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Incidence of dementia and associated risk factors in Japan: The Osaki-Tajiri Project

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Abstract

The incidence of dementia and risk factors has not been fully investigated in Japan. Following a prevalence study in 1998, we investigated the incidence and associated factors in the same population in 2003 and 2005. Randomly selected 771 residents in Tajiri were targeted. The final participants included 204 (65.2%) healthy older adults (Clinical Dementia Rating, CDR 0) and 335 (73.1%) people with questionable dementia (CDR 0.5). We analyzed the incidence of dementia and dementing diseases, and possible risk factors. The risk factors included demographics, lifestyle-related factors, vascular risk factors, cognitive functions, and MRI findings. Overall, 3.9% of the CDR 0 and 37.0% of the CDR 0.5 participants developed dementia during the 5-year period, whereas 40.2% of the CDR 0.5 participants developed dementia during the 7-year period. Older adults had a higher incidence. Higher CDR Box scores had a higher incidence. Of the dementing diseases, 60.8% of participants developed Alzheimer' disease (AD), followed by vascular dementia (VaD), 17.9%. Logistic regression analyses showed that age, MMSE, cognitive functions such as recent memory, and generalized atrophy were significant predictors of progression to AD. Similarly, predictive factors for progression to VaD were age, MMSE, cognitive functions such as frontal function, and white matter lesions and cerebrovascular diseases. A comprehensive system including CDR, cognitive tests, and MRI, is recommended in community-based health policy planning.

Keywords: Dementia incidence; Alzheimer's disease; Vascular dementia; CDR 0.5; MRI; Cognitive tests

1. Introduction

Age-specific incidence of dementia was reported in several countries [1–5], consistently showing a higher incidence in older age. However, few studies in Japan have been performed, compared with the USA and the EU. Studies identifying risk factors for predicting the incidence produced variable results, with reported associated factors including lifestyle such as alcohol uptake [6] and social support [7], psychosocial activities [8] for prevention, and vascular factors for the risk such as hypertension [9], cardiovascular diseases [10], and diabetes mellitus [11]. Alcohol uptake was conversely reported to be the risk [12] or diabetes was of no effect [13]. The variety of results is due to different methodology and further data are required for healthy policy planning.

Patients with cerebrovascular diseases (CVD) were also reported to be at risk for both vascular dementia (VaD) and Alzheimer's disease (AD) [14]. Previous studies using magnetic resonance imaging (MRI) reported that not only white matter lesions affect cognitive decline in the non-demented

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population cross-sectionally [15], but also that silent infarcts almost double the risk of dementia longitudinally [16].

Many studies reported the rate of progression from the borderline condition between normal and dementia to dementia, such as mild cognitive impairment (MCI) [17] and Clinical Dementia Rating [18] (CDR) 0.5 (questionable dementia), the results varying due to different methodology. Palmer et al [19] reviewed recent results: 15–38% for 1-year, 24–80% for 2-year, and 11–40% for 3-year follow up studies. For health policy planning for dementia prevention (primary or secondary), it is important to diagnose the borderline condition as early as possible and to determine risk factors in a community. However, there are few research fields for follow MCI and making a diagnosis of dementing diseases using MRI.

The Osaki–Tajiri Project, previously called the Tajiri Project, is a community-based project to investigate stroke, dementia, and bed-confinement prevention in Tajiri, northern Japan, and provided neuropsycho-epidemiologic findings on aging and dementia [20]. We performed a survey in 1998 and reported the prevalence of dementia to be 8.5%, and that of CDR 0.5 to be 30.1% [21]. In this study, we followed non-dementia people in the 1998 study and investigated the incidence of dementia over 5- and 7-year periods. This is the first, community-based, MRI-performed, incidence study on dementia in Asia and Japan.

2. Methods

2.1. Selection of participants

Fig. 1 illustrates the protocol for selecting participants. We performed the prevalence study in 1998 [20,21]: all older residents ($n=3207$) were targeted and finally 51.6% ($n=1654$) were included in the study. The respondents/population for each age group were 404/1066 (65–69 years), 560/856 (70–74 years), 349/607 (75–79 years), 212/397 (80–84 years), and 129/281 (85 years and older). The reasons for refusal were mainly "psychological" (25.6%) and "physical" reasons (14.6%).

Due to the administrative situation brought about by the formation of a new city of Osaki in 2006 through the merger of several towns including Tajiri, the incidence study had to be separated for twice, in 2003 and 2005.

For the prevalence study in 1998, 497 participants were randomly selected to receive MRI, finally consisting 346 CDR 0, 119 CDR 0.5, and 32 CDR 1+. Based on the database, the non-demented population (CDR 0 and 0.5) who had undergone MRI were targeted for the incidence study 2003 (henceforth referred to as Study 2003), and the remaining CDR 0.5 people who had not undergone MRI were targeted for the incidence study 2005 (defined as Study 2005): CDR 0 people were not included due to the economic constraints.

Namely, 346 CDR 0 (healthy) and 119 CDR 0.5 participants were selected for Study 2003, and all remaining CDR 0.5 participants ($n=395$) were selected for Study 2005. Their CDR status had been determined according to the systematic method (see below). None of the CDR 0.5 participants met the DSM-IV criteria for dementia.

Among the population planned for inclusion in Study 2003, 33 CDR 0 (9.5%) and 19 CDR 0.5 people (16.0%) had died due to cancer (50.0% of the CDR 0 deaths vs. 29.2% of the CDR 0.5 deaths), stroke (11.8% vs. 12.5%), or cardiac diseases (11.8% vs. 25.0%). Therefore, 313 CDR 0 and 100 CDR 0.5 adults were targeted, and final totals of 204 CDR 0 (65.2%) and 54 CDR 0.5 adults (54.0%) agreed to participate in Study 2003 (defined as Participants 2003 population). Among the population planned for Study 2005, 37 CDR 0.5

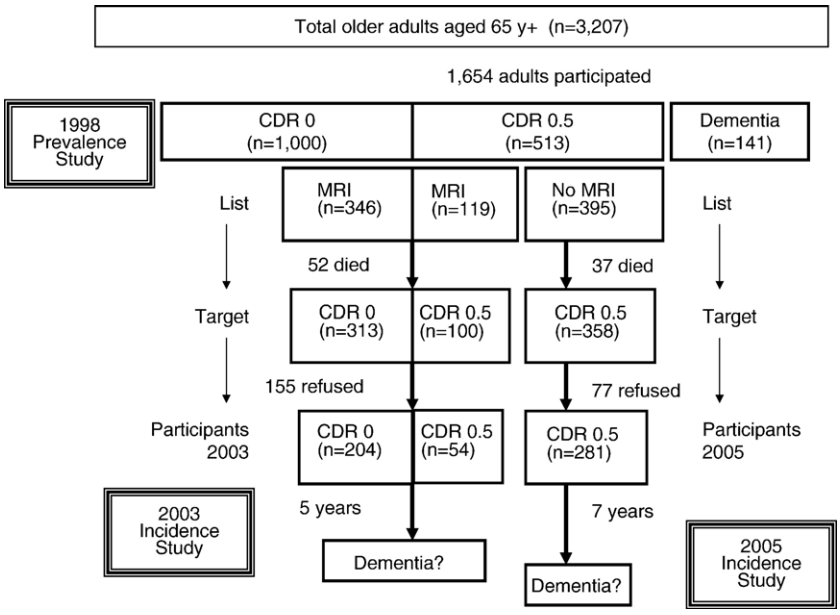

Fig. 1. CDR = clinical dementia rating, MRI = magnetic resonance imaging.

people (9.4%) had died due to cancer (29.0%), stroke (12.9%), or cardiac diseases (22.6%). Therefore, 358 CDR 0.5 people were targeted and a total of 281 CDR 0.5 adults (78.5%) agreed to participate in Study 2005 (defined as Participants 2005).

The 232 eligible people who refused to participate gave main reasons as old age, physical reasons, and not wanting to participate in brain research. At baseline, responders in Study 2003 had a higher rate of CDR 0 (65.2% vs. 54.0%, $p=0.045$), were more educated (mean: 8.3 vs. 7.8 years, $p=0.007$), and had higher MMSE scores (mean: 26.1 vs. 25.0, $p=0.001$) than the non-responders. Responders in Study 2005 also had higher MMSE scores (mean: 23.6 vs. 22.6, $p=0.032$).

All were used in Analysis 1 and Participants 2003 was used in Analyses 2 and 3 (see below). Written informed consent was obtained from all the healthy and the CDR 0.5 participants, and from the family of the CDR 0.5 participants and those with dementia. The Ethical Committee of the Tajiri SKIP Center approved the study.

2.2. Demographics, lifestyle and vascular risk factors

Demographic variables included age (years), sex (men/women), and educational level (years), and the lifestyle variables examined were alcohol intake (the average number of glasses of Japanese Sake per day), smoking (the average number of cigarette per day), and social support network. The social support network was evaluated using the number of people that the participants could ask for help with emotional and financial issues [22]. Past medical histories included assessment of the presence of hypertension, hyperlipidemia, ischemic hear disease, atrial fibrillation, and diabetes mellitus; each disease was diagnosed using established criteria [23]. The medical records and medication review in the town were used to confirm the participants' medical histories. Board-certified neurologists (K.M, H.I) examined all participants in this study especially for focal neurological signs for diagnosis of VaD (see below).

2.3. CDR assessment

A clinical team comprising medical doctors and public health nurses determined the CDR blindly to the cognitive tests as follows: before being interviewed by the doctors, public health nurses visited the participants' homes to evaluate their daily activities. Observations by family regarding the participants' lives were described in a semi-structured questionnaire; for participants who lived alone, public health nurses visited them frequently to evaluate their daily lives. The participants were interviewed by doctors to assess episodic memory, orientation, etc. Finally, with reference to the information provided by family, the participants' CDR stages were decided at a joint meeting. A reliable Japanese version of the CDR Work Sheet [24] was established, and dementia was diagnosed based on DSM-IV criteria (American Psychiatric Association, 1994). Two of the authors (K.M, M.M) were certified as a CDR rater at the Alzheimer's Disease Research Center Memory and Aging Project, Washington University School of Medicine.

2.4. Cognitive assessment

A team of trained psychologists performed cognitive tests blindly to the diagnosis and CDR. These tests used included the Mini-Mental State Examination (MMSE) [25] and Cognitive Abilities Screening Instrument (CASI) [26]. The CASI contains 9 domains: *long-term memory (remote memory), short-term memory (recent memory), attention, concentration/mental manipulation*, *orientation*, *visual construction, abstraction and judgment*, *list-generating fluency*, and *language*.

2.5. MRI

The method for assessment of MRI has been described previously [27], summarized as follows. We used the 1.5T-MRI (SIERRA, GE-Yokogawa, Japan), imaging sections being axial, coronal, sagittal, and the long axis of the hippocampus. Using T_1-weighted images (TR/TE=400/14), we performed a 4-grade evaluation for cortical, hippocampal and amygdala atrophy, and ventricular enlargement. Using T_2-weighted images (TR/TE=3000/90), we also performed a 4-grade evaluation periventricular hyperintensity (PVH) identified as symmetrical lesions adjacent to the lateral ventricles, and white matter high signal (WMHS) intensity observed as asymmetrical lesions not adjacent to the ventricles. A lesion with a high T_2 and a low T_1 signal intensities in the same area was regarded as an "état criblé" when its maximum dimension was under 4 mm, and as an infarction when the size was 4 mm or larger.

The images were visually evaluated by 3 teams, consisted of 5 neurologists (2 neurologists for 2 teams, and 1 senior neurologist). We used the evaluation point which was consistent with more than 2 teams. For example of atrophy evaluation, suppose the points were 2, 3, 3, then we regard it as point 3. As for the numbers of CVD, we used the mean numbers of the closest 2 teams. Consistency rate of closest 2 teams was calculated by the equation below and the rate was more than 95%.

$$\text{Rate of consistency} = 1 - (x-y) \div (x+y)/2$$

2.6. Outcome and dementing diseases

The outcome was the dementia (DSM-IV and CDR 1+). A clinical team comprising medical doctors and public health nurses determined the follow-up CDR blindly to the previous CDR stages, baseline cognitive test scores, and MRI data. The procedure was the same as previously described.

In Participants 2003, for which MRI information was available, dementing diseases were also diagnosed

according to the following criteria: NINCDS-ADRDA [28] for probable AD; NINDS-AIREN [29] for possible AD with CVD; NINDS-AIREN for probable VaD; the consensus guidelines for diagnosis of dementia with Lewy bodies (DLB) [30], and the Lund and Manchester Groups criteria for frontotemporal dementia [31].

Based on a previous study [32], the presence of at least one of the following focal neurological signs was used for diagnosis of VaD: hemianopia, lower facial weakness, dysarthria, motor or sensory hemisyndrome, hemiplegic gait, or a positive Babinski sign. Since criteria for VaD have been reported to show poor interchangeability [32], we used probable criteria only.

According to NINDS-AIREN, we did not use the concept for "mixed dementia," and thus the patients were diagnosed with "AD with CVD" provided that the vascular effect on dementia was considered too ambiguous to diagnose VaD.

3. Analyses

3.1. Analysis 1: Overall dementia incidence (Participants 2003 and 2005) and dementing diseases (Participants 2003)

Age- and sex-specific rates of onset of all dementia per 1000 persons-years in the non-dementia population (CDR 0 in Participants 2003 plus CDR 0.5 in both Participants 2003 and 2005) were calculated with reference to the person-years, i.e., the numbers of people multiplied by follow-up periods (5 or 7 years). In Participants 2003, for which MRI information was available, dementing diseases were also diagnosed as earlier described.

3.2. Analysis 2: Predicting CDR 0.5 decliners to dementia using baseline characteristics (Participants 2003)

Using Participants 2003, logistic regression analyses were performed by setting the dependent variable as the CDR 0.5 decliner to dementia (DSM-IV and CDR 1+). Regarding dementing diseases, two most common diseases were mainly analyzed, i.e., AD and VaD; AD included AD with CVD. Other dementing conditions such as DLB or FTD were not analyzed due to small sample.

Two analyses were performed using AD or VaD as the dependent variables. The following independent variables were used: demographics and lifestyle, past medical histories, MMSE and 9 CASI domains scores, and MRI findings. The effect of the CDR Sum of Boxes score was also analyzed.

For possible cumulative effect of each risk, we also performed stepwise multiple regression analysis.

4. Results

4.1. Analysis 1

Overall, 3.9% (8/204) of CDR 0 and 37.0% (20/54) of CDR 0.5 people in Participants 2003 developed dementia during the 5-year period, whereas 40.2% (113/281) of Participants 2005 (CDR 0.5) developed dementia during the 7-year period. Among the participants initially assessed as CDR 0.5, 1.8% (1/54) of Participants 2003 (CDR 0.5) and 7.8% (22/281) of Participants 2005 (CDR 0.5) were assessed as CDR 0 in this study.

Table 1 shows age- and sex-specific rates of onset of all dementia per 1000 persons-years in the non-dementia population stratified by CDR stages (CDR 0 in Participants 2003 plus CDR 0.5 in both Participants 2003 and 2005). Incidence rates were calculated with reference to the person-years, i.e., the numbers of people multiplied by follow-up periods (5 or 7 years).

For CDR 0, no participants declined to dementia in the 65–69 years groups. As for CDR 0.5, older adults had higher incidence rates of dementia, with younger old women having low rates and older old women having the highest rates.

Table 1
Age- and sex-specific rates of dementia per 1000 person-years observations of the CDR 0 (a) and CDR 0.5 (b) populations

	Sex	Age group (years)	Person-years	No. of cases	Rate (‰)	(95% CI)
(a) CDR 0	Men	65–69	305 a	0	0	0
		70–79	170	1	5.9	(0–17.4)
		80+	120	2	16.7	(0–39.6)
	Women	65–69	245	0	0	0
		70–79	270	2	7.4	(0–17.6)
		80+	180	3	16.7	(0–35.4)
(b) CDR 0.5	Men	65–69	206 b	8	38.8	(12.4–65.2)
		70–79	436	21	48.2	(28.1–68.3)
		80+	177	16	90.4	(48.2–100)
	Women	65–69	184	1	5.4	(0–16.0)
		70–79	945	56	59.3	(44.3–74.3)
		80+	289	31	107.3	(19.7–91.1)

a: Regarding 65–69 years CDR 0 men, 61 people were followed for 5 years, thus the person–year was 305 (61 * 5).
b: As for 65–69 years CDR 0.5 men, 9 people were followed for 5 years and 23 people were followed for 7 years, thus the person–year was 206 (9 * 5 + 23 * 7).
CDR = clinical dementia rating, CI = confidence interval.

For dementing diseases, 42.9% of participants who declined into dementia developed AD, followed by AD with CVD (17.9%), VaD (17.9%), and DLB (7.1%). Other forms of dementia included brain tumors ($n=2$), metabolic dementia ($n=1$), and subdural hematoma ($n=1$).

4.2. Analysis 2

Age was found to be a significant predictive factor for a decline to all dementia and to AD (Odds Ratio=1.192, $p<0.001$). However, no lifestyle-associated activities showed an association with decline, and neither did the presence of vascular risk factors. Namely, the odds ratios (95% CI, p value) were: alcohol intake, 0.77 (0.36–1.64, $p=0.495$); smoking, 1.00 (0.99–1.00, $p=0.781$); social support network, 1.37 (0.75–2.51, $p=0.309$); hypertension, 1.22 (0.57–2.72, $p=0.584$); hyperlipidemia, 1.24 (0.56–2.72, $p=0.597$); ischemic heart disease, 1.63 (0.81–3.29, $p=0.169$); atrial fibrillation, 1.78 (0.11–30.17, $p=0.690$); and diabetes mellitus, 0.89 (0.39–2.06, $p=0.791$).

In addition, we had previously performed psychosocial intervention for CDR 0.5 people and reported positive findings [33]. Since almost half of the participants had received such intervention during the study period, the effect was analyzed retrospectively; however, no significant effect was noted (data not shown).

Table 2 shows the baseline cognitive test scores for participants who developed all dementia and AD alone. The scores for general cognitive function, memory, and orientation were already low at baseline for participants who developed AD, and the score for frontal function was lower in participants who declined into dementia of all types. This latter result may have been affected by inclusion of VaD patients.

Table 3 illustrates the odds ratios obtained in logistic regression analysis of cognitive test scores (MMSE and CASI) and MRI for predicting AD and VaD. For participants who developed AD, the baseline MMSE and all CASI domains except for *visual construction* and *language* were found to predict further decline. In MRI, generalized atrophy was associated with a further decline to AD, whereas no relationships were noted for PVH and CVD.

Regarding VaD, the baseline MMSE and CASI domains *long-term memory* and *list-generating fluency* were predictive. For MRI, the frontal, temporal, and hippocampal atrophy, the PVH grade and the number of CVD were significant predictors of decline.

The relationship with the CDR Sum of Boxes score was as follows: of participants with a score of 2.0+, 33.3% ($n=4$) and 16.7% ($n=2$) progressed to AD and VaD, respectively; for scores of 1.0 and 1.5, these data were 17.8% ($n=8$) and 2.2% ($n=1$), respectively; and for scores of 0 and 0.5, 2.5% ($n=5$) and 1.0% ($n=2$), respectively.

For possible cumulative effect of each factor, we performed stepwise multiple regression analyses for all dementia (due to sample size), and found as follows.

Step 1: CASI total score ($df=1$, OR=0.83, $p=0.005$) was noted to be significant.

Table 2
Cognitive test scores of converters to all dementia and Alzheimer's disease at baseline

	Participants 2003						Participants 2005		
	Non-converter	Converter					Non-converter	Converter	
		All dementia	p value[a]	Alzheimer	F value	p value[b]		All dementia	p value[a]
n	230	27		17[c]			168	113	
MMSE	26.5	22.6	<0.001	22.8	16.65	<0.001	24.3	22.4	<0.001
CASI									
Total score	88.4	77.4	<0.001	78.1	22.41	<0.001	81.5	76.9	<0.001
Long-term memory	10.0	9.5	0.052	9.5	15.26	<0.001	9.9	9.8	0.259
Short-term memory	10.2	8.3	<0.001	8.3	11.28	<0.001	8.4	6.8	<0.001
Attention	6.7	5.3	0.003	5.1	4.56	–	5.9	5.4	0.259
Concentration/ mental manipulation	7.9	6.1	0.002	5.9	7.72	<0.001	7.1	6.6	0.300
Orientation	17.7	16.7	0.011	16.6	9.44	<0.001	17.4	17.0	0.057
Visual construction	9.6	9.5	0.413	9.8	1.03	1.000	9.5	9.1	0.010
Abstraction and judgment	8.7	6.8	<0.001	6.8	7.96	<0.001	7.3	6.7	0.016
List-generating fluency	7.6	5.8	<0.001	6.3	7.00	0.022	7.1	6.0	<0.001
Language	9.8	9.3	0.074	9.6	5.05	–	9.6	9.4	0.361

Shown are the means.
CDR = clinical dementia rating, SOB = sum of boxes, MMSE = mini mental state examination, CASI = cognitive abilities screening instrument.
[a] t-test for two groups (non-converters vs. converters to all dementia).
[b] Post hoc tests between two groups (non-converters vs. Alzheimer) after finding a significant ($p<0.001$) group effect among three groups (non-converters, Alzheimer, and other dementias) by one-way ANOVA with the covariances of age and education.
[c] 17 Alzheimer patients are included in the 27 all dementia.

Table 3
Odds rations by logistic regression analyses of cognitive test scores and MRI findings for predicting AD and VaD

	AD		VaD	
	OR	*p* value	OR	*p* value
Age	1.21	****	1.18	*
Sex	0.15	*	5.15	ns
Education	0.90	ns	0.58	*
CDR sum of boxes	4.53	****	2.59	*
MMSE	0.69	****	0.71	***
CASI total score	0.85	****	0.86	***
Long-term memory	0.17	*	0.17	**
Short-term memory	0.61	****	0.71	ns
Attention	0.63	****	0.63	ns
Concentration/mental manipulation	0.65	****	0.87	ns
Orientation	0.67	**	0.84	ns
Visual construction	0.97	ns	0.88	ns
Abstraction and judgment	0.57	****	0.64	ns
List-generating fluency	0.70	***	0.42	**
Language	0.75	ns	0.73	ns
MRI findings				
Frontal lobe				
Rt	2.28	***	3.18	*
Lt	2.44	***	3.17	*
Temporal lobe				
Rt	3.74	****	7.93	****
Lt	4.24	****	7.59	***
Hippocampus				
Rt	2.89	****	4.06	**
Lt	3.31	****	3.57	*
Amygdala				
Rt	2.26	**	2.84	ns
Lt	2.36	**	2.85	*
Parietal lobe				
Rt	3.54	****	2.05	ns
Lt	4.11	****	1.94	ns
Occipital lobe				
Rt	1.75	ns	2.64	ns
Lt	1.75	ns	2.64	ns
Lateral ventricle				
Rt	2.24	**	3.08	ns
Lt	2.32	**	2.90	ns
PVH	0.78	ns	4.14	***
WMH				
Rt	1.07	ns	4.04	*
Lt	1.02	ns	3.27	*
Mild CVD				
Rt	0.90	ns	1.36	ns
Lt	0.87	ns	2.12	*
Large CVD				
Rt	0.00	ns	6.00	****
Lt	0.71	ns	4.48	****

MRI = magnetic resonance imaging, AD = Alzheimer's disease, VaD = vascular dementia, CDR = clinical dementia rating, MMSE = mini-mental state exam, CASI = cognitive abilities screening instrument, PVH = periventricular hyperintensity, WMH = white matter hypersignal, CVD = cerebrovascular diseases * $p<0.05$, ** $p<0.01$, *** $p<0.005$, **** $p<0.001$.

Step 2: CASI total score ($df=1$, OR=0.84, $p=0.0174$) and left parietal lobe atrophy ($df=1$, OR=8.30, $p=0.0122$) were found to be significant.

5. Discussion

5.1. Methodological issues

We should first mention some limitations of the study. To assess incidence one would better to follow the entire conception cohort. From the 497 people who underwent MRI in 1998, dementia status in 2003 was assessed in 258. Unfortunately no information was available on the recent cognitive status of the 239 people who died before 2003 or refused re-examination. Since death and drop-out is likely related to cognitive status, this is likely the explanation for the low incidence rates. Also, we performed an evaluation at only 2 points, and annual evaluations as originally planned. The earlier described administrative situation prevented us from performing the study with our original design. In the cognitive tests, assessments such as the WMS-R for memory and the WAIS-R for general intelligence would have provided more information, but the time limitation for assessing older residents in a community setting prevented performance of more extensive tests. However, we consider that the CASI provided sufficient useful information.

5.2. Dementia incidence and dementing diseases

According to previous studies, the yearly incidence of dementia ranges varied but all consistently shows a higher incidence in older age [1–5]. In comparison, our incidence was relatively low, close to the Framingham [1] and Rochester [2] studies. We suggest that the high mortality rate of the CDR 0.5 with CVD group (data not shown) might have caused an underestimation of the incidence, since these people died before onset. In addition, the conversion rate from MCI to normal was reported to be about half [34]. Our results showed a lower conversion rate, but since we ruled out a depressive state and other possible diseases which might affect cognitive function, and assessed the CDR extensively, we consider that our CDR 0.5 population was not masked by a healthy population.

Regarding dementing diseases, about 60% of our participants developed AD. Based on the prevalence study in 1998, we reported that the most common dementing disease in Japan was not VaD, as previously thought; rather, AD with CVD was more common. Several vascular risk factors for AD were reported [9–11], resulting in some researchers advocating that AD should be thought of as a 'vascular disease' [35]. However, most studies have not performed MRI for distinguishing 'pure' AD without CVD from AD with CVD, and such vascular risk factors might be associated with concomitant CVD. A long-term follow-up study from middle age is required to clarify this issue.

Our findings that the CDR 0.5 with higher Box scores had a higher incidence are in agreement with the study of Morris et al. [36], in which all participants in the higher Box scores converted to clinical AD. Daly et al. [37] also showed those with higher Boxes scores had higher conversion rates. Our

progression rate to dementia was somewhat lower than previous studies; this may have been because our participants were community residents and did not always meet the criteria for very mild AD.

5.3. Predicting CDR 0.5 decliners using baseline characteristics

We were unable to identify any demographic factors or lifestyle-associated diseases that predicted a further decline into dementia, except for a higher age. Previous studies reported that risk factors include age, hypertension, diabetes mellitus, cardiovascular diseases, etc. as earlier described [9–13]. These effects might have been masked due to the relatively small number in the study, or the higher prevalence of hypertension in Tajiri (data not shown). However, several factors discussed in previous studies were based on mid-life data, whereas our data suggest that vascular risk factors detected in older adults may not affect the incidence of dementia; a longitudinal study from middle age would be of interest to examine this issue further.

A stronger social support network or psychosocial intervention may protect against dementia [9]. However, the results in support of this conclusion were not based on a randomized controlled trial (RCT) including a placebo and negative controls. In this study, we found that psychosocial intervention did not prevent the incidence of dementia; however, we used a retrospective analysis, and a further investigation using a follow-up RCT design is required to examine this relationship.

Previous studies showed that participants with lower cognitive function had a higher rate of progression to AD [38]. MCI participants with a more atrophied hippocampus showed greater progression to AD [39], and our results for AD supported these findings and suggested that CDR 0.5 decliners to AD already had very mild AD changes in the brain. Given this conclusion, we are planning to analyze the significance of a combination of cognitive tests for early screening of CDR 0.5 decliners. We analyzed a cumulative effect of factors with the multiple regression analyses, and found that the global cognitive decline (CASI total score) was the strongest predictor. For additional effect of left parietal atrophy, statistical artifact cannot be ruled out. As for no additional effect of hippocampal atrophy, we consider that the effect of CASI total score was strong so that the effect of atrophy might be masked.

In contrast to AD, the progression to VaD is controversial [40]. We found the PVH grade and the number of CVD, with frontal function, significantly predicting a further decline to VaD. Some patients were diagnosed as subcortical VaD [41]. A further investigation using larger sample would be needed to clarify the topic.

6. Conclusions

Our findings suggest that observation of functional decline of older adults is important for early detection of CDR 0.5 decliners to dementia. A comprehensive medical and welfare system including the CDR, cognitive tests, and MRI, is recommended in community-based health policy planning for dementia.

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