





ORIGINAL ARTICLE

EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Olfactory-cognitive index distinguishes involvement of frontal lobe shrinkage, as in sarcopenia from shrinkage of medial temporal areas, and global brain, as in Kihon Checklist frailty/dependence, in older adults with progression of normal cognition to Alzheimer's disease

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Aim: Olfactory impairment as a prodromal symptom, as well as sarcopenia, frailty and dependence as geriatric syndromes, is often associated with cognitive decline in older adults with progression of Alzheimer's disease. The present study aimed to evaluate the associations of olfactory and cognitive decline with these geriatric syndromes, and with structural changes of the brain in older adults.

Methods: The participants were 135 older adults (47 men and 88 women, mean age 79.5 years), consisting of 64 with normal cognition, 23 with mild cognitive impairment and 48 with Alzheimer's disease. Olfactory function was evaluated by the Open Essence odor identification test. Shrinkage of the regional brain was determined by magnetic resonance imaging.

Results: Logistic regression analysis with Open Essence, Mini-Mental State Examination, age and sex as covariates showed higher olfactory-cognitive index (|coefficient for Open Essence (a) / coefficient for Mini-Mental State Examination (b)|) in participants with sarcopenia (Asia Working Group for Sarcopenia), and lower values of (|a/b|) in participants with Barthel Index dependence, Kihon Checklist frailty, Lawton Index dependence and support/care-need certification as objective variables. Logistic regression analysis adjusted by age and sex also showed significant shrinkage of the frontal lobe in participants with AWGS sarcopenia, especially in women, and shrinkage of the medial temporal areas and global brain in participants with Kihon Checklist frailty/dependence.

Conclusions: Olfactory-cognitive index (|a/b|) might be a useful tool to distinguish involvement of frontal lobe shrinkage, as in sarcopenia from shrinkage of the medial temporal areas, and global brain, as in frailty/dependence, in older adults with progression of normal cognition to Alzheimer's disease. *Geriatr Gerontol Int* 2021; 21: 291–298.

Keywords: clinical medicine, geriatric medicine, nervous system disorders, otolaryngology and sensory organ surgery.

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Introduction

Olfactory decline occurs early in the course of Alzheimer's disease (AD), and sometimes appears as a prodromal marker preceding the onset of other neurological symptoms,^{1,2} being significantly correlated with a decline of the Mini-Mental State Examination (MMSE).² Furthermore, olfactory impairment meets the criteria as one of five combined early markers that strongly predicted conversion from mild cognitive impairment (MCI) to AD.³ This parallel running of olfactory and cognitive decline in the course of AD progression might be caused by the unique anatomical organization of the brain olfactory processing network with intimate structural overlap with the limbic systems mediating emotion and memory, located between the primary (piriform) and secondary (orbitofrontal) olfactory cortexes.⁴

Besides the olfactory decline, common geriatric syndromes, including sarcopenia,^{5,6} decline of Barthel Index as an indicator of basic activities of daily living (ADL) and Lawton Index as an indicator of instrumental ADL (IADL),⁷ and Kihon Checklist frailty⁸ often occur in the course of AD progression. Although AD is characterized by progressive cognitive decline accompanied by medial temporal lobe atrophy, structural changes of the brain regions responsible for these common geriatric syndromes are not well elucidated.^{9,10}

To delineate the difference between the associations of olfactory and cognitive function with the occurrence of these geriatric syndromes in the course of AD progression, we newly adopted

the olfactory-cognitive index, calculated as the absolute value of the ratio of coefficients for olfactory function to that for MMSE in the logistic regression equation with occurrence of these geriatric syndromes as objective variables. We here report our attempt at a cross-sectional study to clarify the associations of the olfactory-cognitive index with these common geriatric syndromes, and with respective structural changes of the brain determined by magnetic resonance imaging (MRI) in older adults in the course of normal cognition (NC) to AD progression.

Methods

Study population

The present study included 135 outpatients with a mean (\pm SD) age of 79.5 ± 6.8 years (range 65–93 years), including 64 older adults with NC, 23 with MCI and 48 with AD who attended the outpatient clinic of the Center for Comprehensive Care on Memory Disorders at Kanazawa Medical University Hospital, Uchinada, Japan. Patients with probable AD had to meet the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition.¹¹ All the outpatients underwent general physical and neurological examinations, laboratory tests, and brain MRI evaluation to exclude other potential causes of dementia. Cognitive decline was assessed by the MMSE. Patients with probable AD were divided into MCI (MMSE score 27–24) and AD (MMSE score ≤ 23). Individuals with a history of stroke, Parkinson's disease, dementia with

Table 1 Baseline characteristics of groups according to sex, and olfactory and cognitive functions

	Total				Olfactory function			Cognitive function		
	Women [†] n = 88	Men n = 47	Normosmia [†] n = 34	Dyosmia ^{††} n = 44	Anosmia n = 57	Normal [†] n = 64	MCI ^{††} n = 23	AD n = 48		
<i>Demographics</i>										
Age (years)	79.5 ± 6.8	79.8 ± 6.2	74.9 ± 5.1	80.3 ± 6.5***	81.6 ± 6.7***	77.2 ± 5.9	81.3 ± 8.1*	81.7 ± 6.3***		
Women, n (%)	88 (65.2%)		24 (70.6%)	30 (68.2%)	34 (59.6%)	40 (62.5%)	16 (69.6%)	32 (66.7%)		
<i>Geriatric indexes</i>										
Open Essence range	12-0		12-7	6-4	3-0					
Open Essence (12)	4.75 ± 3.01	4.49 ± 2.87	8.18 ± 1.67	4.91 ± 0.80***	1.77 ± 1.15****	6.14 ± 2.50	3.55 ± 2.24***	2.66 ± 2.26***		
MMSE range	30-11					30-28	27-24	23-11		
MMSE (30)	25.2 ± 5.2	25.3 ± 5.0	28.7 ± 3.2	25.8 ± 4.7***	22.2 ± 5.1****	29.5 ± 0.8	25.6 ± 0.9***	19.0 ± 3.3****		
AWGS sarcopenia, n (%)	53 (39.3%)	15 (31.9%)	9 (26.5%)	15 (34.9%)	29 (50.9%)*	16 (25.0%)	15 (65.2%)**	22 (45.8%)*		
ASMI <cut-off, n (%)	75 (55.6%)	23 (48.9%)	17 (50.0%)	21 (48.8%)	37 (64.9%)	29 (45.3%)	19 (82.6%)**	27 (56.3%)		
Grip strength <cut-off, n (%)	60 (44.4%)	15 (31.9%)*	12 (35.3%)	19 (43.2%)	29 (50.9%)*	21 (32.8%)	13 (56.5%)*	26 (54.2%)**		
Walking speed <0.8 m/s, n (%)	65 (48.1%)	25 (53.2%)	11 (32.4%)	21 (47.7%)	33 (57.9%)*	21 (32.8%)	12 (52.2%)	32 (66.7%)**		
Barthel ADL dependence (<85/100), n (%)	25 (18.5%)	8 (17.0%)	2 (5.9%)	7 (15.9%)	16 (28.1%)**	3 (4.7%)	4 (17.4%)	18 (37.5%)***		
KCL frailty (≥8/25), n (%)	61 (45.2%)	19 (40.4%)	10 (29.4%)	18 (40.9%)	33 (57.9%)**	18 (28.1%)	9 (39.1%)	34(70.8%)****		
Lawton IADL dependence (<4/5), n (%)	70 (51.9%)	25 (53.2%)	8 (23.5%)	21 (47.7%)*	41 (71.9%)****	15 (23.4%)	14 (60.9%)**	41 (85.4%)****		
Support/care-need certification, n (%)	39 (28.9%)	9 (19.1%)	3 (8.8%)*	13 (29.5%)*	23 (40.4%)**	7 (10.9%)	8 (34.8%)*	24 (50.0%)***		
<i>Remaining regional brain</i>										
Olfactory bulb (left + right, mm ³)	72.6 ± 24.7	73.1 ± 22.3	81.2 ± 25.8	80.6 ± 28.2	61.3 ± 15.4****	83.0 ± 28.5	71.3 ± 14.6	58.5 ± 12.3****		
Medial temporal areas (%)	62.2 ± 34.8	64.0 ± 35.3	79.3 ± 28.0	65.7 ± 31.1*	50.0 ± 36.7***	83.6 ± 21.0	55.7 ± 33.0***	39.1 ± 33.7****		
Frontal lobe (%)	71.6 ± 7.6	73.0 ± 7.5	73.9 ± 6.8	72.2 ± 7.6	69.4 ± 7.7*	74.2 ± 7.1	69.1 ± 7.5*	68.9 ± 7.3**		
Global brain gray matter (%)	94.4 ± 3.2	94.6 ± 2.8	95.9 ± 2.1	94.5 ± 3.8	93.4 ± 2.9****	95.9 ± 2.1	94.7 ± 2.6*	92.3 ± 3.5****		
White matter lesions (%)	1.96 ± 2.33	2.11 ± 2.52	1.16 ± 1.80	2.17 ± 2.48*	2.28 ± 2.43**	1.36 ± 1.85	2.02 ± 2.52	2.70 ± 2.61**		

Results are expressed as mean ± S.D or n (%). Mann-Whitney U-test or χ^2 -test (or Fisher's exact test when required) was used. *P < 0.05, **P < 0.01, ***P < 0.001 versus [†]group, and ^{††}P < 0.05, ^{†††}P < 0.001 versus ^{††††}group, for each category.

Cut-off values for appendicular skeletal muscle mass index (ASMI) were 5.7 kg/m² for women and 7.0 kg/m² for men, and those for grip strength were 18 kg for women and 26 kg for men. AD, Alzheimer's disease; ADL, activities of daily living; AWGS, Asian Working Group for Sarcopenia; IADL, instrumental activities of daily living; KCL, Kihon Checklist; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.

Lewy bodies, major depression, or olfactory or sinonasal diseases were excluded. We also excluded outpatients using a wheelchair.

Olfactory function

Olfactory identification was evaluated using a card-type olfactory test, the Open Essence (OE) test, with 12 odorants (FUJIFILM Wako Pure Chemical, Osaka, Japan).¹² According to the OE score, participants were divided into normosmia (OE score 12–7), dysosmia (OE score 6–4) and anosmia (OE score ≤3).

Common geriatric syndromes

Appendicular skeletal muscle mass index (ASMI) was assessed by bioimpedance analysis using an InBody720 (BioSpace, Seoul, Korea) with cut-off values of <5.7 kg/m² for women and <7.0 kg/m² for men, according to the recommendations of the Asia Working Group for Sarcopenia (AWGS).¹³ Usual walking speed was measured with a Walk-way MW1000 (Anima Corp, Tokyo, Japan), with cutoff value of <0.8 m/s.¹³ Grip strength was measured with a Smedley's hand dynamometer, with cutoff value of <18 kg for women and <26 kg for men.¹³ AWGS sarcopenia was defined as both ASMI <cut-off value plus usual walking speed <cut-off value and/or grip strength <cut-off value. Barthel ADL functional dependence was defined as ≤85/100.¹⁴ Kihon Checklist frailty was defined as ≥8/25.⁸ Among the eight items of the Lawton IADL Scale,⁷ five items including ability to use a telephone, ability to do shopping, independent travel, ability to manage own-medication, and ability to handle finances were selected as gender-common items. Lawton IADL dependence was defined as ≤4/5.

Brain MRI imaging

MRI imaging was determined using a 1.5-T MRI unit (Vantage Titan; Canon Medical Systems, Otawara, Japan). Olfactory bulb volume was measured from 2-mm slices of the olfactory bulb.¹⁵ Frontal lobe remaining rate was measured as frontal brain area/intracranial frontal space on an MRI image in which the lateral ventricle was visualized with the maximum size.¹⁶ Remaining rates of bilateral medial temporal areas including the entorhinal cortex (MTA-ERC) and global brain gray matter were determined using the voxel-based specific regional analysis system for Alzheimer's disease.¹⁷ White matter lesions including periventricular hyperintensity and deep white matter hyperintensity were measured using ImageJ (National Institute of Health, Bethesda, MD, USA) in the same MRI image as used for the frontal lobe remaining rate.

Statistical analysis

We used the Mann-Whitney *U*-test for the distribution of ordinal variables and χ^2 -test (Fisher's exact test when required) for categorical variables to compare the two groups. Spearman's rank correlation analysis was used for determination of the link between two parameters. Multivariate logistic regression analysis was used to determine the associations of olfactory and cognitive impairment with common geriatric syndromes, and the associations of specific shrinkage and/or lesions of the brain with these geriatric syndromes, adjusted by age and sex. Data were analyzed by SPSS Windows (version 25.0; Chicago, IL, USA).

Table 2 Association of age, olfactory function and cognitive function with geriatric index in total participants, in women and in men

	Total (n = 135)		Women (n = 88)		Men (n = 47)	
	vs OE	vs MMSE	vs OE	vs MMSE	vs OE	vs MMSE
<i>Demographics</i>						
Age (years)	-0.401 ^{###}	-0.378 ^{###}	-0.406 ^{###}	-0.355 ^{###}	-0.351 [#]	-0.382 ^{##}
<i>Geriatric indexes</i>						
Open Essence (/12)		0.634 ^{###}		0.631 ^{###}		0.656 ^{###}
MMSE (/30)	0.634 ^{###}		0.631 ^{###}		0.656 ^{###}	
AWGS sarcopenia, n (%)	-0.276 ^{##}	-0.259 ^{##}	-0.302 ^{##}	-0.289 [#]	-0.268	-0.195
ASMI <cut-off, n (%)	-0.184 [#]	-0.120	-0.230 [#]	-0.237 [#]	-0.181	-0.048
Grip strength <cut-off, n (%)	-0.314 ^{##}	-0.405 ^{###}	-0.288 [#]	-0.397 ^{###}	-0.494 ^{##}	-0.412 ^{##}
Walking speed <0.8 m/s, n (%)	-0.232 [#]	-0.338 ^{###}	-0.222 [#]	-0.307 ^{##}	-0.287 [#]	-0.416 ^{##}
Barthel ADL dependent (≤85/100), n (%)	-0.231 [#]	-0.435 ^{###}	-0.219 [#]	-0.371 ^{###}	-0.331 [#]	-0.575 ^{###}
KCL frailty (≥8/25), n (%)	-0.329 ^{###}	-0.455 ^{###}	-0.343 ^{##}	-0.465 ^{###}	-0.323 [#]	-0.431 ^{##}
Lawton IADL dependent (≤4/5), n (%)	-0.442 ^{###}	-0.618 ^{###}	-0.397 ^{###}	-0.601 ^{###}	-0.539 ^{###}	-0.667 ^{###}
Support/care-need certification, n (%)	-0.274 ^{##}	-0.426 ^{##}	-0.274 [#]	-0.381 ^{###}	-0.360 [#]	-0.524 ^{###}
<i>Remaining regional brain</i>						
Olfactory bulb (left + right, mm ³)	0.477 ^{###}	0.506 ^{###}	0.529 ^{###}	0.559 ^{###}	0.411 ^{##}	0.431 ^{##}
Medial temporal areas (%)	0.426 ^{###}	0.595 ^{###}	0.390 ^{##}	0.590 ^{###}	0.466 ^{##}	0.622 ^{###}
Frontal lobe (%)	0.200 [#]	0.302 ^{###}	0.221 [#]	0.385 ^{###}	0.155	0.269
Global brain gray matter (%)	0.429 ^{###}	0.575 ^{###}	0.403 ^{###}	0.572 ^{###}	0.496 ^{##}	0.614 ^{###}
White matter lesions (%)	-0.271 ^{##}	-0.332 ^{###}	-0.273 [#]	-0.388 ^{###}	-0.275	-0.193

Results are expressed as Spearman's ρ by Spearman's rank correlation analysis.

[#]*P*<0.05.

^{##}*P*<0.01.

^{###}*P*<0.001.

AD, Alzheimer's disease; ADL, activities of daily living; ASMI, appendicular skeletal muscle mass index; AWGS, Asian Working Group for Sarcopenia; IADL, instrumental activities of daily living; KCL, Kihon Checklist; MMSE, Mini-Mental State Examination.

Ethical considerations

The clinical research ethics committee of Kanazawa Medical University Hospital reviewed and approved all study procedures (receipt No. I361). All participants gave written informed consent.

Results

Geriatric syndrome and brain structural changes according to sex and olfactory and cognitive decline

Table 1 summarizes the baseline characteristics of the participants according to sex and olfactory and cognitive decline. Women had a significantly higher mean frontal lobe remaining rate compared with men. Compared with normosmia participants, anosmia participants had significantly higher mean age, lower MMSE score, higher prevalence of sarcopenia, Barthel ADL dependence, KCL frailty, Lawton IADL dependence and support/care-need certification, greater shrinkage of all brain regions, and an increase in white-matter lesions. Similarly, compared with participants with NC, AD patients had a significantly lower OE score and significantly higher prevalence of these geriatric syndromes, greater shrinkage of all brain regions and larger area of white matter lesions. Among these variables, a significant decline of OE score, significant increase in the prevalence of sarcopenia, as well as ASMI less than the cut-off and

grip strength less than the cut-off, and significant shrinkage of the frontal lobe occurred mainly with progression from NC to MCI, and no further significant change was observed with progression from MCI to AD. However, significant shrinkage of the olfactory bulb, MTA-ERC and global brain was observed with progression from NC to MCI and further from MCI to AD (Table 1).

Spearman's rank correlation analysis showed that olfactory and cognitive decline significantly correlated with each other ($\rho = 0.634$, $P < 0.001$), and that both parameters were similarly and significantly associated with a higher prevalence of geriatric syndromes, greater shrinkage of all brain regions and larger area of white matter lesions, but no significant association of MMSE decline with ASMI less than the cut-off in total participants, or of either OE or MMSE with sarcopenia, ASMI less than the cut-off, frontal lobe shrinkage rate or white matter lesions in men (Table 2).

Olfactory-cognitive index ($|a/b|$)

To delineate the difference in associations of olfactory and cognitive decline with these geriatric syndromes, we newly adopted the olfactory-cognitive index ($|a/b|$) calculated by the logistic regression equation (occurrence of geriatric syndrome = $a[\text{OE}] + b[\text{MMSE}] + c[\text{age}] + d[\text{sex}] + e$) (Table 3). Higher olfactory-cognitive index ($|a/b|$) as for AWGS sarcopenia ($|a/b| = 13.64$ in total

Table 3 Geriatric syndromes in order of olfactory-cognitive index ($|a/b|$)

Geriatric syndrome =	a(OE)	b(MMSE)	c(age)	d(sex)	e	
	a	b	c	d	e	($ a/b $)
Total participants						
AWGS sarcopenia	-0.191*	0.014	0.117**	-0.732	-9.075**	13.64
ASMI <cut-off	-0.117	0.032	0.078*	-0.597	-4.680*	3.66
Grip strength <cut-off	-0.146	-0.072	0.135**	-1.337**	-7.648*	2.04
Walking speed <0.8 m/s	-0.005	-0.093*	0.106**	0.466	-6.347*	0.05
Barthel ADL dependence ($\leq 85/100$)	0.268	-0.319***	0.219***	0.292	-13.262**	0.84
KCL frailty ($\geq 8/25$)	-0.080	-0.169**	0.038	-0.026	-1.613	0.47
Lawton IADL dependence ($\leq 4/5$)	-0.040	-0.298***	0.116**	0.470	-1.436	0.13
Support/care-need certification	0.021	-0.168**	0.113**	-0.864	-5.729	0.13
Women						
AWGS sarcopenia	-0.130	0.013	0.112**		-8.219*	10.00
ASMI <cut-off	-0.032	-0.011	0.104**		-7.331*	2.91
Grip strength <cut-off	-0.049	-0.089	0.143**		-8.272*	0.55
Walking speed <0.8 m/s	0.049	-0.102	0.105**		-6.216	0.48
Barthel ADL dependence ($\leq 85/100$)	0.281	-0.230**	0.255**		-6.610**	1.22
KCL frailty ($\geq 8/25$)	-0.050	-0.171*	0.050		0.605	0.29
Lawton IADL dependence ($\leq 4/5$)	0.047	-0.306***	0.131**		-2.843	0.15
Support/care-need certification	-0.012	-0.139*	0.083*		-3.922	0.09
Men						
AWGS sarcopenia	-0.219	0.044	0.126		-11.172	4.98
ASMI <cut-off	-0.194	0.075	0.045		-4.775	2.59
Grip strength <cut-off	-0.146	-0.041	0.128		-8.237	3.56
Walking speed <0.8 m/s	-0.047	-0.102	0.135*		-7.808	0.46
Barthel ADL dependence ($\leq 85/100$)	0.687	-0.745*	0.267		-9.069	0.92
KCL frailty ($\geq 8/25$)	-0.027	-0.206	0.021		3.666	0.13
Lawton IADL dependence ($\leq 4/5$)	-0.342	-0.317*	0.096		2.379	1.08
Support/care-need certification	0.374	-0.413*	0.256*		-14.056	0.91

Olfactory-cognitive index ($|a/b|$) was calculated as the absolute value of the ratio of the coefficient for Open Essence (a) to that for MMSE (b) in the logistic regression equation (Occurrence of geriatric syndrome = $a[\text{Open Essence}] + b[\text{MMSE}] + c[\text{age}] + d[\text{women } 0, \text{ men } 1] + e$).

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$, in a to e for logistic regression analysis.

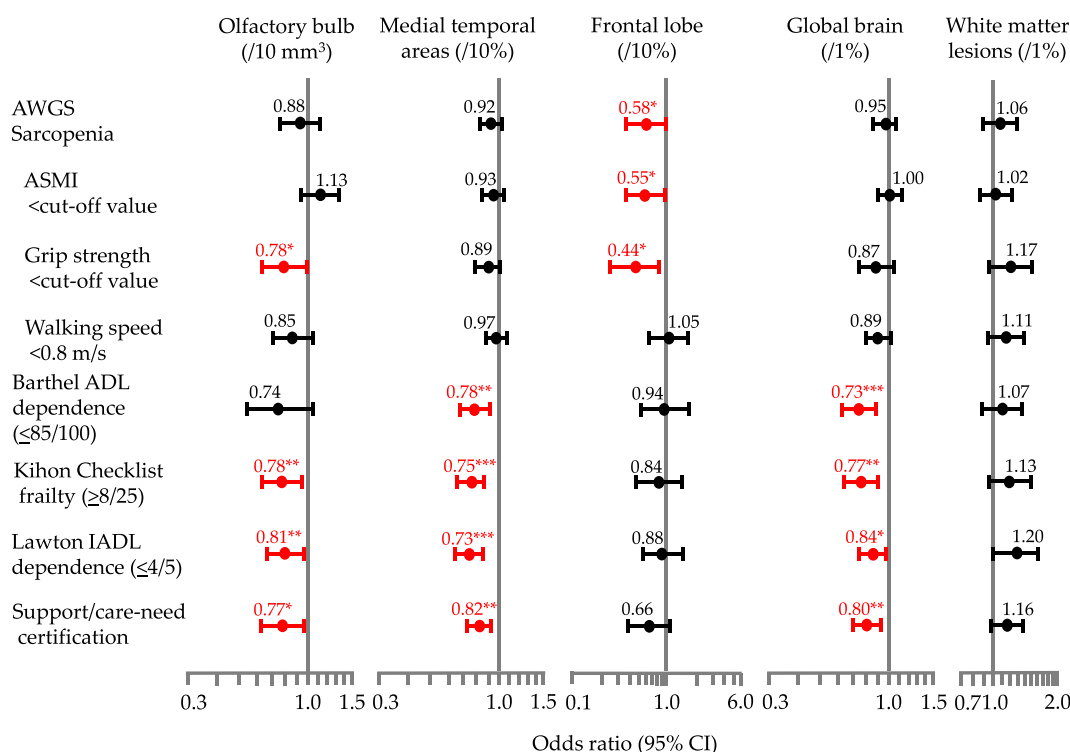


Figure 1 Structural changes of brain regions according to the presence of geriatric syndromes in total participants. Results are expressed as odds ratios and 95% confidential intervals adjusted by age and sex. * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ versus absence of respective geriatric syndromes. ADL, activities of daily living; ASMI, appendicular skeletal muscle mass index; AWGS, Asia Working Group for Sarcopenia; IADL, instrumental activities of daily living.

participants, 10.0 in women) indicates that the relevant geriatric syndrome occurred with a greater association with olfactory decline rather than cognitive decline. Among the screening items for AWGS sarcopenia, ASMI less than the cut-off ($|a/b| = 3.66$ in total participants) and grip strength less than the cut-off ($|a/b| = 2.04$ in total participants) were also associated with higher olfactory-cognitive index. Instead, Barthel ADL dependence ($|a/b| = 0.84$ in total participants), KCL frailty ($|a/b| = 0.47$ in total participants), Lawton IADL dependence ($|a/b| = 0.13$ in total participants) and support/care-need certification ($|a/b| = 0.13$ in total participants) accompanied by lower olfactory-cognitive index occurred with a greater association with cognitive decline rather than with olfactory decline.

Common geriatric syndromes and structural changes of brain

Logistic regression analysis adjusted by age and sex showed that AWGS sarcopenia, as well as its screening items including ASMI less than the cut-off and grip strength less than the cut-off, accompanied by a higher olfactory-cognitive index was associated with significant shrinkage of the frontal lobe in total participants (Fig. 1). Instead, Barthel ADL dependence, KCL frailty, Lawton IADL dependence and support/care-need certification accompanied by lower values of olfactory-cognitive index were associated with shrinkage of MTA-ERC and the global brain, and often with shrinkage of the olfactory bulb (Fig. 1). Logistic regression analysis adjusted by age showed that sarcopenia was associated with significant shrinkage of the frontal lobe in women, but not in men (Fig. 2).

Discussion

Previous studies have repeatedly shown similarities between olfactory and cognitive decline in the course of AD progression.¹⁻³ The present study also showed close resemblance between the associations of olfactory and cognitive decline with common geriatric syndromes in the course of AD progression (Tables 1, 2). To delineate the difference between the roles of the two functions, we adopted the olfactory-cognitive index calculated as the absolute value of the ratio of the coefficient for olfactory function to that for cognitive function with age and sex as covariates in logistic regression equation using various common geriatric syndromes as objective variables. The results of the present study showed that a higher olfactory-cognitive index, as for sarcopenia, was associated with frontal lobe shrinkage, and that a lower olfactory-cognitive index, as for Barthel ADL dependence, KCL frailty, Lawton IADL dependence and support/care-need certification, was related to shrinkage of MTA-ERC and the global brain, and often with olfactory bulb shrinkage (Fig. 1). The olfactory network includes not only the olfactory bulb, primary olfactory cortex (piriform) and secondary olfactory cortex (orbitofrontal), but also the hippocampus.¹⁸ This functional connectivity between the olfactory network and the hippocampus is interrupted in early-stage AD in proportion to the decrease of MMSE.¹⁹ Adjustment of olfactory function by MMSE in logistic regression analysis, therefore, might unleash the olfactory network from limbic overlap, and thus emphasize the role of the frontal lobe domain of the network. Conversely, adjustment of MMSE by olfactory function might emphasize the role of the hippocampal domain of the network.

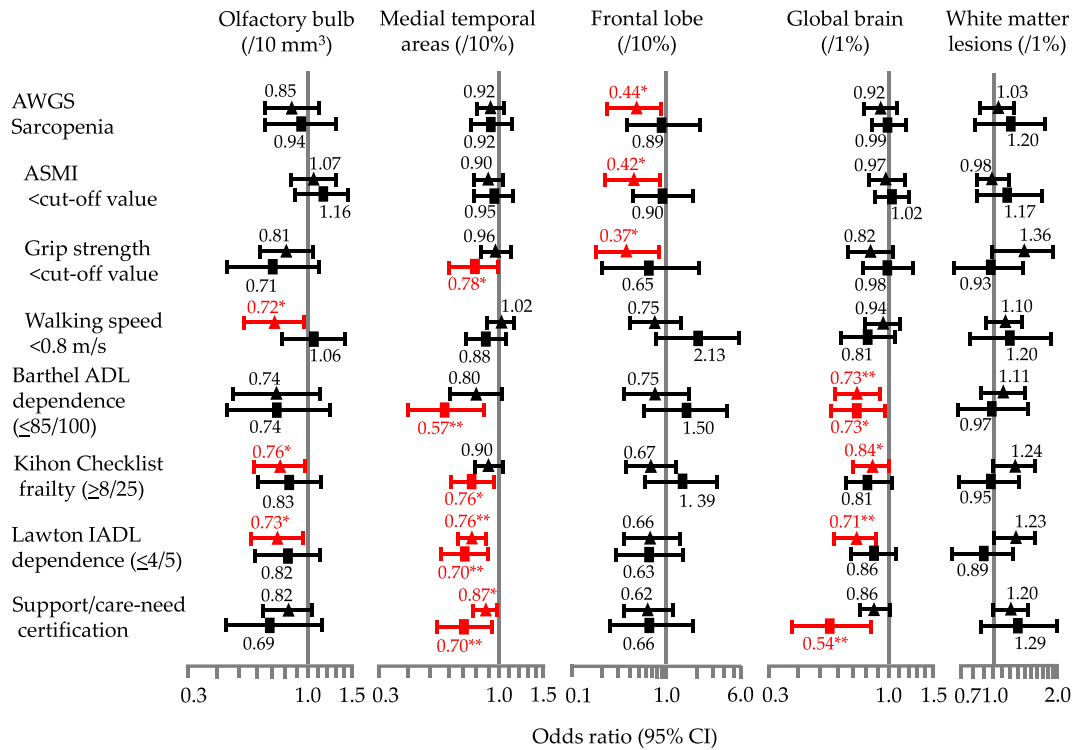


Figure 2 Structural changes of brain regions according to the presence of geriatric syndromes in women (▲) and men (■). Results are expressed as odds ratios and 95% confidential intervals adjusted by age. ADL, activities of daily living; ASMI, appendicular skeletal muscle mass index; AWGS, Asia Working Group for Sarcopenia; IADL, instrumental activities of daily living.

Frailty and decline in physical performance in the course of AD progression were related to structural changes of the brain evaluated by MRI. Diffuse cortical atrophy was associated with a decline in physical performance and falls in community-dwelling older adults with cognitive impairment,²⁰ whereas medial temporal lobe atrophy was also associated with frailty in individuals with MCI and mild-to-moderate AD,²¹ and with a decline in 6-min walking capacity in community-dwelling older adults with MCI.²² The results of the present study of the association of shrinkage of MTA-ESR and global brain gray matter with geriatric syndromes accompanied by a lower olfactory-cognitive index were partially compatible with these previous studies.²⁰⁻²²

Sarcopenia was also related to poor cognition in the course of AD progression.^{5,6} Among the screening items for sarcopenia, slow walking speed and weak grip strength were significantly related to cognitive dysfunction of MCI and AD, although lower skeletal muscle mass was not.^{5,6,23} In the present study, grip strength less than the cut-off and walking speed less than the cut-off were significantly correlated with both olfactory and cognitive decline in the total participants, in women and in men, but ASMI less than the cut-off value was not (Table 2), being partly similar to the results of these previous studies.^{5,6,23} In the present study, logistic regression analysis adjusted by age and sex showed a direct association of frontal lobe shrinkage with ASMI less than the cut-off value and grip strength less than the cut-off value, besides sarcopenia itself, in the course of AD progression (Fig. 1), indicating the importance of frontal lobe shrinkage in the decrease of muscle mass/strength in the course of AD progression. Indeed, a decrease in lower extremity muscular strength was linked to worse performance in frontal lobe executive function in community-dwelling older adults.²⁴ Furthermore, grey matter in the frontal lobe, as

well as the hippocampus, was most affected by age-related shrinkage, whereas grey matter volume in other brain regions, such as the parietal and occipital cortices, changed slightly with increasing age.²⁵ Cardiovascular fitness in community-dwelling older adults most markedly improved frontal lobe executive function, and reduced the age-related decline in cortical density of the frontal lobe.²⁶ All these previous studies support the present findings of a close association of frontal lobe shrinkage with sarcopenia, as well as lower muscle mass accompanied by a higher olfactory-cognitive index in the present study.

An association of frontal lobe shrinkage with sarcopenia in the course of AD progression was observed in women, but not in men (Fig. 2) in the present study. The reason(s) for the sex difference in this interaction between brain structural change and skeletal muscle mass/strength is not clear. A greater decrease in frontal lobe volume occurs with normal aging in men than in women.²⁷ In fact, the mean remaining rate of the frontal lobe was larger in women than in men in the present study (Table 1). However, once AD progressed, AD neuropathology in the brain showed a higher grade in women than in men.²⁸ Indeed, significant correlations of olfactory and cognitive decline with frontal lobe shrinkage were observed in women, but not in men in the present study (Table 2). In fact, a previous study showed that sarcopenia had stronger associations with MCI and AD in women than in men.⁶ Furthermore, women are at greater risk of losing functional muscle mass and strength than men, as women at any given age originally have significantly lower absolute skeletal muscle mass compared with men, which decreases noticeably in the sixth decade and thereafter.²⁹ The higher value of the olfactory-cognitive index for sarcopenia in women compared with men in the present study (Table 3) would indicate a stronger association

of frontal lobe shrinkage with decline in muscle mass/strength in women than in men. The precise mechanism(s) for the association of frontal lobe shrinkage with sarcopenia in the course of AD progression, and for the predominant appearance of the association in older women, should be elucidated in future studies.

Limitations of the present study must be considered. First, as this was a cross-sectional study, we could not determine the longitudinal relationships of these findings. Second, besides the protective effect of exercise on age-related frontal lobe shrinkage in older adults,²⁶ aerobic exercise training was also effective at reversing hippocampal volume loss and improving memory function in older adults.³⁰ Further studies will be necessary to elucidate the causal relationship among regional brain shrinkage, decline of muscle mass/strength and decreased physical performance in the course of AD progression.

In conclusion, the olfactory-cognitive index (a/b) might be a useful tool to distinguish involvement of frontal lobe shrinkage, as for sarcopenia from shrinkage of MTA-ERC, and global brain, as for KCL frailty and dependence, in older adults with NC to AD progression.

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Disclosure statement

The authors declare no conflict of interest.

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