

Investigation of the risk and preventive factors for progression of mild cognitive impairment to dementia: a 6-year follow-up study

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Research Article

Keywords: Mild cognitive impairment; dementia; ordered logistic regression analysis; education; diabetes; past occupation

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Abstract

Background: To investigate the cognition change of mild cognitive impairment (MCI) during a 6-year follow-up, and to evaluate the preventive and risk factors for MCI progression to dementia.

Methods: This cross-sectional study was based on the results of the epidemiological survey in 2011 (No. PKJ2010-Y26). A total of 441 MCI individuals, 60 years and above were involved. Cognitive function was measured by the mini-mental status examination (MMSE), clinical dementia rating (CDR), montreal cognitive assessment (MoCA), and daily living scale (ADL). The association between demographic characteristics and MCI outcomes were evaluated using single-and multi-factor ordered logistic regression analysis models.

Results: Exclusion of the relocated community, the final follow-up rate was 43.8%. Individuals who were older, had more children, not in marriage, and with high income were easily lost to follow-up. Of the 441 MCI, 77 progressed to dementia (MCIp, 17.5%, 95% CI: 14.4-21.6%), 356 remained stable (MCI_s, 80.7%, 95% CI: 77.0-88.4%), and 8 reverted to normal cognition (MCI_r, 1.8%, 95% CI: 0.6-3.0%) at follow-up in 2017. Diabetes ($P=0.047$) and past occupations as managers ($P=0.028$) increased the risk of MCI progression to dementia. While, high education ($P=0.006$) was the protective factor of MCI progression.

Conclusions: High education, nondiabetic, and past occupation as a technical staff might prevent the progression of MCI to dementia.

Keywords: Mild cognitive impairment; dementia; ordered logistic regression analysis; education; diabetes; past occupation.

Background

Mild cognitive impairment (MCI) is thought to be a transitional stage between normal cognitive function and dementia among aging individuals. Compared with normal elderly people whose age and education level are matched, patients have mild cognitive decline without significant decline in functional activities of daily living [1]. MCI with significant memory impairment is the initial clinical manifestation of Alzheimer's disease (AD) [2]. Bennett and Morris et al. reported that more than 34% MCI individuals developed to AD over 5 years, while, 9.5 years later, the conversion was 100% [3, 4]. A longitudinal clinical study showed that about 80% AD were developed from MCI [5]. By the time AD was diagnosed, the cognitive decline began many years ago and accelerated during the course of the disease [5]. Substantial and irreversible neurological damage has occurred in patients with AD, and there is currently no effective treatment. Therefore, early diagnosis and prevention of AD are particularly important, and reasonable intervention in MCI may be effective for AD [6].

The number of older patients that over age 60 with multiple comorbid diseases is significantly increased recently [7]. Epidemiological surveys show that the occurrence of cognitive impairment in the elderly was closely related to the metabolic diseases [8, 9]. Beyboud et al. conducted a meta-analysis containing 247

studies (cross-sectional and cohort studies) to analyze the modifiable factors associated with cognition and dementia. The results showed that higher homocysteine levels, lower educational attainment, and decreased physical activity were particularly strong predictors of incident AD [10]. The effect of some factors, such as occupations, economic income, hypertension, and other chronic physical diseases on the cognitive function requires further research.

The present study was based on the research conducted in 2011 (No. PKJ2010-Y26) [7] for the aim of investigation of the cognition changes in MCI, and analysis of the protective and risk factors for MCI progression to dementia by follow-up on the same community elderly in 2017.

Methods

Study design and ethical considerations

Based on the probability-proportional-to-size (PPS) sampling method, community elderly involved in the cross-sectional epidemiological survey (No. PKJ2010-Y26) from July 2011 to July 2012 were involved in this study. Aged 60 years and above with audiovisual levels to complete the necessary examinations were considered as the inclusion criteria. Flow chart of follow-up process was summarized in Figure 1. Excluding the rejected and relocated communities, the remaining 17 communities participated in the follow-up survey, of which 1,253 were followed up and 1,609 were lost (the follow-up rate was 43.8%). The present study was approved by Ethics Committee of Shanghai Pudong New Area Mental Health Center: 2016001 and all participants signed informed consents.

Demographic characteristics

Demographic characteristics were counted based on the questionnaires, including gender, age, height and weight, education level, marital status, occupation, economic income, health insurance, personality, the number of children, care method, family status, family history of dementia, and history of diabetes, hypertension, hyperlipidemia and mental illness. The investigation was conducted by psychiatric medical staff with more than 2 years of clinical work experience from the district mental health center. Before the survey, investigators were trained with mini-mental state examination (MMSE), clinical dementia rating (CDR), and Petersen diagnostic assessments to ensure the Kappa values ranged from 0.82 to 0.88 [7], followed by reviewing by the middle or senior psychiatrists. The survey was conducted by door-to-door interview.

Diagnosis of MCI and dementia

According to Petersen's diagnostic criteria [11], participants who had the following symptoms were diagnosed as the MCI: subjective memory complaints or reported by family members for obvious memory impairment over 3 months; normal total cognitive function assessed by MMSE (illiteracy >17 points, primary school >20 points, others >24 points) [12]; CDR score of 0.5 [13]; montreal cognitive assessment (MoCA) score of ≤ 26 points [14]; intact activities of daily living assessed by activities of daily

living scale (ADL) [15]; and no dementia [16]. Diagnostic criteria for dementia: according to MMSE, illiterate group ≤ 17 points, primary school group ≤ 20 points, middle school or above group ≤ 24 points [12]; obvious blindness, loss of speech and difficulty in verbal expression. Diagnostic criteria for normal cognitive: MoCA > 26 points (fewer than 12 years of education, added one point) and MMSE > 24 points; MMSE score > 18 points for illiteracy; MMSE score > 21 points for primary school education. Hachinski ischemic score (HIS) was used for identification of the vascular dementia [17].

Statistical analysis

Statistical analysis was performed by SPSS 19.0 software (IBM, Armonk, New York), with $P < 0.05$ indicating statistical significance. For quantitative data, the normal distribution was checked by One-Sample Kolmogorov-Smirnov Test (1 sample K-S Test) and histogram. Quantitative data was expressed by mean \pm standard deviation (normal distribution) or spacing values (median, quartile, extremes) for non-normal distribution. Differences between groups were analyzed by independent-samples t test (normal distribution) or non-parametric tests (mann-whitney U test, non-normal distribution). Qualitative data was expressed as percentages, and χ^2 test was used to compare proportions between the groups. Six-year follow-up outcomes of MCI were used as the dependent variable, while, the subjects' general demographic information and physical illnesses were used as the independent variables. Then, ordered logistic regression analysis model (single-factor and multi-factor regression analysis) was established, and Supplementary Table 1 showed the variable assignment. The factors with the P value < 0.1 in the single-factor were involved in the multi-factor regression analysis which was completed by the full entry model. Odds ratios (OR) of correlations were estimated with their 95% confidence interval (CI).

Results

Demographic characteristics of participants and lost to follow-up population

This study was based on a survey of 6 years ago (PKJ2010-y26), using the same tools to re-investigate the community elderly to understand the cognition changes of MCI. The baseline characteristics between the participants and lost to follow-up populations were displayed in Table 1. Individuals who were older, had more children, not in marriage, and those with high income were easily lost to follow-up. While, there was no significant difference in the history of hypertension and hyperlipidemia between two groups.

The outcome of MCI patients based on the follow-up study

Among the 1229 participants with complete information, 441 individuals were diagnosed as MCI in 2011. Of the 441 MCI, 77 progressed to dementia (MCIp, 17.5%, 95% CI: 14.4-21.6%), 356 remained stable (MCIs, 80.7%, 95% CI: 77.0-88.4%), and 8 reverted to normal cognition (MCIr, 1.8%, 95% CI: 0.6-3.0%) at follow-up in 2017. According to the HIS score, dementia was classified into vascular dementia in 3 cases (3.9%), Alzheimer's disease in 59 cases (76.6%), and mixed dementia in 15 cases (19.5%).

The ordered logistic regression analysis of outcome of MCI patients

The results of single-factor ordered logistic regression analysis of outcome of MCI patients were presented in Table 2. Among the baseline characteristics, the *P* values of diabetes, marriage status, college degree, high/secondary school, junior high school, primary school, worker, and civil servant were <0.1. These factors were subsequently subjected to multi-factor ordered logistic regression analysis. As shown in Table 3, cognitive function changes in the MCI population were closely associated to diabetes, education, and occupation. The MCIs and MCIr of diabetic was 0.48 (95% CI 0.23, 0.99) times that of nondiabetics MCI patients (*P*=0.047). Compared to illiterate, those with 14 years of formal education (college degree) had OR of 54.27 (95% CI 3.18 to 927.04, *P*=0.006) for the stability and reversion of MCI. Besides, past occupation also significantly influenced whether MCI patients remain stable and reversible (manager vs. technical staff, OR: 0.10, 95% CI 0.01 to 0.77, *P*=0.028). The results indicated that low education, diabetes and past occupations as managers were risk factors for MCI progression to dementia. In another word, factors such as non-diabetes, high education, and past occupations as technical staff were protective factors for MCI, reducing the risk of progression of MCI to dementia.

Discussion

The present study mainly focused on the 441 MCI and analyzed their progression to dementia, reversion to normal cognition, and remained stable during 6 years of follow up. There were 17.5% MCI community elderly progressed to dementia and 80.7% remained stable. Low education level, diabetes, and past occupation as a manager increased the risk of MCI progressing to dementia.

A meta-analysis conducted by our team showed that the probability of community elderly MCI progression to dementia was 34% (95% CI: 26-42%), which was lower than clinic-based outcomes [18]. Gao et al. followed up 208 MCI (among of the 437 participants older than 55 years) in Singapore and found that 4% MCI progressed to dementia and 44% MCI reversed to normal cognition during the six-year follow-up [19]. Besides, Pandya et al. reported that 35% of the 1,208 participants meeting MCI criteria progressed to dementia at two-years [20]. While, in this study, the MCI progression ratio was 17.5%. The different operational diagnostic criteria, assessment process, regional difference and participant backgrounds might explain the widely possibility of MCI progression to dementia. Verlinden et al. investigated trajectories of cognition and daily functioning in preclinical dementia, during 18 years of follow-up, revealing that dementia cases first reported memory complaints 16 years before diagnosis, followed by decline in MMSE and ADL [21]. Therefore, the age of memory complaints also affected the length of time for MCI progression to dementia.

In this study, low education increased the risk of MCI progression to dementia, which was similar to those of many studies at home and abroad [22]. A survey of cognitive abilities of the elderly in Shanghai suburbs showed that low education was associated with impairment of cognitive function, and the risk of dementia was gradually declined as the years of schooling increasing [23]. However, a systematic

literature review revealed that lower education was associated with a greater risk for dementia in many but not all studies [24]. Unhealthy lifestyles of the less educated compared with higher educated individuals was usually used to explain the relevance of low education and dementia. While, at present, the “greater cognitive reserve hypothesis” rather than “lifestyle hypothesis” was more precisely. High education individuals may have a greater cognitive reserve which may postpone the clinical manifestation of dementia [22, 25].

Besides, diabetes also increases the risk of progression of MCI to dementia. In our study, compared with those without diabetes, the risk of diabetes MCI progression to dementia was three times higher. There were plenty evidence to support the results. Neuropathologic studies have revealed cerebral atrophy and subclinical brain infarction evidence in diabetes patients without dementia [26]. Presumably, small-vessel disease and high levels of glycated hemoglobin which were common symptoms of chronic hyperglycemia increased the oxidative stress as well as the accumulation of advanced glycation end products, then led to the alterations in synaptic plasticity and damage of the central nervous cells [27-29]. According to Ji et al. fasting blood glucose and glycated hemoglobin levels were inversely associated with cognitive function scores, meaning that the higher the blood glucose level, the more severe the cognitive dysfunction [30]. This finding was similar to those of previous studies conducted in Beijing [31, 32], which indicated that fasting blood glucose and insulin resistance (HOMA-IR, $\beta=1.313$, $p=0.01$) were independent influencing factors of cognitive impairment (MMSE assessment) in elderly type 2 diabetic patients. Diabetes, impaired glucose tolerance, and metabolic syndrome increased the risk of MCI progression [33, 34]. High fasting blood glucose level increased the risk of dementia even in non-diabetes individuals [35].

Interestingly, hypoglycemia, a common adverse effect in diabetes treatment by insulin or anti-diabetes drugs, may also increase the risk for dementia. According to Frier et al., hypoglycemia caused cognitive impairment probably through neuronal cell death, hippocampal atrophy, and microvascular infarction (mainly induced by platelet aggregation) [36]. As we all know, the severe hypoglycemia could cause irreversible damage to cognitive function. While, mild hypoglycemia which was less noticeable due to mild symptoms would be more harmful [36]. Diabetic individuals who had a history of hypoglycemic episodes faced a higher risk of dementia [37]. The control and maintenance of the normal blood glucose level displayed protective effect on the cognitive function in the elderly [38].

Moreover, past occupation as a manager was another risk factor for MCI. In our study, the MCIs and MCIr of managers was 0.1 times that of technical staff. Keohane et al. found that complex work which required higher mental stimulation may be protective for cognitive function. It was possible due to the continuously use of the brain increased the cognitive reserve in the technical staff [39]. The more you use your brains, the slower the cognitive function declines, and this advantage became more apparent after age 65 [40].

The present study has several limitations. First, in order to save time and economic cost, this study used a non-invasive MMSE and MoCA screening scale with high reliability and validity, rather than high-cost

detection methods such as magnetic resonance and genetic testing to reflect the cognitive changes. Second, in our previous study, the mean MMSE score of MCI (2011, n=441, ≥ 55 years old) was 26.58 ± 2.48 , which was higher than that of other investigators (2008, n=2809 cases, ≥ 60 years old) with 24.37 ± 4.071 [23]. This may be one of the reasons for the low MCIp rate in this study. While, this study specifically investigated the relevant factors of the MCI outcomes among the older population in Shanghai. We hope that our findings would be of guiding significance for preventing MCI progression to dementia.

Conclusions

Of the 441 MCI participants, about 17.5% progressed to dementia and 80.7% remained stable during the 6-year follow-up. Education, diabetes, and past occupations were significantly associated with the cognition changes of MCI. High education, nondiabetic, and past occupation as a technical staff were the preventive factors of MCI progression to dementia.

Abbreviations

mild cognitive impairment (MCI)

mini-mental status examination (MMSE)

clinical dementia rating (CDR)

montreal cognitive assessment (MoCA)

daily living scale (ADL)

progressed to dementia (MCIp)

remained stable (MCIs)

reverted to normal cognition (MCIr)

Alzheimer's disease (AD)

probability-proportional-to-size (PPS)

Hachinski ischemic score (HIS)

One-Sample Kolmogorov-Smirnov Test (1 sample K-S Test)

Odds ratios (OR)

confidence interval (CI)

Declarations

Ethics approval and consent to participate

The present study was approved by Ethics Committee of Shanghai Pudong New Area Mental Health Center: 2016001. There were no severe dementias among of the participants and all informed consents were signed by the participants themselves.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during this study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

Conception and design of the research: CH; acquisition of data: LW; statistical analysis: YG; analysis and interpretation of data: ZC,YL; obtaining funding: CH; drafting the manuscript: CH, HQ; revision of manuscript for important intellectual content: HQ. All authors read and approved the final manuscript.

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Tables

Table 1. Demographic difference between participants and lost to follow-up population

variables	FU (n=1253)	LFU (n=1609)	Z/ χ^2	P
Age *	66.0 (61.0, 72.0)	68.0 (62.0, 76.0)	6.503	<0.001**
Num of children*	2.0 (1.0, 2.0)	2.0 (1.0, 3.0)	3.594	<0.001**
Not in marriage (cases %) *			8.823	0.003**
Yes	210 (17.0)	341(21.63)		
No	1040 (83.0)	1266 (78.37)		
Education level (cases %)			20.414	0.001**
Illiteracy	144 (14.6)	267 (16.7)		
Primary school	296 (23.8)	347 (21.7)		
Junior high school	482 (38.7)	572 (35.7)		
High/secondary school	229 (18.4)	262 (16.4)		
College degree	54 (4.3)	89 (5.6)		
Bachelor degree or above	41 (3.3)	64 (4.0)		
Economic income (cases %)*			10.279	0.016*
<1300Yuan/month	238 (19.1)	236 (14.7)		
1300<≤2000 Yuan/month	552 (44.2)	721 (45.0)		
2000<≤4000 Yuan/month	441 (35.3)	619 (38.7)		
>4000 Yuan/month	17 (1.4)	25 (1.6)		
Care frequency			1.522	0.217
Height (m)	1.60 (1.56, 1.66)	1.60 (1.56, 1.67)	0.730	0.466
Weight (Kg)	62.0 (55.0, 70.0)	62.0 (55.0, 70.0)	0.667	0.505
BMI (Kg/m ²)	23.88 (21.78, 25.95)	23.82 (21.55, 25.97)	1.022	0.307
Occupation			6.431	0.490
Personality			0.864	0.649
Family status			1.331	0.722
Family history of dementia			0.405	0.524
Health insurance			1.579	0.209
Care-frequency			1.522	0.217
Memory decline			0.091	0.764
Type II diabetes			1.825	0.177
Hypertension			2.942	0.086
Hyperlipidemia			1.248	0.264

* p<0.05; ** p<0.01; Num: number; FU: follow up; LFU: lost to follow up.

Table 2. The single-factor logistic regression analysis of outcome of MCI patients

Factors	logOR	Se	Sig.	95%CI of logOR	OR	95%CI of OR
Age (>60)	-0.533	0.334	0.110	-1.187 0.121	0.59	0.31 1.13
Family history without dementia	0.272	0.399	0.495	-0.510 1.053	1.31	0.60 2.87
Memory decline	0.099	0.314	0.753	-0.516 0.713	1.10	0.60 2.04
Diabetes	-0.695	0.358	0.052	-1.396 0.005	0.50	0.25 1.01
Hypertension	0.045	0.244	0.852	-0.432 0.523	1.05	0.65 1.69
Hyperlipemia	0.295	0.642	0.646	-0.963 1.553	1.34	0.38 4.73
Male	-0.109	0.265	0.682	-0.628 0.411	0.90	0.53 1.51
Marriage	-0.633	0.287	0.028	-1.195 -0.070	0.53	0.30 0.93
Health insurance	0.098	0.278	0.724	-0.446 0.642	1.10	0.64 1.90
Care method	-0.306	0.271	0.258	-0.837 0.224	0.74	0.43 1.25
Care frequency	-0.003	0.246	0.991	-0.484 0.479	1.00	0.62 1.61
BMI (≥ 28.0)	0.068	0.406	0.866	-0.723 0.858	1.07	0.49 2.36
BMI (24.0-27.9)	-0.133	0.259	0.609	-0.640 0.375	0.88	0.53 1.45
Neutral personality	-0.506	0.318	0.112	-1.129 0.117	0.60	0.32 1.12
Outward personality	-0.109	0.346	0.752	-0.786 0.568	0.90	0.46 1.76
Bachelor or above	1.802	2.304	0.434	-2.713 6.317	6.06	0.07 553.91
College degree	4.003	1.289	0.002	1.477 6.529	54.76	4.38 684.71
High/secondary school	1.048	0.618	0.090	1.477 6.539	2.85	4.38 691.59
Junior high school	0.629	0.296	0.033	0.049 1.208	1.88	1.05 3.35
Primary school	0.667	0.320	0.037	0.039 1.295	1.95	1.04 3.65
Occupation (other)	-0.896	0.642	0.163	-2.155 0.363	0.41	0.12 1.44
Worker	-1.052	0.580	0.069	-2.188 0.084	0.35	0.11 1.09
Peasant	-0.961	0.614	0.117	-2.164 0.241	0.38	0.11 1.27
Service staff	-0.984	1.165	0.398	-3.267 1.300	0.37	0.04 3.67
Businessman	-0.615	1.069	0.565	-2.711 1.481	0.54	0.07 4.40
Clerk	-0.615	1.069	0.565	-2.711 1.481	0.54	0.07 4.40
Manager	-1.825	1.024	0.075	-3.831 0.181	0.16	0.02 1.20
Stem family	0.583	0.402	0.147	-0.204 1.370	1.79	0.82 3.94
Core family	0.418	0.387	0.280	-0.340 1.176	1.52	0.71 3.24
≤ 2000 Yuan/month	1.119	1.812	0.537	-2.433 4.670	3.06	0.09 106.70
$2000 < \leq 4000$ Yuan/month	-0.176	0.324	0.586	-0.811 0.458	0.84	0.44 1.58
> 4000 Yuan/month	-0.155	0.289	0.593	-0.721 0.412	0.86	0.49 1.51

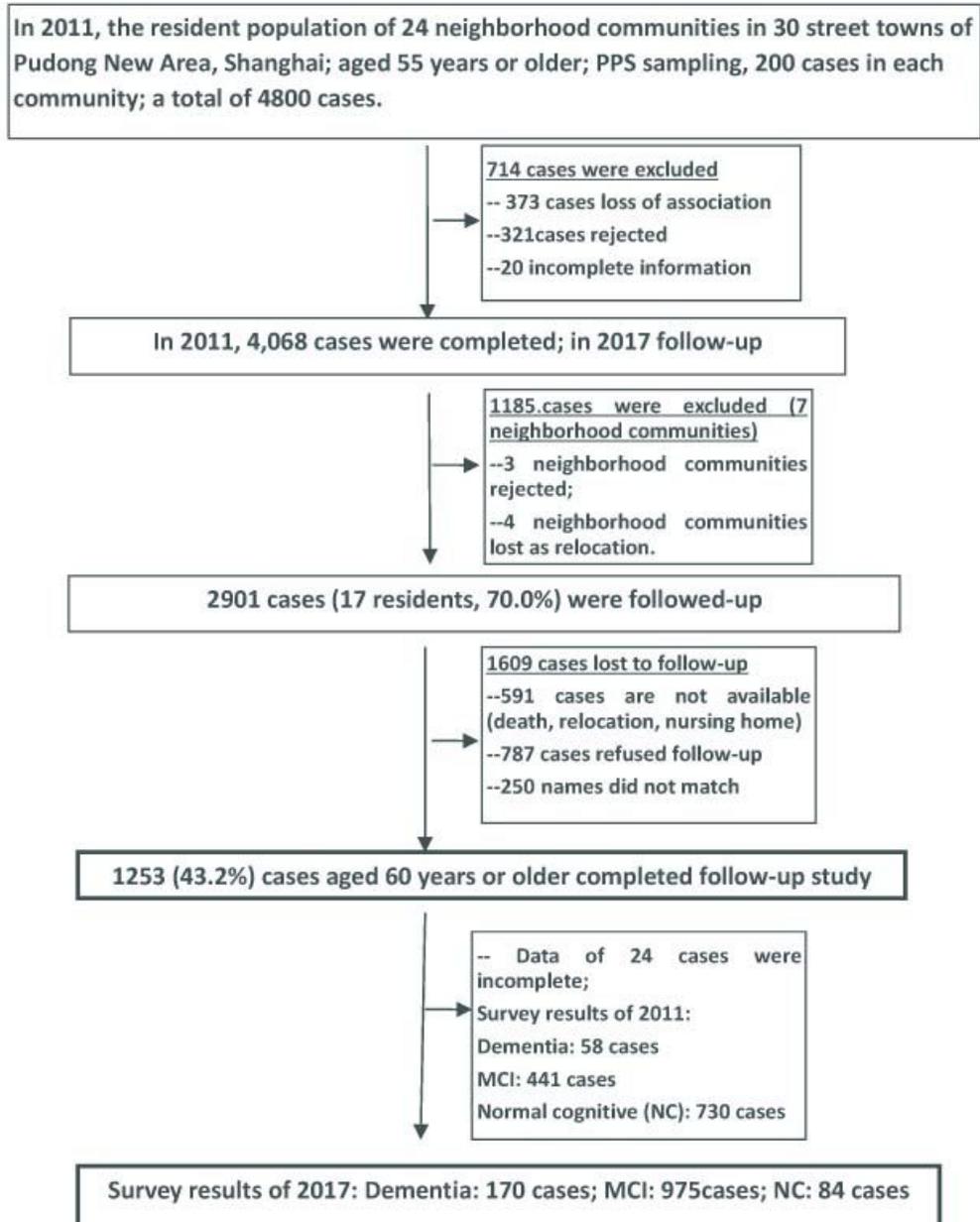
Stem family: A family contains grandparents or grandmothers, parents and third generation. Core family: A family only contains parents and unmarried children. For marriage, the control group was "married"; For health insurance, the control group was "type 1"; For care method, the control group was "mode 6"; For care frequency, the control group was "care degree 6"; For the personality, the control group was "Introverted type"; For occupation, control group is "technical staff"; For family, control group is "living alone"; For economic income, control group is "1300 Yuan/month".

Table 3. The multi-factor logistic regression analysis of outcome of MCI patients

Factors	logOR	Se	Sig.	95%CI of logOR		OR	95%CI of OR	
Diabetes	-0.733	0.369	0.047*	-1.455	-0.010	0.48	0.23	0.99
Marriage	-0.439	0.312	0.159	-1.051	0.172	0.64	0.35	1.19
Bachelor or above	2.334	2.018	0.247	-1.620	6.289	10.32	0.20	538.61
College degree	3.994	1.448	0.006*	1.156	6.832	54.27	3.18	927.04
High/secondary school	1.028	0.664	0.122	-0.274	2.329	2.80	0.76	10.27
Junior high school	0.536	0.327	0.101	-0.104	1.177	1.71	0.90	3.24
Primary school	0.640	0.335	0.056	-0.016	1.297	1.90	0.98	3.66
Occupation (other)	-0.488	0.643	0.448	-1.748	0.772	0.61	0.17	2.16
Worker	-0.482	0.584	0.409	-1.626	0.663	0.62	0.20	1.94
Peasant	-0.386	0.631	0.541	-1.624	0.851	0.68	0.20	2.34
Service staff	-0.459	1.180	0.697	-2.771	1.853	0.63	0.06	6.38
Businessman	-0.213	1.088	0.845	-2.345	1.919	0.81	0.10	6.81
Clerk	-0.265	1.092	0.809	-2.405	1.876	0.77	0.09	6.53
Manager	-2.327	1.056	0.028*	-4.397	-0.258	0.10	0.01	0.77

*P<0.05.

Figures



Flow chart of investigation on cognitive function of community elderly in 2017

Figure 1

Flow chart of investigation on cognitive function of community elderly in 2017.

Supplementary Files

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- [supplement1.docx](#)