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Neuroimaging

Peak width of skeletonized mean diffusivity and its association with age-related cognitive alterations and vascular risk factors

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Abstract

Introduction: Only two studies investigated the associations between peak width of skeletonized mean diffusivity (PSMD) and age-related cognitive alterations, whereas none of the studies investigated the association with vascular risk factors.

Methods: We evaluated 801 stroke- and dementia-free elderlies with baseline and 3-year follow-up assessments. Regression analyses were used to assess the association between age-related cognitive functions and PSMD. Simple mediation models were used to study the mediation effect of PSMD between vascular risk factors and age-related cognitive outcomes.

Results: PSMD was negatively associated with processing speed at baseline and negatively associated with processing and memory scores at 3-year follow-up. The association between vascular risk factors and age-related cognition was mediated by PSMD, as well as other diffusion tensor imaging markers.

Discussion: PSMD is preferred over other diffusion tensor imaging markers as it is sensitive to age-related cognitive alterations and calculation is fully automated. PSMD is proposed as a research tool to monitor age-related cognitive alterations.

Keywords: Small vessel disease; Diffusion tensor imaging; Peak width of skeletonized mean diffusivity; Processing speed; Community subjects

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1. Background

Cognition and cognitive health are matters not only in older adults but across the life span. Cognitive aging includes age-related changes in multiple cognitive domains such as processing speed, memory, and executive functions that may decline, not change, or improve. These changes are not clinically defined neurological or psychiatric disease and do not inevitably lead to neuronal death and neurodegenerative disease. However, cognitive aging may pose an impact on functional abilities, such as driving, making financial and health care decisions, and independence [1–3]. Cognitive aging is not easily defined by a clear threshold on cognitive tests due to variability in culture, education level, and other environmental factors. Although it is known that cognitive aging is associated with modifiable risk factors such as vascular risk factors and structural and functional brain changes, there is still a large gap in the understanding of the biological foundations of cognitive aging. A better understanding of the profiles of cognitive aging will assist us to identify those who may be at risk of cognitive decline in older adults.

Advances in neuroimaging allow us to examine the relation between cognition and the neural substrates in aging. Age-related decline in the white matter varies across different brain regions. Similar to the gray matter changes, there is a greater decline in the frontal areas in the anterior and superior brain regions, which might reflect later development of myelination in these regions in older adults [4]. Interestingly, white matter volume declined disproportionately more than gray matter in normal aging in older adults [5].

Diffusion tensor imaging (DTI), which measures the microstructural integrity of cerebral white matter, provides a unique perspective on cognition in normal healthy aging. A novel DTI marker, the peak width of skeletonized mean diffusivity (PSMD), was introduced [6]. PSMD combined two processing techniques for DTI data, skeletonization, and histogram analysis. Furthermore, it is fully automated, robust, and simple to administer. PSMD overcomes issues that traditional DTI parameter, such as mean diffusivity (MD), poses; for example, extensive data postprocessing for the removal of prominent cerebrospinal fluid signal from MD images. PSMD did not only allow a more straightforward and fully automated measure of white matter integrity but was also shown to be superior over conventional MRI small vessel disease (SVD) markers in evaluating processing speed among symptomatic sporadic and genetically defined SVD [6].

To date, two independent studies have applied PSMD on community healthy elderlies and measure the association between PSMD and multiple cognitive domains. One study showed PSMD significantly associated with processing speed in those with white matter lesions or cognitive impairment only but not in healthy controls [7]. Another study showed PSMD in a community cohort found a significant association between PSMD and processing speed, as well as visuospatial, memory, and general cognition. However, PSMD did not outperform other imaging measures in the community cohort [8]. Because there were mixed findings on the application of PSMD and cognition in community elderlies, we aim to better understand cognitive aging by investigating the clinical and imaging risk factors for cognitive aging in a large community cohort. Finally, the co-occurrence of vascular risk factors affected late-life white matter integrity changes [9]. However, there is no study investigating how vascular risk factors pose influences on cognition through the promising DTI marker PSMD.

In this present study, we further explored the utility of PSMD in a large cohort of community-dwelling stroke- and dementia-free elderlies. The objectives of this study are to investigate (1) the association between PSMD and age-related cognitive functions in the community elderlies at baseline; (2) the association between PSMD and age-related cognitive functions at 3-year follow-up; and (3) the mediation effects of PSMD between classical vascular factors (e.g., hypertension, smoking, etc.) and age-related cognitive functions.

2. Methods

This is a prospective 3-year longitudinal study. This study is part of the "Brain Health Brings Health" Programme of the Division of Neurology at the Chinese University of Hong Kong. The work described was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and was approved by the Joint Chinese University of Hong Kong–New Territories East Cluster Ethics Committee (ethics approval reference number: CRE-2011.090). Written informed consent was obtained from all patients (or carers of patients) participating in the study.

2.1. Study population

Subjects were identified from a community-based cohort called the Chinese University of Hong Kong–Risk Index for Subclinical brain lesions in Hong Kong (CU-RISK), which aims to derive a risk index consisting of cognitive, motor, behavioral, vascular, and metabolic measures that may predict the presence of subclinical SVD lesions among healthy community-dwelling elderlies. Details of the inclusion criteria of CU-RISK were as follows: (1) aged 65-85 years old; (2) Chinese ethnicity; and (3) functionally independent (Barthel index $\geq$ 18). Exclusion criteria were as follows: (1) history of stroke or TIA; (2) dementia according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition or any cognitive symptoms that were severe enough to cause the subjects to seek medical attention; (3) obtaining a Mini–Mental State Examination score lower than the education-adjusted cutoff for cognitive impairment. The locally validated education-adjusted cutoff was as follow: $<$22 for those with more than 2 years of education, $<$20 for those with 1-2 years of education, and $<$18 for those

with no schooling [10]; (4) severe medical illnesses (e.g., malignancy, end-stage renal diseases); (5) contraindication for MRI (e.g., claustrophobia, metallic implants); and (6) excessive head movements or poor MRI quality for analysis.

2.2. Data collection

2.2.1. Clinical and neuropsychological assessments

Clinical demographics and medical history were taken from the subjects. Clinical risk factors to be measured include age, gender, education, the presence of hypertension, diabetes mellitus, hyperlipidemia, ischemic heart disease, atrial fibrillation, and smoking status. Patients were labeled as having hypertension if they had a history of hypertension or were using antihypertensive medication. For more details, please refer to the Supplemental Material.

The Mini–Mental State Examination was used as a measure of general cognitive functions during subject recruitment [11]. Memory and executive function were measured by the respective subscores on the Montreal Cognitive Assessment (MoCA) [12,13], whereas processing speed was measured using the Symbol Digit Modalities Test [14].

2.2.2. Imaging assessments and variables of interest

Subjects underwent MRI in a 3 Tesla scanner (Achieva 3.0 T Tx series; Philips Medical System, Best, the Netherlands). Images were required using an 8-channel receiver-only head coil. Sequences acquired include T1-weighted, T2-weighted, flair-attenuated inversion recovery (FLAIR), diffusion tensor imaging (DTI), and T2*gradient echo (GRE). Most of the subjects (n = 771) underwent scanning protocol 1, detailed as follows: T1-weighted (TR/TE: 7.49/3.46 ms, reconstructed voxel size: $0.60\times1.04\times1.04$ mm^3); T2-weighted (TR/TE: 2743.89/80 ms, reconstructed voxel size: $5.5\times0.22\times0.22$ mm^3); 3D FLAIR (TR/TE/TI: 8000/328.6/2400 ms, reconstructed voxel size: $0.55\times0.44\times0.44$ mm^3); DTI (TR/TE: 8944/60 ms, reconstructed voxel size: $1\times1\times1$ mm^3; b-value = 1000, 32 diffusion directions); T2*GRE (TR/TE: 18/26 ms, reconstructed voxel size: NA). A small portion of subjects (n = 33) underwent scanning protocol 2. The main difference between the protocols was that a 3D FLAIR was used in protocol 1 while a 2D FLAIR was used in protocol 2. For more information, please see Table 1.

PSMD was calculated using a publicly available (http://psmd-marker.com) script based on (1) DTI sequence on MRI; (2) white matter tract skeletonization (as implemented in the FMRIB software library v5.0—tract-based spatial statistics); (3) a custom mask to exclude regions prone to CSF contamination; and (4) histogram analysis of mean diffusivity values within the skeleton [6]. For details of PSMD postprocessing, please refer to the Supplemental Material. In addition, other diffusion parameters, such as the median fractional anisotropy (FA), median MD, were also generated using the DTIFIT (FMRIB software library v5.0) and the same custom mask used in the calculation of PSMD.

Table 1
Brain MRI acquisition protocol

Protocol	CUHK protocol 1 (n = 771)	CUHK protocol 2 (n = 30)
Model, Vendor	Achieva, Philips Healthcare	Achieva, Philips Healthcare
Field strength (T)	3	3
Software	R5	R5
Type	Multi-coil	Multi-coil
No. of channels	8	8
T1W TR/TE (ms) (3D)	7.49/3.46	6.49/3.11
T1 reconstructed voxel size (mm)	$0.60\times1.04\times1.04$	$1.2\times1.0\times1.0$
T2W TR/TE (ms)	1888.60/80 (DUAL) 2743.89/80 (T2W)	2366.86/80(T2W)
T2 reconstructed voxel size (mm)	$5.5\times0.22\times0.22$	$5.5\times0.22\times0.22$
3D FLAIR TR/TE/TI (ms)	8000/328.6/2400	N/A
3D FLAIR reconstructed voxel size (mm)	$0.55\times0.44\times0.44$	N/A
2D FLAIR TR/TE/TI (ms)	N/A	11,000/125/2800
2D FLAIR reconstructed voxel size (mm)	N/A	$0.33\times0.33\times5.5$
Diffusion TR/TE (ms)	8944/60	8647.64/60
Diffusion b-value (s/mm2)/no of directions	1000/32	1000/32
Diffusion voxel size (mm)	$1\times1\times1$	$1\times1\times1$
T2*GRE TR/TE (ms)	18/26	N/A
T2*GRE reconstructed voxel size (mm)	N/A	$5.5\times0.22\times0.22$

NOTE. This table illustrates the MRI scanning protocols used in the study.

Abbreviations: TR, repetition time; TE, echo time; FLAIR, fluid-attenuated inversion recovery; GRE, gradient echo.

Conventional imaging markers which included (1) WMH, (2) lacunes, (3) microbleeds, (4) brain volume [15], and (5) hippocampal volume corrected with intracranial volume was also measured [16]. For more details, please refer to the Supplemental Material.

2.3. Statistical analysis

The associations between imaging risk factors and cognitive functions were examined using linear regression. Several regression models were generated, each with three predictors: the variable of interest, age, and education. For regression models examining the association between follow-up cognitive scores and imaging, age, education, and baseline cognitive score were entered as covariates. As we have performed regression models on 3 dependent variables, the independent variable entered into the regression model was only regarded as significant if $P < .017$, corrected for multiple comparisons using Bonferroni correction. Simple mediation model was performed and included age and education as covariates. All analyses were performed using IBM SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Mac OS, Version 24.0. Armonk, NY: IBM Corp).

3. Results

In the CU-RISK study, 851 elderlies fitted the study criteria and were assessed using clinical, neuropsychological tests, and underwent MRI procedures. A total of 831 subjects had completed postprocessing and successful imaging registration for WMH volumetric measure, whereas 801 subjects had completed diffusion scans and postprocessing of PSMD and were included in the final analysis (see Fig. 1). The clinical demographics, clinical, and neuroimaging characteristics of the subjects were shown in Table 2.

Follow-up assessments were conducted on 515 subjects at 3-year follow-up (3.3 ± 0.3 years). Clinical and cognitive assessments that were similar to baseline assessments were performed. The median time difference between baseline clinical assessment and MRI scan was 5.0 ± 4.9 months. The clinical and imaging characteristics of the subjects who had completed follow-up compared to those who were lost to follow-up were presented in eTable 1.

3.1. Association between imaging markers and cognitive functions at baseline

At baseline, PSMD (standardized β = −0.089; $P = .001$), other DTI parameters (median FA: standardized β = 0.122; $P < .0001$; median MD: standardized β = −0.105; $P < .0001$), and brain parenchymal fraction (standardized β = 0.072; $P = .010$) were associated with processing speed. Furthermore, median MD (standardized β = −0.104; $P = .002$), microbleed count (standardized β = −0.078; $P = .016$), and hippocampal ratio (standardized β = 0.113; $P < .0001$) were associated with MoCA memory. All regression models were adjusted for age and education. A P value of <.017 was considered statistically significant after Bonferroni correction (see Table 3).

3.2. Association between imaging markers and cognitive functions at follow-up

At follow-up, baseline PSMD (standardized β = −0.071; $P = .003$), median FA (standardized β = 0.075; $P = .001$), and brain parenchymal fraction (standardized β = 0.109; $P < .0001$) were associated with year 3 processing speed scores. In addition, baseline PSMD (standardized β = −0.107; $P = .009$), median FA (standardized β = −0.099; $P = .014$), and the brain parenchymal fraction (standardized β = 0.131; $P = .003$) were also associated with year 3 MoCA memory. The 3rd year follow-up absolute cognitive score was used in the analyses, instead of the change in score due to the changes of cognitive scores in these community subjects being relatively mild. All regression models were adjusted for age, education, and baseline cognitive score (see Table 4).

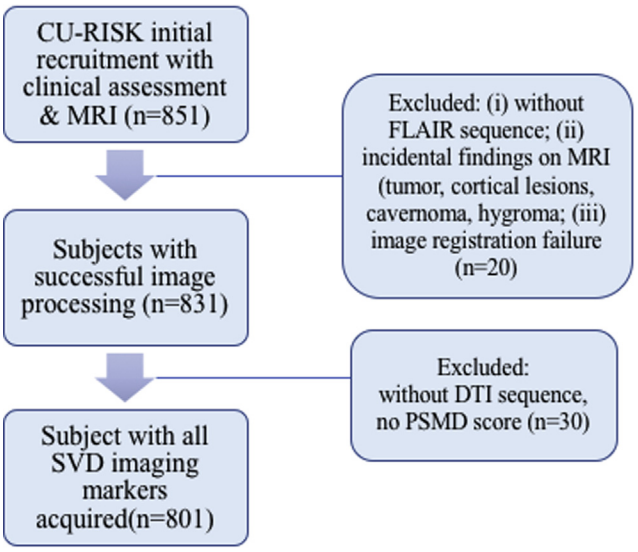

Fig. 1. Illustration of the recruitment flowchart of the Chinese University of Hong Kong–Risk Index for Subclinical brain lesions in Hong Kong (CU-RISK) study. Abbreviations: DTI, diffusion tensor imaging; FLAIR, fluid-attenuated inversion recovery; PSMD, peak width of skeletonized mean diffusivity; SVD, small vessel disease.

3.3. Mediation effects of imaging markers between vascular risk factors and cognitive functions

Simple mediation tests showed that the association between vascular risk factors and baseline cognition was mostly mediated by DTI metrics (PSMD, median FA, and median MD). In particular, PSMD showed mediation effects between (1) hypertension & processing speed; (2) diabetes mellitus & processing speed; (3) smoking & processing speed; and (4) smoking & MoCA memory domain (see Fig. 2).

Among all imaging variables, PSMD illustrated the greatest mediation effect between (1) smoking and processing speed (indirect effect (B) = −0.36; bootstrap 95% CI = −0.67 to −0.124); (2) smoking and MoCA memory (indirect effect (B) = −0.05; bootstrap 95% CI = −0.10 to −0.0009).

Median MD illustrated the greatest mediation effects between (1) hypertension and processing speed (indirect effect (B) = −0.39; bootstrap 95% CI = −0.69 to −0.16); (2) diabetes mellitus and processing speed (indirect effect (B) = −0.40; bootstrap 95% CI = −0.73 to −0.15); (3) hypertension and MoCA memory (indirect effect (B) = −0.06; bootstrap 95% CI = −0.11 to −0.01); diabetes mellitus and MoCA memory (indirect effect (B) = −0.06; bootstrap 95% CI = −0.12 to −0.02).

Median FA illustrated the greatest mediation effect between diabetes mellitus and MoCA executive function (indirect effect (B) = −0.02; bootstrap 95% CI = −0.05 to −0.0002).

Other non-DTI markers, such as the brain parenchymal fraction and hippocampal volume, did show a significant association between vascular risk factors and cognition functions but the mediation effects were smaller compared with the DTI markers (see Fig. 2).

Table 2
Clinical and imaging characteristics of community elderlies

Demographic characteristics	Baseline (n = 801)
Age, yr, mean ± SD (min; max)	71.80 ± 5.08 (63.3; 89.8)
Education, yr, mean ± SD (min; max)	7.87 ± 4.92 (0; 22)
Female (%)	495 (61.8)
Vascular risk factors, (%)	
Current smoker	30 (3.7)
Past smoker	148 (18.5)
Hypertension	486 (60.7)
Hyperlipidemia	242 (30.2)
Diabetes mellitus	181 (22.6)
Ischemic heart disease	45 (5.6)
Atrial fibrillation	15 (1.9)
Other clinical variables	
Gait speed, sec, median; IQR (min; max)	10.00; 2.80 (5.0; 25.8)
Depressive symptoms, median; IQR (min; max)	2.00; 4.00 (0; 15)
Barthel index, median; IQR (min; max)	20.00; 0.00 (18; 20)
Cognitive scores	
MoCA, median; IQR (min; max)	23; 6 (9; 30)
MoCA Memory, median; IQR (min; max)	9; 6 (0; 15)
MoCA Executive, median; IQR (min; max)	1; 3 (2; 13)
Processing speed, median; IQR (min; max)	29.00; 16.75 (1; 69)
Imaging variables	
PSMD, 10^{-4} mm^2/s, median; IQR (min; max)	2.72; 0.42 (2.07; 5.25)
FA, median; IQR (min; max)	0.51; 0.03 (0.43; 0.56)
MD, 10^{-4} mm^2/s, median; IQR (min; max)	7.50; 0.41 (6.7; 8.5)
Normalized WMH volume, mL, median; IQR (min; max)	4.03; 6.35 (0; 43.07)
Presence of lacunes (%)	52 (6.5)
Presence of microbleeds (%)	171 (21.8)
Brain parenchymal fraction, median; IQR (min; max)	0.75; 0.08 (0.51; 0.88)
Hippocampal volume/ICV median; IQR (min; max)	0.46; 0.06 (0.29; 0.62)

NOTE. This table illustrates the clinical and imaging characteristics of community elderlies.

Abbreviations: MoCA, Montreal Cognitive Assessment; PSMD, peak width of skeletonized mean diffusivity; FA, fractional anisotropy; MD, mean diffusivity; WMH, white matter hyperintensity; ICV, intracranial volume.

4. Discussion

This study measured the association between the novel DTI marker, PSMD, and multiple cognitive domains (processing speed, memory, and executive function) in a large longitudinal community-based cohort with stroke- and dementia-free elderlies. It is also the first to examine the mediation effects of PSMD between age-related cognition and vascular risk factors. This study highlights that PSMD was associated with cognition (processing speed and memory) in community subjects at both baseline and follow-up, after adjusting for age and education. More specifically, PSMD was negatively associated with processing speed at baseline. At the 3rd year follow-up, baseline PSMD was negatively associated with both the processing and memory scores. In general mediation models, DTI parameters were consistently shown to be a mediator between vascular risk factors and cognition. In particular, PSMD illustrated the greatest mediation effect between smoking and processing speed, as well as smoking and MoCA memory. Although PSMD was associated with cognitive performance, as well as showing a mediation effect between vascular risk factors and cognition, these associations were not exclusive to PSMD, nor did we demonstrate that PSMD outperforms other DTI markers. However, these results corroborated the contribution of white matter disruption to these age-related cognitive alterations.

Although most associations were found between DTI markers and cognition, we have included conventional imaging markers in this study for comparison. Normalized brain volume was also positively associated with processing speed scores at baseline. Further analysis illustrated the positive association between normalized brain volume and processing speed was mediated by PSMD (indirect effect (B) = 6.83; bootstrap 95% CI = 1.48 to 12.53). The baseline microbleed count was negatively associated with memory function. However, the results were mainly driven by a few outliers as the association between microbleed and memory became not significant after the outliers were removed. Considering that this is a community-based study, we tend to accept some variability in the sample; therefore, all subjects were included in the final analysis. Although it is not surprising to see a positive association between hippocampal size and memory function in Alzheimer's disease patients, this positive association in healthy older adults was also reported in a previous meta-analysis [17].

When examining follow-up analyses, DTI markers were strongly associated with follow-up processing speed and memory scores. Normalized brain volume was also positively associated with follow-up 3rd year follow-up processing speed scores and memory. We have further demonstrated that the positive association between normalized brain volume and the follow-up processing speed was mediated by PSMD (indirect effect (B) = 9.38; bootstrap 95% CI = 2.38 to 17.15). It must be noted that the absolute cognitive scores from baseline and the 3rd year follow-up was used, instead of the "change in score" due to the changes of cognitive scores in these community subjects being relatively mild. For example, the processing speed scores did not differ between the two time points ($P = .46$). Therefore, PSMD was not able to detect a change in processing speed score over time. We have, therefore, adjusted for baseline cognitive scores in the regression models examining the association between 3rd year follow-up cognitive scores and imaging risk factors. The negative associations between PSMD and year 3 processing speed, as well as PSMD and year 3 MoCA memory, remain statistically significant.

Interestingly, DTI markers illustrated the strongest mediation effects between vascular risk factors such as hypertension, diabetes mellitus, smoking, and hyperlipidemia and age-related cognitive functions. This proposed that vascular etiology plays an important role in normal cognitive aging and that

Table 3
Regression analyses showing the association between imaging variables and cognitive functions in community elderlies at baseline

	All subjects (n = 801)					
	Processing speed		MoCA memory		MoCA executive	
Baseline	Std β	*P*	Std β	*P*	Std β	*P*
PSMD	−0.089	.001	−0.075	.031	−0.013	.686
Median FA	0.122	<.0001	0.073	.031	0.063	.041
Median MD	−0.105	<.0001	−0.104	.002	−0.015	.624
Normalized WMH volume	−0.029	.259	−0.003	.921	−0.045	.140
Lacune count	−0.016	.524	0.007	.839	−0.046	.121
Microbleed count	−0.034	.174	−0.078	.016	−0.030	.315
Brain parenchymal fraction	0.072	.010	0.082	.026	0.041	.228
Hippocampal volume/ICV	−0.009	.716	0.113	<.0001	−0.042	.153

NOTE. This table shows the regression analyses between imaging variables and cognitive functions in community elderlies at baseline. Independent variable entered into the regression model was only regarded as significant if $P < .017$, corrected for multiple comparisons using Bonferroni correction. PSMD and MD were adjusted to 10^{-4} mm^2/s.

Abbreviations: MoCA, Montreal Cognitive Assessment; PSMD, peak width of skeletonized mean diffusivity; FA, fractional anisotropy; MD, mean diffusivity; WMH, white matter hyperintensity; ICV, intracranial volume.

Table 4
Regression analyses showing the association between imaging variables and cognitive functions in community elderlies at follow-up

	All subjects (n = 515)					
	Yr 3 processing speed		Yr 3 MoCA memory		Yr 3 MoCA executive	
3rd year follow-up	Std β	*P*	Std β	*P*	Std β	*P*
PSMD	−0.071	.003	−0.107	.009	−0.010	.789
Median FA	0.075	.001	0.099	.014	0.045	.209
Median MD	−0.041	.079	−0.054	.174	−0.041	.252
Normalized WMH volume	−0.048	.038	−0.053	.181	−0.022	.545
Lacune count	0.018	.412	−0.027	.488	0.054	.118
Microbleed count	0.001	.975	−0.008	.838	0.040	.249
Brain parenchymal fraction	0.109	<.0001	0.131	.003	0.021	.585
Hippocampal volume/ICV	−0.007	.741	−0.003	.943	−0.022	.519

NOTE. This table shows the regression analyses between imaging variables and cognitive functions in community elderlies at follow-up. Independent variable entered into the regression model was only regarded as significant if $P < .017$, corrected for multiple comparisons using Bonferroni correction. PSMD and MD were adjusted to 10^{-4} mm^2/s.

Abbreviations: MoCA, Montreal Cognitive Assessment; PSMD, peak width of skeletonized mean diffusivity; FA, fractional anisotropy; MD, mean diffusivity; WMH, white matter hyperintensity; ICV, intracranial volume.

this was mediated by the disruption of brain white matter as reflected on DTI. The association between DTI and vascular etiology was also shown in previous studies. In particular, PSMD was associated with small vessel disease but not neurodegeneration [6]. One study showed hypertension was associated with a decline in FA and that DTI was the most sensitive indicator of global and regional declines and vascular damage in the aging brain [18]. Another longitudinal study showed that multiple vascular risk factors were associated with DTI metrics (a decrease in FA in the splenium of the corpus callosum) over 3 years in a community study [9]. Our present study suggested that the novel DTI marker, PSMD, as well as other DTI markers such as FA and MD, outperforms other markers in reflecting subtle cognitive alterations and vascular risk factors in community subjects.

In recent years, the utility of DTI in clinical studies has gained special attention. DTI, in particular, the PSMD, has been proposed to be a clinical trial marker for SVD as it is a sensitive marker for cognition and change in white matter integrity over time [6,19]. The added value of DTI on the association with cognitive function in SVD has been reported. In community cases with stroke- and dementia-free cases, DTI also illustrated greater association with cognitive functions compared to conventional imaging markers [9,20–22]. Our results showed DTI was the main contributor to cognitive alterations in processing speed and memory in the community subjects. We speculate that DTI is particularly useful in reflecting overall disease burden in community subjects while the contribution of other conventional imaging markers may become more significant when it becomes more severe or diffuse. More importantly, we have demonstrated that PSMD, the novel DTI marker with custom mask and skeletonization, has a strong association in relating cognitive alterations in community subjects, both at baseline and at 3rd year follow-up. In addition, PSMD mediated the association between vascular risk factors and normal cognitive aging. Although these findings were present in DTI markers in general, not only exclusive to PSMD, the simple and automated approach of PSMD promotes the broader application of this novel marker in clinical research. PSMD overcomes the challenges of traditional DTI marker including extensive data postprocessing for the removal of prominent cerebrospinal fluid signal from MD images. Furthermore, PSMD has also shown to have the highest interscanner reproducibility in multicenter studies, as well as smallest sample size estimates, compared to other MD measures [6]. Therefore, PSMD, which is closely associated with vascular risk factors, as well as a sensitive tool in monitoring age-related cognitive alterations, is a proposed research tool in the monitoring of cognitive alterations in the healthy aged community elderlies.

The strengths of this study included the prospective design of a large community-based cohort study, with longitudinal follow-up of a 3-year interval. All subjects were recruited in the same center and scanned under the same MRI scanner, which minimized the deviations in scanning

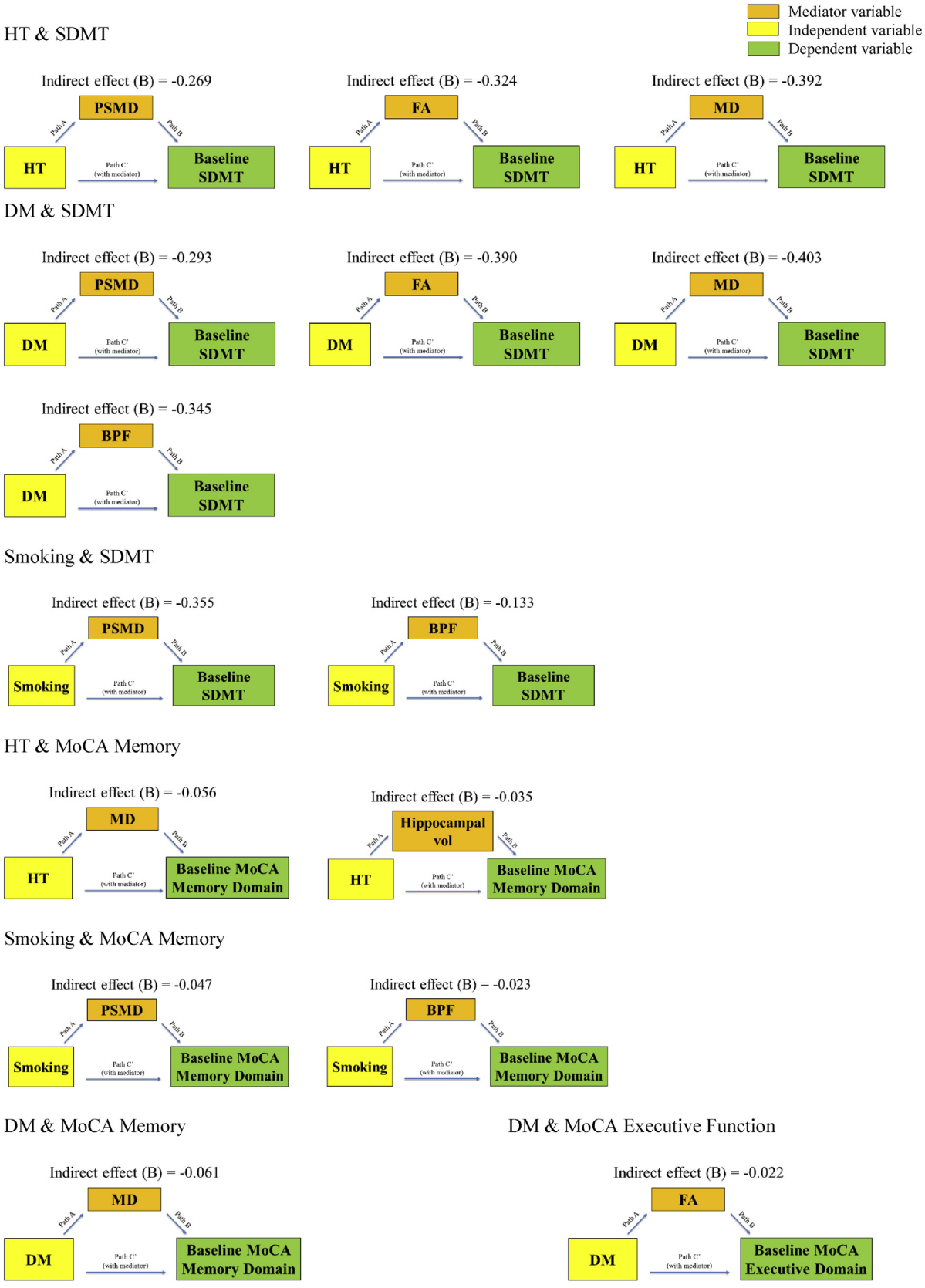

Fig. 2. This figure shows simple mediation models to illustrate the mediation effects of imaging markers between vascular risk factors and cognitive functions. Abbreviations: HT, hypertension; DM, diabetes mellitus; FA, fractional anisotropy; MD, mean diffusivity; BPF, brain parenchymal fraction; PSMD, peak width of skeletonized mean diffusivity; SDMT, symbol digit modality test; MoCA, Montreal Cognitive Assessment.

protocol or neuropsychological test administration. However, there are certain limitations to this study. First, participants recruited for this study were community subjects without apparent cognitive complaints. The association between imaging markers and clinical symptoms might be weak and might not reflect the true magnitude of the association between these markers. However, because associations between PSMD and age-related cognitive alterations have been identified, this suggests PSMD is an imaging marker sensitive enough for detecting age-related cognitive decline in community subjects despite the weak associations. Second, only brief cognitive tests (e.g., MoCA and its subscores) were used. A more detailed neuropsychological battery might be able to show an association between PSMD and other cognitive functions. Yet, the significant association between PSMD and memory using a crude MoCA subscore highlighted the sensitivity of PSMD. Third, although none of the recruited subjects were under medical investigation or management of cognitive complaints, possibly some subjects might have undiagnosed mild cognitive impairment. Yet overall, the clinical impairment, if present, should not be severe enough to impair daily functioning. Fourth, we cannot completely rule out the contribution to cognitive deficits from other common neurodegenerative diseases (e.g., AD) as we did not collect biomarkers for AD (e.g., Apolipoprotein E in blood, Aβ/tau in cerebrospinal fluid, amyloid/tau positron emission tomography). However, an increase in PSMD has shown to be associated with the vascular component but not neurodegeneration [6]. Fifth, we investigated the association between the global WMH volume and total number of lacunes and microbleeds with cognitive performance but did not investigate the lesions located in the strategic regions for the cognitive alterations. This may underestimate the cognitive impact that is dependent on lesion location [23,24].

It is well accepted that cognitive tests are insensitive to longitudinal change while DTI marker has shown to be more sensitive in predicting longitudinal changes [25,26]. We plan to acquire serial imaging to capture progression of brain changes, parallel to the cognitive changes. This study sets the basis for our future direction to investigate the association between longitudinal changes of PSMD and cognition, and to measure the sensitivity of PSMD in reflecting longitudinal cognitive changes or other clinical events (e.g., stroke, parkinsonism, depression) and whether it can be used to predict the development of conventional imaging markers (e.g., lacunes, WMH, microbleeds).

Our study revealed two important findings. First, PSMD was a sensitive marker to detect age-related cognitive alterations in community elderlies at both baseline and 3rd year follow-up. Second, PSMD mediated the associations between vascular risk factors and age-related cognitive aging. We concluded that vascular etiology plays an important contribution to normal cognitive aging and PSMD can be included as a research tool in the monitoring of brain alterations in community elderlies.

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.dadm.2019.09.003.

RESEARCH IN CONTEXT

1. Systematic review: The PubMed search included studies investigating the association between cognition, vascular risk factors, and diffusion tensor imaging (DTI) in the aging population. Only two studies investigated the associations between the novel DTI marker, peak width of skeletonized mean diffusivity (PSMD), and age-related cognitive alterations, whereas none of the studies investigated the association with vascular risk factors.
2. Interpretation: Our findings showed the strongest associations between age-related cognitive outcomes and vascular risk factors in the community elderlies were found in PSMD and other DTI markers. In particular, PSMD was negatively associated with processing speed at baseline and negatively associated with processing and memory scores at 3rd year follow-up. PSMD mediated the association between vascular risk factors and cognitive alterations.
3. Future directions: Vascular etiology contributed to normal cognitive aging and PSMD is proposed to be used as a research tool in the monitoring of brain alterations in community elderlies.

References

[1] Dumas JA. What is normal cognitive aging? Evidence from task-based functional neuroimaging. Curr Behav Neurosci Rep 2015;2:256–61.

[2] Blazer DG, Yaffe K, Karlawish J. Cognitive aging: a report from the Institute of Medicine. JAMA 2015;313:2121–2.

[3] Harada CN, Natelson Love MC, Triebel K. Normal cognitive aging. Clin Geriatr Med 2013;29:737–52.

[4] Madden DJ, Bennett IJ, Burzynska A, Potter GG, Chen N-K, Song AW. Diffusion tensor imaging of cerebral white matter integrity in cognitive aging. Biochim Biophys Acta 2012;1822:386–400.

[5] Salat DH, Kaye JA, Janowsky JS. Prefrontal gray and white matter volumes in healthy aging and Alzheimer disease. Arch Neurol 1999; 56:338–44.

[6] Baykara E, Gesierich B, Adam R, Tuladhar AM, Biesbroek JM, Koek HL, et al. A novel imaging marker for small vessel disease based on skeletonization of white matter tracts and diffusion histograms. Ann Neurol 2016;80:581–92.

[7] Wei N, Deng Y, Yao L, Jia W, Wang J, Shi Q, et al. A neuroimaging marker based on diffusion tensor imaging and cognitive impairment due to cerebral white matter lesions. Front Neurol 2019;10:81.

[8] Deary IJ, Ritchie SJ, Maniega SM, Cox SR, Hernández MCV, Starr JM, et al. Brain peak width of skeletonised mean diffusivity (PSMD), processing speed, and other cognitive domains. bioRxiv 2018:385013.

[9] Maillard P, Carmichael OT, Reed B, Mungas D, DeCarli C. Co-Occurrence of vascular risk factors and late-life white matter integrity changes. Neurobiol Aging 2015;36:1670–7.

[10] Chiu HFK, Lam LC, Leung T, Li SW, Law WT, Chung DW, et al. Prevalence of dementia in Chinese elderly in Hong Kong. Neurology 1998; 50:1002–9.

[11] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.

[12] Lam B, Middleton Laura E, Masellis M, Stuss Donald T, Harry Robin D, Kiss A, et al. Criterion and convergent validity of the montreal cognitive assessment with screening and standardized neuropsychological testing. J Am Geriatr Soc 2013;61:2181–5.

[13] Wong A, Xiong YY, Kwan PWL, Chan AYY, Lam WWM, Wang K, et al. The validity, reliability and clinical utility of the Hong Kong Montreal Cognitive Assessment (HK-MoCA) in patients with cerebral small vessel disease. Demen Geriatr Cogn Disord 2009;28:81–7.

[14] Smith A. The Symbol-Digit Modalities Test: A Neuropsychologic Test of Learning and Other Cerebral Disorders. Seattle: Special Child Publications; 1968.

[15] Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 2013;12:822–38.

[16] Abrigo J, Shi L, Luo Y, Chen Q, Chu WCW, Mok VCT, et al. Standardization of hippocampus volumetry using automated brain structure volumetry tool for an initial Alzheimer's disease imaging biomarker. Acta Radiologica 2018;60:769–76.

[17] Van Petten C. Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. Neuropsychologia 2004;42:1394–413.

[18] Burgmans S, van Boxtel MPJ, Gronenschild EHBM, Vuurman EFPM, Hofman P, Uylings HBM, et al. Multiple indicators of age-related differences in cerebral white matter and the modifying effects of hypertension. NeuroImage 2010;49:2083–93.

[19] Croall ID, Lohner V, Moynihan B, Khan U, Hassan A, O'Brien JT, et al. Using DTI to assess white matter microstructure in cerebral small vessel disease (SVD) in multicentre studies. Clin Sci 2017; 131:1361–73.

[20] Ikram MA, van der Lugt A, Niessen WJ, Koudstaal PJ, Krestin GP, Hofman A, et al. The Rotterdam Scan Study: design update 2016 and main findings. Eur J Epidemiol 2015;30:1299–315.

[21] Power MC, Tingle JV, Reid RI, Huang J, Sharrett AR, Coresh J, et al. Midlife and late-life vascular risk factors and white matter microstructural integrity: the atherosclerosis risk in communities neurocognitive study. J Am Heart Assoc 2017;6. https://doi.org/10.1161/JAHA.117.005608.

[22] Charlton RA, Schiavone F, Barrick TR, Morris RG, Markus HS. Diffusion tensor imaging detects age related white matter change over a 2 year follow-up which is associated with working memory decline. J Neurol Neurosurg Psychiatry 2010;81:13–9.

[23] Biesbroek JM, Weaver NA, Biessels GJ. Lesion location and cognitive impact of cerebral small vessel disease. Clin Sci 2017; 131:715–28.

[24] Wang Z, Wong A, Liu W, Yang J, Chu WCW, Au L, et al. Cerebral microbleeds and cognitive function in ischemic stroke or transient ischemic attack patients. Demen Geriatr Cogn Disord 2015; 40:130–6.

[25] Zeestraten EA, Benjamin P, Lambert C, Lawrence AJ, Williams OA, Morris RG, et al. Application of diffusion tensor imaging parameters to detect change in longitudinal studies in cerebral small vessel disease. PLoS One 2016;11:e0147836.

[26] Zeestraten EA, Lawrence AJ, Lambert C, Benjamin P, Brookes RL, Mackinnon AD, et al. Change in multimodal MRI markers predicts dementia risk in cerebral small vessel disease. Neurology 2017; 89:1869–76.