA) criteria for probable AD dementia.[29] Vascular dementia (VaD) was diagnosed following the National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria for probable vascular dementia.[30]

2.2.7 | Olfactory function assessment

Olfactory function was assessed using the adapted 16-item Sniffin' Sticks identification test (SSIT, Burghardt, Wedel, Germany), consisting of 16 felt-tip pens with common and everyday odors (orange, leather, peppermint, banana, lemon, liquorice, garlic, apple, clove, pineapple, rose, anise, fish, mushroom, soy sauce, and sesame oil).[31] In addition, the self-reported olfactory function, information on history of nasal diseases, and nasal surgery were also collected during the interview.

2.2.8 | Sleep quality and sleep disturbances

Sleep patterns and sleep disturbances over one month prior to the survey were assessed with the Pittsburgh Sleep Quality Index (PSQI).[32] We used the Epworth Sleepiness Scale (ESS) and the self-administered Berlin Questionnaire to evaluate excessive daytime sleepiness and obstructive sleep apnea, respectively.[33,34] Objective sleep quality, sleep structure, and sleep-disordered breathing for a sub-sample were also assessed using CPC analysis (see section 2.3.4).

2.2.9 | Biochemical analysis of blood specimens

After an overnight fast, peripheral blood sample (≈15 mL) was drawn into two vacutainers with ethylenediaminetetraacetic acid-K2 (EDTA-K2) and two vacutainers with procoagulant separating gel. Biochemical analysis was performed at the laboratory of Yanlou Town Hospital, which is licensed by the local quality and technical control authority. The automated blood cell analyzer (BC-1800, Mindray Corporation, Shenzhen, China) was used for routine blood tests. Serum hepatitis B surface antigen (HBsAg) was measured using colloidal gold method

(InTec PRODUCTS, INC., Xiamen, China). Serum and plasma samples were aliquoted and then stored at −80°C for future analysis.

2.2.10 | Medical records

Medical records from annual health check-up for local residents who were aged ≥65 years were available since 2010 in Yanlou Town Hospital. Data collected during the annual health check-up included lifestyles, cardiometabolic factors, health history and conditions, use of medical drugs, and blood biochemical profiles.

2.3 | Specific modules of baseline assessments

Additional modules of specific examinations were performed for subsamples within MIND-China, which included brain multimodal magnetic resonance imaging (MRI) scans, genetic and peripheral biomarkers, actigraphy testing, ECG-based CPC analysis, audiometric examination (PTA), and OCT examination. Overall, the cluster (village)–based subsamples were selected from three arms of the interventions for participation in different modules.

2.3.1 | MIND-China brain MRI substudy

The structural and functional brain MRI scans were performed for a sub-sample (n = 1304). Eligible participants were scanned either on the Philips Ingenia 3.0T MR System in Southwestern Lu Hospital (n = 1178) or the Philips Archiva 3.0T MR System in Liaocheng People's Hospital (n = 126). The core MRI protocol included the following sequences: sagittal 3D sT1W, axial T2W, sagittal 3D fluid attenuated inversion recovery (FLAIR), axial susceptibility weighted imaging (SWI), resting-state functional MRI (rs-fMRI), and axial magnetic resonance angiography (MRA). Table 1 shows the parameters of the core MRI sequences.

2.3.2 | Genetic and peripheral biomarkers

Multiple-PCR amplification analysis of genomic DNA was performed for 5508 participants to detect 67 single nucleotide polymorphism (SNP) risk loci (eg, *APOE*, translocase of outer mitochondrial membrane 40 [*TOMM40*], and KIdney and BRAin expressed protein [*KIBRA*] genes) and exon region of 20 genes that were potentially associated with AD and dementia.[35] In a subsample from the same villages as the MRI subsample (n = 1452), plasma total-tau, amyloid beta 40 (Aβ40), Aβ42, and neurofilament light chain (NfL) levels were measured on a single molecule array (SIMOA) platform (Quanterix Corp, MA, USA) with Human Neurology 3-Plex A assay (N3PA) and NF-light advantage Kit, following the manufacturers' instructions.[36] In addition, commercial kits (Meso Scale Discovery [MSD] V-PLEX Assays) were used to measure serum cytokines and vascular injury biomarkers (n = 1872): interferon gamma (IFN-γ), interleukin-6 (IL-6),

TABLE 1 Parameters of core sequences of multimodal brain magnetic resonance imaging scans

MRI sequences	Slice thickness (mm)	Matrix	FOV (mm)	TR (ms)	TE (ms)	FA (°)
Sagittal 3D sT1W	1	240 × 219	240 × 219	8.3	3.8	8
Axial T2W	5	384 × 330	230 × 210	4000	106	90
Sagittal 3D FLAIR	1.12	224 × 224	250 × 250	4800	296	–
Axial SWI	1.2	220 × 183	221 × 182	18	25	10
rs-fMRI	5	96 × 94	230 × 230	3000	35	90
Axial MRA	1.2	400 × 203	180 × 180	25	2.9	20

Abbreviations: FA, flip angle.; FLAIR, fluid-attenuated inversion recovery; FOV, field of view; MRA, magnetic resonance angiography; rs-fMRI, resting-state functional magnetic resonance imaging; SWI, susceptibility weighted imaging; TE, echo time; TR, repetition time.

interleukin-8 (IL-8), interleukin-10 (IL-10), tumor necrosis factor alpha (TNF-α), interleukin-17A (IL-17A), eotaxin-3, monocyte chemotactic protein-1 (MCP-1), intercellular cell adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1).

2.3.3 | Actigraphy testing

In a sub-sample (n = 2505), we used the triaxial accelerometer (Acti-Graph wGT3X-BT, ActiGraph LLC, FL, USA) to objectively document participant's physical activity and sedentary behavior over seven consecutive days.[37] Participants wore an ActiGraph wGT3X-BT triaxial accelerometer on their hip, affixed to an elastic belt, during all waking hours for seven consecutive days, and removed it only for swimming or bathing. Parameters include raw acceleration (G's), activity counts, energy expenditure, metabolic equivalents rates (METs), steps taken, intensity of physical activity, activity bouts, sedentary bouts, and body position.

2.3.4 | CPC analysis

In a sub-sample of 2340 participants, objective sleep quality and apnea-hypopnea index were assessed using the ECG-based CPC analysis (AECG-600D, Nanjing Fengshengyongkang Software Technology Co., Ltd., Jiangsu, China). The CPC is obtained solely from a continuous single-lead ECG signal using the Fourier transform to analyze heart rate variability and ECG derived respiratory (EDR) signal.

2.3.5 | Audiometric testing

Audiometric examination was performed in a quiet (sound isolating) room following the standard audiometric procedures in a sub-sample (n = 3012).[38] PTA was used to measure bilateral bone conduction thresholds at the frequencies of 0.25, 0.5, 1, 2, and 4 kHz and bilateral air conduction thresholds at the frequencies of 0.125, 0.25, 0.5, 1, 2, 4, and 8 kHz with a diagnostic audiometer (GSI AudioStr, Grason-Stadler Inc., MN, USA). All frequencies were included in the calculation of the average hearing threshold.

2.3.6 | OCT examination

The OCT examination was conducted by ophthalmologists in Yanlou Town Hospital (n = 1004) and Southwestern Lu Hospital in a subsample (n = 306). In the Yanlou Town Hospital, we used Primus 200 (Carl Zeiss Meditec, Germany) to image internal cross-sectional microstructure of retinal tissues. In Southwestern Lu Hospital, we used Spectralis HRA+OCT (Software Version 1.10.2.0; Heidelberg Engineering, Inc., Heidelberg, Germany) to image retinal tissues. The retinal thickness measurements in the nine subfields (ie, central, inner superior, innerinferior, innernasal, innertemporal, outersuperior, outerinferior, outernasal, and outertemporal) were acquired using the built-in software.

2.4 | Quality control procedures

The Quality Management Committee of MIND-China (project principal investigators, coordinator, specialists, and local town hospital administrators) is responsible for data collection, data assessments, database management, and collection and storage of biological samples. The study protocol and structured questionnaires were developed following brainstorm discussions among national and international scientists. Prior to the start of the assessments, all research staff (eg, clinicians and interviewers) were trained and certified according to the operations manual. Then, we conducted the pilot study to test the feasibility of the assessment procedure and the questionnaire. The automated biochemical analyzer and instruments (eg, electronic blood pressure monitor, 12-lead resting ECG, ultrasonic machine, and automated blood cell analyzer) are calibrated regularly and standardized following the manufacturer's instructions. For the peripheral biomarker assays, the pooled and quality control samples were run in each plate.

2.5 | Statistical analysis

Descriptive analysis was performed to report mean (standard deviation, SD) for continuous variables with normal distribution, median (interquartile range, IQR) for those with skewed distribution, and frequency (proportion) for categorical variables. Characteristics of the

study participants by sex were compared using the chi-square test for categorical and *t*-test or Mann-Whitney rank tests for normally and not normally distributed continuous variables. IBM SPSS Statistics 26 (IBM Corp, Armonk, NY, USA) was used for all the analyses. A two-tailed $P < .05$ was considered to be statistically significant.

3 | RESULTS

3.1 | Characteristics of baseline participants

A total of 5765 participants were enrolled in the baseline examination of MIND-China study (Table 2). The mean age was 70.9 years (SD 5.9), 57.2% were women, 40.6% were illiterate, and 88.3% were farmers. Overall, compared with men, women were less educated, more likely to be farmers, and less likely to smoke, consume alcohol, and participate in leisure activities ($P < .001$). *APOE* ε4 allele carriers accounted for 16.0% of all participants, and women were more likely than man to carry the ε4 allele ($P < .05$). In addition, we assessed the burden of 15 common chronic diseases among older adults (ie, hypertension, diabetes, dyslipidemia, obesity, stroke, coronary heart disease, heart failure, atrial fibrillation, cancer, depressive symptoms, dementia, chronic obstructive pulmonary disease, chronic kidney disease, thyroid dysfunction, and cataract). Overall, 87.1% of the participants had at least 2 of the 15 chronic diseases, with the proportion being higher in women than in men (89.3% vs 84.2%, $P < .001$).

3.2 | Age and sex distribution of major physical and mental health conditions

The overall prevalence of hypertension, diabetes, dyslipidemia, obesity, stroke, heart disease, depressive symptoms, and dementia was 67.2%, 14.4%, 23.4%, 19.4%, 15.8%, 23.5%, 10.5%, and 5.4%, respectively. The prevalence of all these chronic diseases, except stroke, was higher in women than men (Table 2). The prevalence increased with age in hypertension, heart disease, and dementia (P for trend $< .001$), decreased with age in diabetes and obesity (P for trend $< .001$), but was relatively stable in dyslipidemia, stroke, and depressive symptoms (P for trend $> .05$) (Figure 3).

3.3 | Demographic characteristics of participants in substudies

Table 3 summarizes the demographic features and key parameters of participants in the core and specific modules. Overall, participants who were examined for the specific modules were younger than those who were not ($P < .001$), except in the PTA and OCT modules where there was no significant difference in age. There were more women in the modules of plasma AD biomarkers ($P < .001$), inflammatory markers ($P < .001$), and actigraphy testing ($P < .05$). Participants were less likely to be illiterate than non-participants in the specific modules of brain

MRI scans ($P < .001$), genetic markers ($P < .01$), actigraphy testing ($P < .05$), CPC examination ($P < .001$), and PTA test ($P < .01$).

4 | DISCUSSION

MIND-China engages older adults who are living in the rural communities of the western Shandong province, China. Prior to the recruitment of participants for the interventions, we conducted interdisciplinary assessments that integrated conventional approaches with unique technologies such as multimodal brain MRI scans, SIMOA, ActiGraph, CPC, PTA, and OCT examinations. This makes the MIND-China database particularly unique and valuable in exploring a range of scientific questions related to aging and health in general, especially brain aging and dementias.

Since the late 1980s, several well-designed population-based cohort studies have contributed significantly to the understanding of epidemiology of dementias, in which epidemiological, neuropsychological, and clinical data are usually collected following the standardized procedures in most of these studies, as in the MIND-China. Of note, demographic and sociocultural features of our study population were taken into account when the study was designed. For instance, we deliberately chose the neuropsychological tests (eg, AVLT, VFT, DSF, and DSB) that were suitable for illiterate or low-educated persons. In addition, we used the validated scales among Chinese elderly people to assess depressive symptoms (GDS-15) and social support (SSRS).[19,20] All these tests were feasible and well accepted by the study participants who had no or limited education. Moreover, these assessments were similar enough to allow future harmonization and joint analyses with other studies in the World-Wide FINGERS Network.[15]

Recent advances in technology of neuroimaging and peripheral biomarker assays provide the potential for detection of AD pathological changes in the very early phases of the disease. We applied the state-of-the-art techniques (eg, multimodal MRI, SIMOA assay, ActiGraph, and CPC) to the baseline assessments. Multimodal brain MRI scan can provide reliable markers for structural brain changes and microvascular lesions, which will help shed light on neuropathological mechanisms underlying cognitive phenotypes. Furthermore, evidence has emerged that plasma biomarkers for AD and neurodegeneration (eg, Aβ, p-tau, and NfL) are associated with cognitive decline and dementia.[36] Similarly, data on plasma biomarkers in MIND-China will contribute to the further understanding of neurobiological and pathophysiological pathways linking genetic and environmental factors to the onset and progression of mild cognitive impairment (MCI) and dementia.

Findings from epidemiological studies remain controversial with regard to several risk or protective factors for dementias, such as physical activity or sedentary behavior, sleep disturbances, and age-related hearing loss, largely due to the use of self-reported measures.[39] For instance, the temporal association of physical inactivity with risk of dementia remains inconclusive.[40] One possible explanation is that most studies used self-reported physical activity, which is prone to reporting bias and does not capture cumulative effects. ActiGraph test

TABLE 2 Characteristics of baseline participants in MIND-China by sex

Characteristics	Total sample (n = 5765)	Men (n = 2468)	Women (n = 3297)	P-value[b]
Age (years)	70.9 (5.9)	70.8 (5.8)	71.0 (6.0)	.134
Age group (years), n (%)				.003
60–64	519 (9.0)	221 (9.0)	298 (9.0)	
65–69	2209 (38.3)	969 (39.3)	1240 (37.6)	
70–74	1688 (29.3)	703 (28.5)	985 (29.9)	
75–79	792 (13.7)	371 (15.0)	421 (12.8)	
≥80	557 (9.7)	204 (8.3)	353 (10.7)	
Education, n (%)				<.001
Illiterate	2338 (40.6)	344 (13.9)	1994 (60.5)	
Primary school	2415 (41.9)	1279 (51.8)	1136 (34.5)	
Middle school or above	1012 (17.6)	845 (34.2)	167 (5.1)	
Occupation, n (%)[a]				<.001
Farmers	4962 (88.3)	1861 (77.4)	3101 (96.4)	
Non-farmers	657 (11.7)	542 (22.6)	115 (3.6)	
Smoking, n (%)[a]				<.001
Never	3710 (64.4)	491 (19.9)	3219 (97.7)	
Former	843 (14.6)	807 (32.8)	36 (1.1)	
Current	1206 (20.9)	1166 (47.3)	40 (1.2)	
Alcohol consumption, n (%)[a]				<.001
Never	3553 (61.7)	503 (20.4)	3050 (92.6)	
Former	537 (9.3)	509 (20.7)	28 (0.8)	
Current	1669 (29.0)	1452 (58.9)	217 (6.6)	
Leisure-time physical activity, n (%)[a]	3579 (64.0)	1593 (66.8)	1986 (62.3)	.001
APOE ε4 carriers, n (%)[a]	882 (16.0)	345 (14.7)	537 (17.0)	.019
Chronic health condition				
Hypertension, n (%)[a]	3849 (67.2)	1599 (65.1)	2250 (68.8)	.003
Diabetes, n (%)	832 (14.4)	281 (11.4)	551 (16.7)	<.001
Dyslipidemia, n (%)[a]	1349 (23.4)	392 (15.9)	957 (29.0)	<.001
Obesity, n (%)[a]	1111 (19.4)	383 (15.7)	728 (22.2)	<.001
Stroke, n (%)[a]	908 (15.8)	417 (16.9)	491 (14.9)	.039
Heart diseases[c], n (%)	1351 (23.5)	485 (19.7)	866 (26.3)	<.001
Depressive symptoms, n (%)[a]	556 (10.5)	189 (8.3)	367 (12.1)	<.001
Dementia, n (%)[a]	307 (5.4)	96 (3.9)	211 (6.5)	<.001
No. of chronic diseases[d], n (%)				<.001
0	16 (0.3)	7 (0.3)	9 (0.3)	
1	729 (12.6)	384 (15.6)	345 (10.5)	
≥2	5020 (87.1)	2077 (84.2)	2943 (89.3)	

Note: Data are mean (standard deviation), unless otherwise specified.

Abbreviation: APOE, apolipoprotein E gene.

[a]Information was missing in 146 persons for occupation, 6 for smoking, 6 for alcohol consumption, 171 for leisure-time physical activity, 257 for APOE ε4 carrier, 36 for hypertension, 1 for dyslipidemia, 36 for obesity, 7 for stroke, 12 for heart disease, 476 for depressive symptoms, and 49 for dementia.

[b]P-value is for the test of differences between men and women.

[c]Heart diseases included coronary heart disease, heart failure, and atrial fibrillation.

[d]Fifteen chronic diseases were included, that is, hypertension, diabetes, dyslipidemia, obesity, stroke, coronary heart disease, heart failure, atrial fibrillation, cancer, depressive symptoms, dementia, chronic obstructive pulmonary disease, chronic kidney disease, thyroid dysfunction, and cataract.
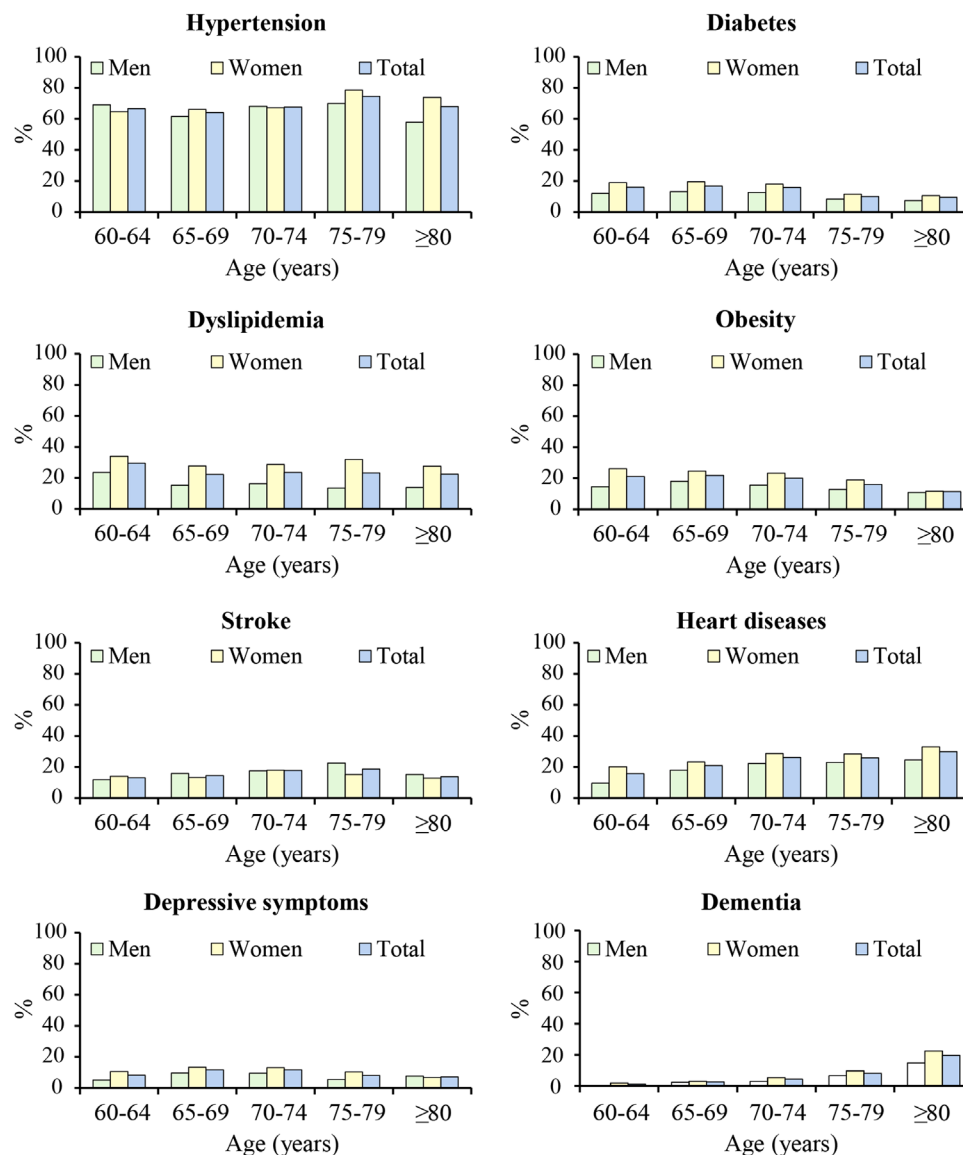
FIGURE 3 Age- and sex-specific prevalence (per 100 population) of major chronic diseases. Heart disease included coronary heart disease, heart failure, and atrial fibrillation. Information was missing in 36 persons for hypertension, 1 for dyslipidemia, 36 for obesity, 7 for stroke, 12 for heart disease, 476 for depressive symptoms, and 49 for dementia

could objectively assess quantitative parameters of physical activity (eg, steps, energy expenditure, and time spent sitting). Similarly, the portable device for CPC analysis could provide objective assessment of the sleep quality, sleep structure, and sleep-disordered breathing by estimating the cyclic alternating pattern rate with a single-lead ECG. These objective measures will be extremely valuable for exploring risk and protective factors, identifying at-risk individuals for early interventions, and understanding the pathophysiological pathways leading to dementia.

The interdisciplinary baseline data of MIND-China provide a unique opportunity to address a range of scientific issues related to aging and health, brain aging, and dementia (Figure 1), such as: (1) Epidemiology of cognitive aging and dementias: we will describe the prevalence and distributions of MCI, dementia, and its subtypes. In addition, given that evidence has emerged that AD biomarkers (eg, tau, Aβ, and

NfL) in plasma measured with ultrasensitive approaches (eg, SIMOA) and central nervous system (CNS) (eg, brain and cerebrospinal fluid [CSF]) are correlated,[41] we may integrate neuroimaging and peripheral biomarkers to define AD following the NIA-AA research framework, and study the epidemiology of biological AD in the general population setting. (2) Risk and protective factors for dementias: rural residents in China have distinct environmental profiles from western populations and even urban populations in China. We have the potential to verify the traditional risk factors but also to identify unique risk and protective factors for AD and dementia. (3) Clinical and imaging markers for AD and dementia: data on retinal thickness, olfactory impairment, hearing impairment, and brain MRI markers may help improve early detection and diagnosis of MCI, dementia, and subtypes. (4) By integrating the interdisciplinary baseline data with subsequent interventions and follow-up assessments of cognitive outcomes (eg, MCI, AD,

TABLE 3 A summary of baseline assessments in different modules

Modules of assessments	n	Age (years), mean (SD)	Women, n (%)	Illiteracy, n (%)	Equipment	Key measurements
Module 0: Core module	5765	70.9 (5.9)	3297 (57.2)	2338 (40.6)	Structured questionnaire; ECG; SSIT; ultrasonic machine; automatic biochemical analyzer	Sociodemographic data; epidemiological data; clinical data; neuropsychological and physical functional data; olfactory data; laboratory biochemical markers
Module 1: Brain MRI scans	1304	69.4 (4.3) *	757 (58.4)	454 (35.0) *	Philips Ingenia and Archiva 3.0T MR	Structural and functional brain MRI measurements
Module 2: Genetic and peripheral markers						
Genetic markers	5508	70.8 (5.8) *	3157 (57.3)	2208 (40.1)‡	Illumina NovaSeq 6000	67 SNPs for genes, e.g., *APOE*, *TOMM40*, and KIBRA genes
Plasma AD biomarkers	1452	70.2 (5.3) *	886 (61.0) *	586 (40.4)	SIMOA HD-X Analyzer;	Total-tau, Aβ40, Aβ42, and NfL
Inflammatory markers	1872	70.2 (5.3) *	1134 (60.6) *	744 (39.7)	MSD MESO QuickPlex SQ 120	IFN-γ, IL-6, IL-8, IL-10, TNF-α, IL-17A, eotaxin-3, MCP-1, ICAM-1, and VCAM-1
Module 3: Actigraphy examination	2505	70.1 (5.0) *	1479 (59.0)†	973 (38.8)†	ActiGraph wGT3X-BT	Raw acceleration (G's), activity counts, energy expenditure, steps taken, PA intensity, activity bouts, sedentary bouts, and body position
Module 4: CPC analysis	2340	69.6 (4.6) *	1330 (57.2)	860 (37.0)*	CPC analysis	Heart rate variability, apnea hyponea index, and EDR signal
Module 5: PTA examination	3012	71.0 (5.1)	1703 (56.5)	1176 (39.0)‡	GSI AudioStr	Bilateral bone conduction thresholds at 0.25, 0.5, 1, 2, and 4 kHz; Bilateral air conduction thresholds at 0.125, 0.25, 0.5, 1, 2, 4, and 8 kHz
Module 6: OCT examination	1310	70.8 (5.2)	757 (57.8)	544 (41.5)	Primus 200; Spectralis HRA+OCT	Average retinal thickness and volume, nerve fiber layer, ganglion cell layer, inner plexiform and nuclear layer, outer plexiform and nuclear layer, and inner and outer retinal layer

Note: *P* was for the test of differences between persons who participated in the assessment of the module and those who did not.

Abbreviations: SD, standard deviation; MRI, magnetic resonance imaging; *APOE*, apolipoprotein E gene; Aβ, amyloid beta; CPC, electrocardiography-based cardiopulmonary coupling; ECG, electrocardiography; EDR signal, ECG-derived respiratory signal; ICAM-1, intercellular cell adhesion molecule-1; IFN-γ, interferon gamma; IL-10, interleukin-10; IL-17A, interleukin-17A; IL-6, interleukin-6; IL-8, interleukin-8; *KIBRA*, KIdney and BRAin expressed protein; MCP-1, monocyte chemotactic protein-1; MET, metabolic equivalents rate; MSD, Meso Scale Discovery; NfL, neurofilament light protein; OCT, optical coherence tomography; PA, physical activity; PTA, pure tone audiometry; SIMOA, single molecule array; SNP, single nucleotide polymorphism; SSIT, Sniffin' Sticks identification test; TNF-α, tumor necrosis factor alpha; TOMM40, translocase of outer mitochondrial membrane 40; VCAM-1, vascular cell adhesion molecule-1.

†$P < .05$, ‡$P < .01$, *$P < .001$.

and dementia), we will be better able to understand the natural history of cognitive aging and the potential mechanisms underlying any effects of the multimodal interventions.

The interdisciplinary baseline assessments in MIND-China provide crucial data sources to explore the complex relationships of various exposures and aging-related health outcomes (eg, dementia, functional dependency, and multimorbidity) as well as potential mechanisms. We

found that cardiovascular risk factors (eg, smoking in men, hypertension, diabetes, dyslipidemia, and obesity) and cardiovascular disease—the main components of risk profiles for brain aging and dementia—are highly prevalent in this rural population. In addition, multimorbidity is common among older people in this rural area (87.1%), which was consistent with previous reports of middle-aged and elderly people in Asia, Europe, and America.[42] Highly prevalent chronic diseases

and multimorbidity pose tremendous burden to health care. MIND-China engaged older adults live in rural communities where the vast majority were farmers and had no or limited formal education. These unique characteristics of the cohort are worth noting because most of current population-based studies of aging and dementia targeted urban populations. MIND-China also has potential limitations. It has been suggested that cardiometabolic risk factors (eg, high blood pressure and high cholesterol), especially when occurring in midlife (eg, 40s–50s years of age), but not necessary in late-life, could contribute to an increased risk of late-life cognitive decline and dementia.[10,11,43] In this context, MIND-China, as an intervention study in older adults (≥60 years of age), is not able to test the potential effect of control of midlife vascular risk factors on late-life cognitive outcomes. In addition, we do not have AD biomarkers from CNS (eg, CSF and brain positron emission tomography-computed tomography [PET/CT] scans) to validate plasma AD biomarkers in our study, although current evidence from literature shows clear correlations of SIMOA-based plasma AD biomarkers with CNS AD biomarkers and we do have the plan to test additional blood biomarkers that are more sensitive for AD (eg, phosphorated-tau 181, 217, and 231) in the future by using frozen baseline blood samples.[44]

In conclusion, we demonstrated the feasibility of applying different conventional and the state-of-the-art techniques to the interdisciplinary assessments of a large-scale population-based project of older adults who were living in the rural communities. The interdisciplinary MIND-China database provides a unique opportunity to investigate a range of scientific research questions related to health in aging in general, and brain aging and dementia in particular. The baseline data show that certain physical and mental chronic disorders as well as multimorbidity conditions are highly prevalent among rural-dwelling older adults. The scientific value of the database will be further enriched when new data from future follow-up assessments along with multimodal interventions become available.

CONFLICT OF INTEREST

Miia Kivipelto received honoraria for lectures from Biogen, Nutricia, Nestlé, and Roche. Miia Kivipelto is on the advisory boards of Combinostics, the Swedish Care International, Roche, and Biogen. Miia Kivipelto is the Chair of the Committee for Clinical Therapy Research at the Swedish Research Council, and ADDF Board of Governors; the WHO Guidelines Development Group; Committee Member of the Global Council on Brain Health; and the Scientific Lead of World-Wide FINGERS Network. Maria Carrillo is in the Advisory Board of US POINTER STUDY. Maria Carrillo and Heather Snyder are full-time employee of the Alzheimer's Association. All other authors have no conflict of interest to declare.

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