筑　波　大　学

博 士 （医 学） 学 位 論 文

Impact of depressive symptoms on conversion from mild cognitive impairment subtypes to Alzheimer's disease: A community-based longitudinal study.

(軽度認知障害からアルツハイマー病への進展における抑うつ症状の影響: 地域縦断的研究から)

２０１５

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Contents

List of abbreviations

AD: Alzheimer's Disease

aMCI: amnestic mild cognitive impairment

CI: Confidence Interval

CN: Cognitively Normal

DLB: Dementia with Lewy Bodies

DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition

FTD: Frontotemporal Dementia

GDS: Geriatric Depression Scale

HR: Hazard Risk

LLD: Late-life Depression

N-ADL: Nishimura's Activities of Daily Living

naMCI: Non-amnestic Mild Cognitive Impairment

SD: Standard Deviation

VaD: Vascular Dementia

WAIS-R: Wechsler Adult Intelligence Scale-Revised

Abstract

Background: While longitudinal studies have investigated the relationships between mild cognitive impairment (MCI) subtypes and dementia subtypes, the results have been contradictory. In addition, some research shows that depression accompanied by MCI might increase the risk of Alzheimer's disease (AD).

Objective: The aim of this study is to longitudinally investigate the relationships between MCI subtypes and dementia subtypes, with special attention to the effect of comorbid depressive symptoms in a Japanese rural community.

Methods: Non-demented participants (N=802) completed a baseline and follow-up study. Outcomes were conversion to dementia especially AD, MCI, or no conversion. A complementary log-log analysis was conducted to investigate the risk of dementia and AD in amnestic MCI (aMCI) compared to nonamnestic MCI (naMCI) groups. The impact of depressive symptoms on the transition from MCI to AD and from cognitively normal to MCI or AD was also analyzed.

Results: The risk of developing dementia, in particular AD, for the aMCI group was significantly higher than that for the naMCI group. In the aMCI

group, the presence of depressive symptoms increased the risk of developing AD, but depressive symptoms in the naMCI group did not. In the cognitively normal group, the presence of depressive symptoms increased the risk of aMCI but not naMCI or AD.

Conclusion: MCI subtyping could be useful in finding a prodrome for dementia and in particular for AD. The differing impacts of depressive symptoms on the development of AD suggest that the relationship between depressive symptoms and cognitive impairment could differ in aMCI and naMCI patients.

Key words depressive symptoms, MCI, Alzheimer's disease, conversion, community

Introduction

Mild cognitive impairment (MCI) was conceptualized as a prodrome for Alzheimer's disease (AD), so its original definition focused on memory impairment without other cognitive domain impairments [1]. However, based on the assumption that prodromal non-AD dementia might manifest cognitive impairments other than amnesia, the Key Symposium dichotomized MCI into subtypes: amnestic MCI (aMCI) single domain and multiple domain, and non-amnestic MCI (naMCI) single domain and multiple domain [2]. Accordingly, aMCI single domain is presumed to convert to AD, aMCI multiple domain to AD and vascular dementia (VaD), naMCI single domain to frontotemporal dementia (FTD) and dementia with Lewy bodies (DLB), and naMCI multiple domain to DLB and VaD [2].

Longitudinal studies investigating the hypothesized relationship between MCI subtypes and dementia subtypes have reported contradictory results [3-9]. This might be due to selection bias, and verification of the hypothesized relationship should ideally be determined in a community-based longitudinal setting. However, only a few studies have satisfied this condition [5-9].

Several studies have examined what specific features of MCI might be

related to conversion to AD. For instance, some longitudinal studies reported that depression, which is often comorbid with MCI, was associated with increased risk of AD [10-13]. However, most of these focused on the transition from aMCI [10, 11, 13] and little attention has been paid to other subtypes of MCI.

We hypothesized that aMCI has a strong relationship with AD, while naMCI does with non-AD dementia subtypes, and depressive symptoms may increase the risk of conversion to AD in both aMCI and naMCI. We initially investigated the hypothesized relationship between MCI subtypes and dementia subtypes in a Japanese community-based longitudinal setting. Next, we investigated the impact of depressive symptoms on the transition from aMCI and naMCI to AD or cognitively normal to aMCI, naMCI and AD. In order to ensure diagnostic accuracy, we employed brain magnetic resonance imaging (MRI) and brain single-photon emission computed tomography (SPECT).

Methods

Subjects

This study was based on the Tone Project [14-19]. Tone is a town located approximately 40 km northeast of Tokyo. Potential candidates were 3,083 inhabitants aged 65 years and older as of 1 May 2001. The proportion of this age group in the total population (15.6%) was similar to the national average (17.2% in the 2000 Census).

The inclusion criteria were that subjects were not demented at the end of the baseline study and that they at least participated in the first follow-up, and the second follow-up if not censored nor demented at the first one. The exclusion criteria were the presence of conditions that might affect cognitive function: psychiatric diseases (other than depression or depressive state), cerebrospinal meningitis, head injury, malignancy and substance abuse. Subjects were stratified by age, sex and education in years, and average scores and SD were calculated.

Seven psychiatrists, eight psychologists and public health nurses were trained for the present study by the primary investigator.

This study was approved by the University of Tsukuba ethics committee (No. 12/2001-11-26 and No.140/2007-11-6) and written informed consent was

obtained from all the participants.

Clinical evaluation

The baseline study conducted between December 2001 and April 2002 is described elsewhere [14], so we have included a summary below. The first and the second follow-up studies were conducted between December 2004 and July 2005, and September 2008 and February 2009, respectively. The method of data collection was the same as that for the baseline study.

Measures

Demographic, medical and psychiatric assessment

We administered a structured questionnaire and assessed demographics and the medical and psychiatric conditions of participants through self-report and inquiries with cohabitating family members. We also received information on the types of drugs taken by the participants at the time of assessments. Blood samples were taken for routine biochemical examination, complete blood count, and genotyping of *apolipoprotein E* (*APOE*). *APOE ε4* was considered to be present when one or two *APOE* alleles

were *ε4*.

Subjective cognitive complaints

We used the *Détérioration Cognitive Observée* (DECO) scale to determine whether a participant had subjective cognitive complaints. DECO consists of 19 items, and was originally developed as an objective assessment of memory difficulty [20]. A participant having one or more positive items was considered to have subjective cognitive complaints.

Activities of daily living (ADL)

ADL was evaluated using Nishimura's Activities of Daily Living (N-ADL) scale [21]. This scale determines the level of independence for five activities: gait/sitting, environment of activity, dressing/bathing, eating and excretion. Participants were considered to be functionally intact if they reported no difficulty with any of the five items.

Neuropsychological battery

All the participants underwent a group assessment using a battery of five tests, named 5-cog, measuring the following cognitive domains: attention,

memory, visuospatial function, language and reasoning. Attention was evaluated with the Japanese version of a set-dependent activity which assesses alternating attention, the capacity for mental flexibility that allows individuals to shift their focus of attention between tasks with different cognitive requirements [22]. In this test, there were three rows on the page (top, middle and bottom) with three Chinese characters that meant "top", "middle" or "bottom". Some of the characters did not match their positions. The participants were required to circle the characters that were placed in the correct rows. Memory was assessed with the category cued recall test [23]. Participants were initially instructed to memorize 32 words with their categories. They were asked later to recall and write down words when provided a clue of the category. To evaluate visuospatial function, the clock drawing test was used [24]. It requires participants to draw a clock dial and hands showing the time at ten past eleven. We examined language ability with the category fluency test [25]. The participants were required to generate as many words as possible from animal category in two minutes. The total number of animals named was the score for the test. Reasoning ability was measured with the similarity subset of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) [26]. The participants were given two words that

belong to a same category. Then they were asked to provide another word.

Evaluation of depressive symptoms

Depressive mood at baseline was measured using the 15-item short version of the Geriatric Depression Scale (GDS) [27, 28]. According to the results of this self-assessment, the participants were dichotomized into the depressed group and the non-depressed group; participants who scored 5 or more on the GDS were classified as depressed and those who scored less than 5 as non-depressed [29]. Self-reported past history of depression and present psychotropic drugs use were also investigated thoroughly in the interview.

MCI diagnosis

Diagnoses of MCI were made for non-demented subjects at a consensus meeting involving healthcare professionals expert in dementia. The standard criteria for MCI were: a) cognitive complaints (defined previously), b) objective impairment in one or more cognitive domains (attention, memory, visuospatial function, language and reasoning) based on the average of the 5-cog scores within that domain and a cut-off of -1SD given the corrections for age, sex and years of education, c) essentially preserved ADL (defined previously), and d)

no diagnosis of dementia at the consensus meeting. Subtypes of MCI were determined according to the 5-cog subscale. aMCI was defined as a state where the memory subscale score was lower than 1 point below -1SD irrespective of the scores of other cognitive domains (attention, visuospatial function, language, and reasoning). naMCI was defined as a state where one or more non-memory subscale scores were lower than 1 point below -1SD, while the memory subscale score was normal.

The diagnostic criteria for dementia

After the follow-up cognitive examination, dementia was diagnosed according to the DSM-III-R criteria [30]. Once dementia was diagnosed, we determined the dementia subtypes (AD, DLB, VaD and FTD) based on the standard clinical criteria: the National Institute of Neurological and Communication Disorders and Stroke-Alzheimer's Disease and Related Disorders Association Criteria (NINCDS-ADRDA criteria) for AD [31], the Consortium on Dementia with Lewy Bodies (CDLB) Guidelines for DLB [32], the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) for VaD [33], and the clinical consensus criteria for FTD [34].

Consensus meeting to diagnose dementia

A consensus meeting was held to confirm the diagnosis of dementia using clinical and neuroimaging data. Three psychiatrists, who are experts in dementia, discussed each case and made clinical diagnoses according to the diagnostic criteria.

Statistical analysis

In comparing the baseline characteristics, the continuous variables were not normally distributed. Thus, we employed the Mann-Whitney U test. The chi-square test or, if appropriate, Fisher's exact test was used for categorical variables. To examine the risk of conversion to dementia, AD or MCI, we used a complementary log-log model [19]. While conversion to MCI, dementia or AD might occur at any time during the observation period, we could only identify such an outcome at one of the two fixed follow-up points. Thus, discrete time survival analysis as a complementary log-log model fits more appropriately than does continuous time survival analysis as a Cox proportional model. In addition, randomization is not required in the study design [35]. We first assessed the risk of dementia or AD for aMCI compared to naMCI (Analysis 1). Secondly, we investigated the impact of depressive symptoms using GDS

scores as depressed group (GDS≧5) vs non-depressed group (GDS<5) or as continuous variables on conversion to AD from MCI (Analysis 2), and that to MCI or AD from cognitive normality (Analysis 3). Analyses 1-1 was adjusted for age, sex, years of education and depressive state (defined as GDS≧5); Analysis 1-2 was adjusted for *APOE ε4* and vascular risk factors including history of hypertension, diabetes mellitus, dyslipidemia and cerebrovascular disease. Analyses 2-1 and 3-1 were adjusted for age, sex, years of education; Analyses 2-2 and 3-2 were adjusted for *APOE ε4* and vascular risk factors including history of hypertension, diabetes mellitus, dyslipidemia and cerebrovascular disease.

Data were analyzed using R software (Version 3.1.2). A statistical significance level of 0.05 was used for all the analyses.

Results

General findings

Of the 2,698 possible candidates, 1,844 (68.3%) met the criteria for participation at the completion of the baseline study. Three participants had a past history of depression according to their self-report. There were three current antidepressant users, but all of them were asymptomatic for depression at that time. We did not find any participants with anxiety disorder from their self-report and information from their family members. Among those depressive participants (GDS $\geqq$ 5), one took anxiolytics. Unexpectedly, among those non-depressive participants (GDS $<$ 5), 3 took anxiolytics.

Of these 1,844 baseline participants, 1,042 were excluded due to confirmed dementia at baseline (n=79), illnesses that might affect the cognitive functions described above (n=7), impaired ADL (n=132), lack of subjective cognitive complaints (n=57), incomplete data (n=129), and no follow-up (deceased: n=141, moved: n=33, declined: n=464). As a result, 802 participants who underwent the first follow-up were included in the analysis (Figure 1). Compared to those included, those excluded were older (average 75.5 vs 72.8 years), more often female (63.1% vs 56.2%), less educated (9.4 vs

10.2 years of school completed), and had higher GDS scores (3.4 vs 2.5) and higher rates of depressive state (GDS score≥5) (28.1% vs 18.1%) significantly ($p<0.05$ for all).

Based on the baseline data, the participants were classified into cognitively normal (n=526), aMCI (n=90) and naMCI (n=186) groups. The rates of depressive state (GDS score≥5) for the cognitively normal, aMCI and naMCI groups were 15.4%, 24.4% and 22.6%, respectively. Comparisons of aMCI and naMCI groups showed that the former (72.0±4.9 years) was significantly younger than the latter (73.7±5.3 years) (p=0.01) (Table1). During 5.2±1.9 years of the follow-up period, 101 participants converted to dementia.

Rates of Conversion to Dementia

Figure 2 shows the outcome of subjects who participated in both the baseline and the first follow-up studies. Of the total 101 participants who converted to dementia, 38 had been cognitively normal, 30 had been aMCI, and 33 had been naMCI at baseline. The rate of conversion to dementia from the cognitively normal group was 7.2%, from the aMCI group was 33.3%, and from the naMCI group was 17.7%. It is of note that some participants reverted

to normal cognition from MCI within the observation period: from the aMCI group, 26 (28.9%) reverted, and 80 (43.0%) reverted from the naMCI group. The reversion rate was higher for naMCI than aMCI (p=0.025). For all subjects, follow-up consensus meetings were held. As a result, a diagnosis consensus was reached. The converters were AD (n=68), VaD (n=16), DLB (n=14) and FTD (n=3) (Figure 2).

Conversion to dementia or AD from aMCI and naMCI

The numbers of converters to dementia were 38 out of 526 cognitively normal participants, 30 out of 90 participants with aMCI and 33 out of 186 participants with naMCI. Those to AD alone were 29, 17 and 22, respectively. AD was the most frequent subtype of dementia for each baseline group. The conversion to non-AD dementia was not confined to naMCI (Figure 2); however, as shown in Table 2, compared to the naMCI group, the risk of converting to dementia for the aMCI group was more than double (HR=2.56, CI=1.46-4.49, p=0.0011). Risk of conversion to AD was about double (HR=2.27, CI=1.11-4.65, p=0.0254).

Conversion to AD from MCI in relation to depressive symptoms

Compared to the non-depressed MCI group, the depressed MCI group had no significant risk of AD in the adjusted model. Compared to the non-depressed aMCI group, the depressed aMCI group had a significantly higher risk of AD (HR=11.37, CI=1.98-65.20, p=0.006). However, the presence of depressive symptoms did not affect the risk of AD among the naMCI group (Table 3). The results did not substantially change when using GDS as a continuous variable.

Conversion to MCI or AD from cognitively normal in relation to depressive symptoms

The presence of depressive symptoms did not increase the risk of converting to MCI or naMCI for cognitively normal participants (Table 4). However, the presence of depressive symptoms did increase the risk of converting to aMCI by nearly 5 times (HR=4.86, CI=1.55-15.69, p=0.007). There was no significant difference in the risk of converting to AD between non-depressed and depressed cognitively normal groups (HR=1.18, CI=0.50-2.83, p=0.705). The results did not substantially change when using GDS as a continuous variable.

Discussion

Here we considered depressive symptoms while examining the hypothesized relationship between MCI subtypes and dementia subtypes. In our study, there was a higher risk of converting to dementia and AD in the aMCI group than in the naMCI group. We also found that depressive symptoms increased the risk of conversion to AD only in the aMCI group. Depressive symptoms also increased the risk of conversion to aMCI, but not to naMCI or AD among participants who were cognitively normal at baseline.

The relationships between MCI subtypes and dementia subtypes are contradictory. A clinic-based study reported that MCI subtype had a major influence on the subsequent type of diagnosed dementia [4], whereas a majority of community-based studies only partially support this hypothesis [5-8]. A community study in Austria, investigating the prognostic validity of aMCI and naMCI in the prediction of AD, VaD and mixed dementia, reported that the hypothesis could be confirmed only for aMCI and incident AD [8]. Our present study strengthens this finding.

The current results also showed that the presence of depressive symptoms increased the risk of aMCI converting to AD. While similar findings have been reported [10, 11, 13], our results additionally showed that this was

not the case with naMCI. There is a possible explanation for this. Steffens reviewed the relationship between brain regions and depression syndromes, and paid particular attention to the following regions: orbitofrontal cortex, anterior cingulate gyrus, dorsolateral prefrontal cortex and hippocampus [36]. Among these four regions, the hippocampus is strongly associated with memory function. Neuroimaging studies have shown hippocampal volume of elderly individuals with aMCI is smaller than that of cognitively normal elderly, but that of elderly individuals with naMCI not so [37, 38]. An MRI study on major depressive disorders reported that reduced hippocampal volumes were associated with deficits in visual and verbal memory performance [39]. A recent study investigating participants with lifetime major depression and remitted or mild symptoms reported that MCI was found in 75.7% and memory change was linked to hippocampal atrophy in the patients [40]. The main lesions of incipient AD are located in the hippocampus and its neighboring regions. Taking these findings together, in considering aMCI alone, aMCI comorbid with depressive symptoms may indicate a higher probability of hippocampal involvement as a background lesion. Jorm and colleagues, along with Butters and colleagues hypothesized several mechanisms that might link depression and dementia: (1) depression may be a

prodrome of dementia, (2) depression can unmask clinical manifestation of dementing diseases, and (3) depression can cause hippocampal damage through raised cortisol levels [41, 42]. These hypotheses are not mutually exclusive, and involvement of the hippocampus may underlie in the case of incipient AD.

On the other hand, why depressive symptoms did not increase the risk of conversion to AD in the naMCI group also deserves attention. One possible explanation is that naMCI per se could be an unstable state, which tends to revert to normal cognition [5]. In the current study, 43.0% of the subjects with naMCI at baseline reverted to normal cognition within the observation period, a figure which is significantly higher than for aMCI (28.9%). On the other hand, according to a study of late-life depression (LLD), 94% of the subjects with a current episode of unipolar major depression and cognitive impairments at baseline still remained cognitively impaired at one year despite their remission [43], suggesting heterogeneity in cognitive course and outcomes in LLD [44]. Following patients with DSM-IV major depressive disorder for at least 18 months, half of them were found to have generalized cognitive impairment compared to healthy controls including memory, processing speed and executive function [45]. The authors showed that

impaired processing speed might be a partial mediator of deficits in other cognitive domains, but did not fully explain the difference between patients and controls; other deficits could exist in parallel. A study investigating relationships between cognitive function of major depressive disorder and subsequent diagnosis of AD longitudinally reported that recall of verbal contextual information was associated with AD to a greater extent than executive functioning [46]. The frontally mediated mild cognitive impairment may not predict conversion to Alzheimer's disease in geriatric depression [47]. Taken those findings and ours together, the regions responsible for concurrent nonamnestic impairment in depressive state might be areas other than hippocampus.

It is possible that aMCI with depressive symptoms might be a reliable prodrome of AD, while naMCI with depressive symptoms may not. Our results showed that the relationship between aMCI and subsequent AD could be better elucidated with the presence of depressive symptoms.

Similar to our study, Richard and colleagues' community-based study investigated depression and subsequent dementia in MCI subtypes, but with different results [48]. They showed that patients with MCI comorbid with depression at baseline had a higher risk of progression to VaD, but not to AD.

Their study focused on cerebrovascular disease as a potential link between depression and dementia. Sampling may explain the inconsistency between their results and ours, since there was a higher burden of hypertension (48% vs 28%) and diabetes mellitus (19% vs 6%). Participants in their community study were also older (77 vs 73 years old), and ethnically different (White, Black and Hispanic vs Mongoloid only). A meta-analysis of community-based cohort studies conducted by Diniz et. al reported that individuals with depression were at much higher risk for converting to VaD compared to AD [49]. Different from these studies, we especially focused on MCI samples. Relatively lower incidence of VaD in the present study also might have prevented from duplicating the finding.

Next, in our study, the presence of depressive symptoms in the cognitively normal group increased the risk of conversion to aMCI, but not to naMCI or collective MCI. While some previous studies have reported that depression increased the risk of conversion to MCI in cognitively normal participants [50, 51], another did not [48]. A recent large population-based study found that depression at baseline increased the risk of incident aMCI but not naMCI, a finding consistent with our result [52]. Considering aMCI itself has a high risk of AD, depressive symptoms antecedent to aMCI may be

a sign of prodromal AD. Alternatively, depressive symptoms and associated neuropathology (e.g. reduced hippocampal volume) might reduce cognitive reserve, and thereby unmask the manifestation of underlying AD.

In terms of limitations, we have no autopsy cases and the neuropathological background of dementia cases remains unknown. Secondly, participants excluded from the analysis were older, more often female, less educated, and had higher GDS scores and higher rates of depressive state (GDS score≥5) than included participants. While these characteristics may precipitate the conversion to dementia, we adjusted all of these covariates in the analysis. The past history of depression was based on participants' self-report. Assessment of depressive illness according to DSM criteria or a similar rigorous gold standard instrument was not included in the current study. Our definition of depressive cases at baseline were based on GDS scores. A cut-off score of GDS≧5 could be a mild depressive state and that might affect the results. Moreover, the ADL measure we used (N-ADL) targeted basic ADLs and was different from more complex instrumental ADLs (IADLs), which could have led to misidentification of some individuals as normal rather than MCI or dementia. We did not take into account psychosocial factors such as participants' personality, life style, environment, life events and so on. For

adjustment of 5-cog, we excluded dementia cases from participants of the Tone project for reference (non-dementia cases). Not only cognitively normal cases, but also MCI cases were included in the reference. This would result in some degree of circulatory. Lastly, the number of events was relatively small in our study. Future reconfirmation with participants with major depression, IADL information, psychosocial information, truly independent normative data from the sample in the analysis or in a larger sample is desirable to generalize these results.

In conclusion, MCI subtyping could be useful only in finding a prodrome for AD. The differing impacts of depressive symptoms on the development of AD appear to suggest that the relationship between depressive symptoms and cognitive impairment for aMCI and naMCI could differ. The relationship between aMCI and subsequent AD could be more clearly elucidated with the presence of depressive symptoms.

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Table 1

Baseline characteristics of all participants (n=802)

Characteristics	CN n=526	aMCI n=90	naMCI n=186	*p-value*[1]
Age, y, mean±SD	72.7±5.1	72.0±4.9	73.7±5.3	0.01
Female, n (%)	287 (54.6)	55 (61.1)	109 (58.6)	0.69
Education, y, mean±SD	10.3±2.6	9.5±2.4	10.0±2.8	0.26
GDS≥5, n (%)	81 (15.4)	22 (24.4)	42 (22.6)	0.73
GDS score, mean±SD	2.2±2.3	2.9±2.3	3.0±2.4	0.72
BMI, kg/㎡, mean±SD	23.1±3.1	23.2±3.0	22.8±3.1	0.33
CVD, n (%)	19 (3.6)	4 (4.4)	5 (2.7)	0.48
Hypertension, n (%)	152 (28.9)	21 (23.3)	50 (26.9)	0.53
Diabetes Mellitus, n (%)	23 (4.4)	4 (4.4)	20 (10.8)	0.08
Dyslipidemia, n (%)	22 (4.2)	1 (1.1)	5 (2.7)	0.67
Smoking, n (%)	198 (37.6)	33 (36.7)	61 (32.8)	0.53
Alcohol, n (%)	194 (36.9)	36 (40.0)	64 (34.4)	0.37
APOE ε 4 carrier, n (%)[2]	86 (17.2)	17 (21.8)	36 (20.7)	0.84

[1]Chisquare or Fisher's exact test and the Mann-Whitney U test for comparisons between aMCI and naMCI. [2]n=501 for cognitively normal, n=78 for aMCI and n=174 for naMCI. CN, cognitively normal; MCI, mild cognitive impairment; aMCI, amnestic MCI; naMCI, nonamnestic MCI; GDS, Geriatric Depression Scale; BMI, body mass index; CVD, cerebrovascular disease; *APOE, apolipoprotein E*.

Table 2

Risk of dementia in participants with amnestic MCI compared to nonamnestic MCI at baseline

	Analysis1-1[1]				Analysis 1-2[2]			
	At risk	Cases	HR (95% CI)	*p*-value	At risk	Cases	HR (95% CI)	*p*-value
Conversion to all dementia	276	63			252	58		
naMCI	186	33	1 (Reference)		174	32	1 (Reference)	
aMCI	90	30	2.74 (1.62-4.62)	0.0002	78	26	2.56 (1.46-4.49)	0.0011
Conversion to AD only	276	39			252	36		
naMCI	186	22	1 (Reference)		174	21	1 (Reference)	
aMCI	90	17	2.05 (1.06-3.98)	0.0337	78	15	2.27 (1.11-4.65)	0.0254

[1]Adjusted for age, sex, years of education and depressive state (defined as GDS≧5). [2]Adjusted for age, sex, years of education, depressive state (defined as GDS≧5), *apolipoprotein E* (*APOE*) *ε4* and vascular risk factors including history of hypertension, diabetes mellitus, dyslipidemia and cerebrovascular disease. The difference in numbers of participants at risk between Analysis 1-1 and Analysis 1-2 was due to missing data on the *APOE* genotype. HR, hazard ratio; CI, confidence interval; MCI, mild cognitive impairment; aMCI, amnestic MCI; naMCI, nonamnestic MCI.

Table 3

Risk of Alzheimer's disease in relation to depressive symptoms among participants with MCI at baseline

		Analysis 2-1[1]				Analysis 2-2[2]			
		At risk	Cases	HR (95% CI)	*p*-value	At risk	Cases	HR (95% CI)	*p*-value
MCI		252	39			230	36		
	GDS＜5	198	25	1 (Reference)		179	23	1 (Reference)	
	GDS≧5	54	14	2.15 (1.10-4.20)	0.025	51	13	1.74 (0.82-3.70)	0.148
	GDS score[3]	252	39	1.12 (0.99-1.27)	0.066	230	36	1.10 (0.96-1.27)	0.179
aMCI		77	17			67	15		
	GDS＜5	60	9	1 (Reference)		51	8	1 (Reference)	
	GDS≧5	17	8	7.79 (2.35-25.84)	0.0008	16	7	11.37 (1.98-65.20)	0.006
	GDS score[3]	77	17	1.27 (1.04-1.55)	0.0187	67	15	1.30 (1.00-1.70)	0.054
naMCI		175	22			163	21		
	GDS＜5	138	16	1 (Reference)		128	15	1 (Reference)	
	GDS≧5	37	6	1.35 (0.52-3.48)	0.535	35	6	0.99 (0.37-2.71)	0.992
	GDS score[3]	175	22	1.08 (0.91-1.27)	0.370	163	21	1.02 (0.84-1.24)	0.853

[1]Adjusted for age, sex, years of education. [2]Adjusted for age, sex, years of education, *apolipoprotein E* (*APOE*) *ε4* and vascular risk factors including history of hypertension, diabetes mellitus, dyslipidemia and cerebrovascular disease. [3]Geriatric Depression Scale (GDS) score examined as a continuous variable in 1-point increment. The difference in numbers of participants at risk between Analysis 2-1 and Analysis 2-2 was due to missing data on the *APOE* genotype. HR, hazard ratio; CI, confidence interval; MCI, mild cognitive impairment; aMCI, amnestic MCI; naMCI, nonamnestic MCI; GDS, Geriatric Depression Scale.

Table 4

Risk of mild cognitive impairment in relation to depressive symptoms among cognitively normal participants at baseline

	Analysis 3-1[1]				Analysis 3-2[2]			
	At risk	Cases	HR (95% CI)	*p*-value	At risk	Cases	HR (95% CI)	*p*-value
Conversion to all MCI	488	76			465	73		
GDS<5	417	64	1 (Reference)		396	61	1 (Reference)	
GDS≧5	71	12	1.10 (0.58-2.06)	0.770	69	12	1.20 (0.63-2.27)	0.581
GDS score[3]	488	76	1.09 (0.99-1.19)	0.089	465	73	1.11 (1.01-1.23)	0.031
Conversion to aMCI	427	15			407	15		
GDS<5	363	10	1 (Reference)		345	10	1 (Reference)	
GDS≧5	64	5	3.50 (1.13-10.82)	0.029	62	5	4.86 (1.55-15.19)	0.007
GDS score[3]	427	15	1.24 (1.01-1.52)	0.039	407	15	1.33 (1.07-1.65)	0.009
Conversion to naMCI	473	61			450	58		
GDS<5	407	54	1 (Reference)		386	51	1 (Reference)	
GDS≧5	66	7	0.74 (0.33-1.65)	0.461	64	7	0.81 (0.36-1.83)	0.609
GDS score[3]	473	61	1.05 (0.95-1.17)	0.338	450	58	1.08 (0.97-1.21)	0.154

[1]Adjusted for age, sex, years of education. [2]Adjusted for age, sex, years of education, *apolipoprotein E* (*APOE*) *ε4* and vascular risk factors including history of hypertension, diabetes mellitus, dyslipidemia and cerebrovascular disease. [3]Geriatric Depression Scale (GDS) score examined as a continuous variable in 1-point increment. The difference in numbers of participants at risk between Analysis 3-1 and Analysis 3-2 was due to missing data on the *APOE* genotype. HR, hazard ratio; CI, confidence interval; MCI, mild cognitive impairment; aMCI, amnestic MCI; naMCI, nonamnestic MCI; GDS, Geriatric Depression Scale.

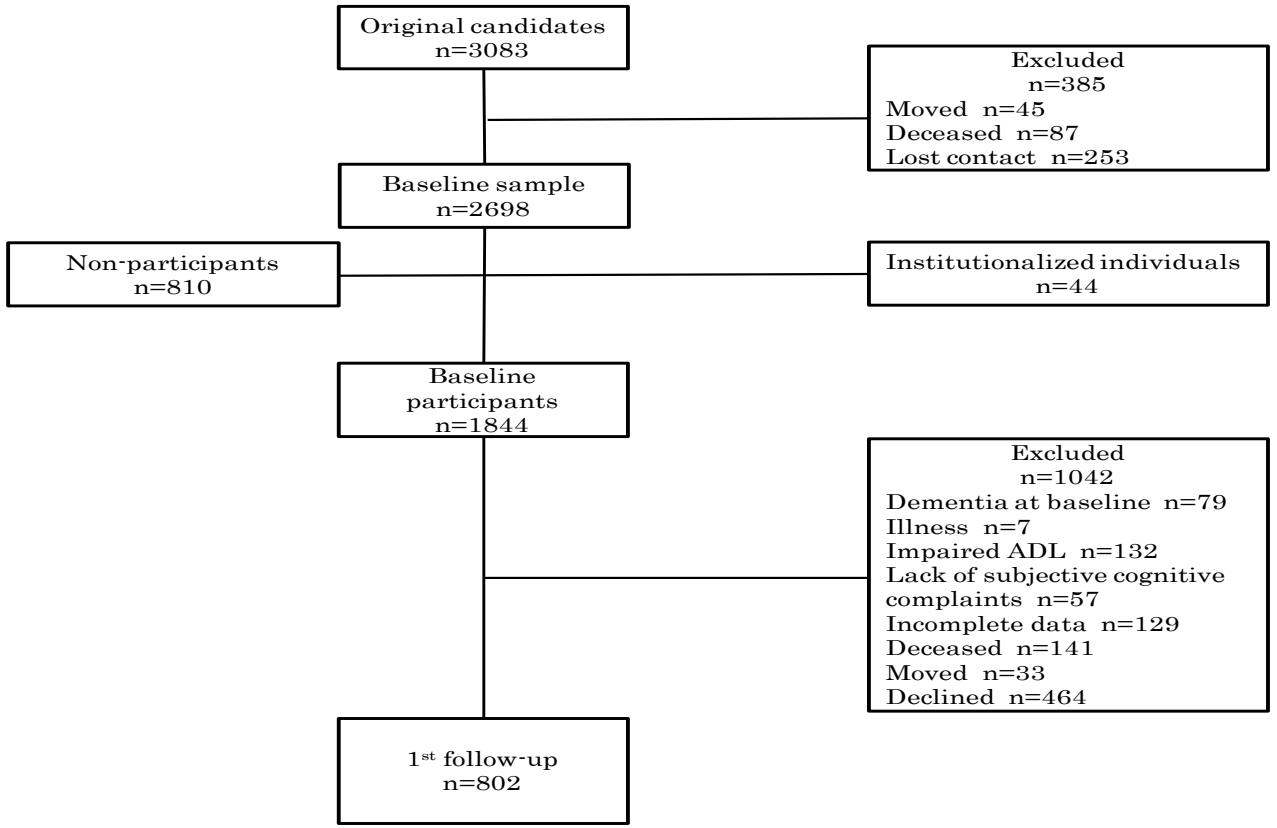

Figure 1. Flow diagram of the sample selection

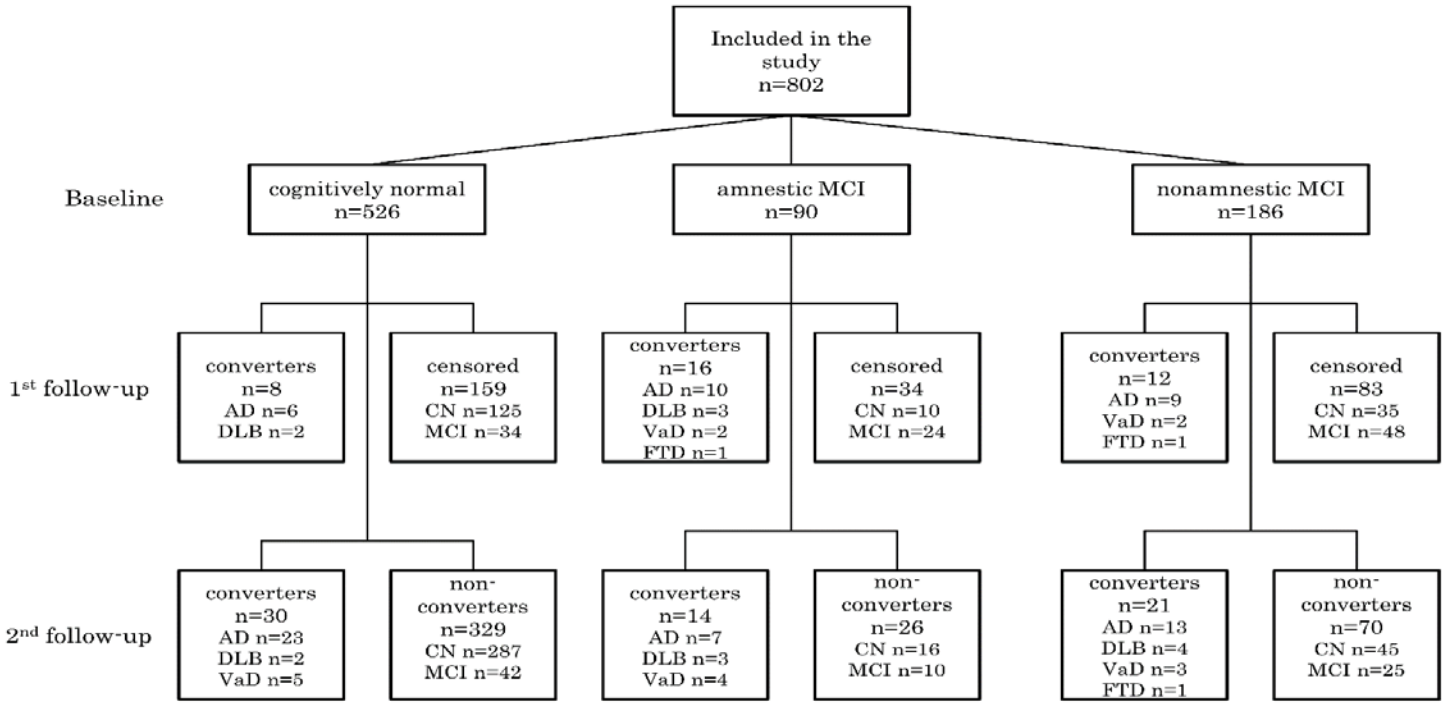

Figure 2. Outcome of the cohort within the observation period