Cerebral Circulation - Cognition and Behavior 3 (2022) 100144

Contents lists available at ScienceDirect

Cerebral Circulation - Cognition and Behavior

journal homepage: www.sciencedirect.com/journal/cerebral-circulation-cognition-and-behavior

Cerebral small vessel disease is associated with concurrent physical and cognitive impairments at preclinical stage

Chih-Ping Chung [a,b,e,*], Li-Ning Peng [b,f], Wei-Ju Lee [b,g], Pei-Ning Wang [a,b,d], Ching-Po Lin [b,c,d], Liang-Kung Chen [b,h,*]

[a] Department of Neurology, Neurological Institute, Taipei Veterans General Hospital, No. 201, Section 2, Shipai Road, Beitou District, Taipei, Taiwan
[b] Aging and Health Research Center, National Yang Ming Chiao Tung University, Taipei, Taiwan
[c] Institute of Neuroscience, National Yang Ming Chiao Tung University, Taipei, Taiwan
[d] Brain Research Center, National Yang Ming Chiao Tung University, Taipei, Taiwan
[e] School of Medicine, National Yang Ming Chiao Tung University College of Medicine, Taipei, Taiwan
[f] Center for Geriatric and Gerontology, Taipei Veterans General Hospital, Taipei, Taiwan
[g] Department of Family Medicine, Taipei Veterans General Hospital Yuanshan Branch, Yi-Lan, Taiwan
[h] Taipei Municipal Gan-Dau Hospital (managed by Taipei Veterans General Hospital), Taipei, Taiwan

A B S T R A C T

Background: Physio-cognitive decline syndrome (PCDS) is a clinical construct of concurrent physical mobility and cognitive impairments in non-demented functional preserved elderly who are at risk of dementia and disable. The present study aimed to evaluate whether cerebral small vessel disease (SVD) is associated with this phenotype of accelerated aging.

Methods: We stratified a non-demented non-stroke community-based population aged 50 or older into four groups: robust, isolated cognitive impairment no dementia (CIND), isolated physical mobility impairment no disable (MIND) and PCDS groups. SVD burden (SVD score) was defined by the presence of severe white matter hyperintensities (WMH), lacune(s) and cerebral microbleed (CMB). Univariate and multivariate analyses were performed to evaluate the cross-sectional relationships between SVD and PCDS.

Results: Seven hundred and nine eligible participants were included. There were 317 (44.7%) classified as robust group, 212 (29.9%) as CIND group, 117 (16.5%) as MIND group and 63 (8.9%) as PCDS group. SVD (SVD score ≥ 2) was significantly associated with PCDS, concurrent mobility physical and cognitive impairments (odds-ratio, OR = 2.3; 95% confidence interval, 95% CI = 1.3-4.0; $p = 0.003$) but not with MIND or CIND, which was independent of age, sex and vascular risk factors. Among three SVD markers, the presence of severe WMH (OR = 1.9; 95% CI = 1.1-3.2; $p = 0.023$) and lacune (OR = 2.5; 95% CI = 1.3-4.8; $p = 0.005$) were significantly and mixed CMB (OR = 2.0; 95% CI = 1.0-4.1; $p = 0.058$) was borderline-significantly associated with PCDS independent of age, sex and vascular risk factors.

Conclusion: SVD was associated with PCDS, a phenotype with concurrent physical mobility and cognitive impairments in the non-demented non-disable elderly population. The present study revealed the clinical features of SVD at early, preclinical stage and has provided insights into the pathophysiology and future management strategy of accelerated functional declines in the elderly.

1. Introduction

Physical and cognitive performance are the major domains of functional ability that affect healthy aging [1,2]. Evidence indicates that physical frailty and cognitive impairment interact significantly during the aging process [3,4]. Several studies have found that physical frailty, particularly gait slowness and handgrip weakness, may increase the risk of future cognitive declines and predict incident dementia of all types [5,6]. In a recent meta-analysis, the risk for dementia was higher among older people with concurrent physical frailty and cognitive impairment compared to those with only cognitive impairment [7]. Therefore, geriatricians have suggested a clinical phenotype of concurrent physical frailty and cognitive impairment, which could predicts future dementia, disability and mortality and help identify the target population with risks of accelerated aging in the community-dwelling elderly. And hopefully, by studying its pathophysiology, we could develop an effective management strategy to reverse the trajectories toward unhealthy aging.

Several operational definitions of this phenotype have been proposed including cognitive frailty, motoric cognitive risk syndrome and physio-cognitive syndrome (PCDS) [8]. PCDS is defined as concurrent mobility impairment (slow gait or/and weak handgrip but without disable) and

* Corresponding authors.
E-mail addresses: cpchung@vghtpe.gov.tw (C.-P. Chung), lkchen2@vghtpe.gov.tw (L.-K. Chen).

https://doi.org/10.1016/j.cccb.2022.100144
Received 13 February 2022; Received in revised form 6 April 2022; Accepted 15 April 2022
Available online 20 April 2022

cognitive impairment (≥1.5 SD below the mean for age-, sex-, and education-matched norms in any cognitive domain but without dementia). In Asian countries, PCDS has a good performance; this defined criterion could identify around 10–15% of community-dwelling older persons without dementia or disability, who are at increased risk for incident disability (Hazard ratio [HR] 3.9, 95% confidence interval [95% CI] 3.0–5.1), incident dementia (HR 3.4, 95% CI 2.4–5.0) and all-cause mortality (HR 6.7, 95% CI 1.8–26.1) [9–13]. The concept and operational definition of PCDS were established by consensus and formally proposed at the 5th Asian Conference of Frailty and Sarcopenia in 2019 [14].

Aging process or/and vascular risk factors cause pathologies in brain microvessels such as arteriosclerosis, lipohyalinosis and amyloid angiopathy [15]. These age-related microvascular pathologies might result in brain parenchymal lesions including brain white matter changes, small infarcts or microhemorrhages which could be detected by brain magnetic resonance imaging (MRI) [15,16]. Brain small vessel disease (SVD) is now diagnosed by these common MRI markers, e.g. severe white matter hyperintensity (WMH), lacune and cerebral microbleed (CMB) [16,17]. SVD is an important etiology of dementia and stroke in the elderly [15]. In several community-based brain MRI cohort studies, before stroke or dementia events occurring, the presence and severity of SVD were also significantly associated with worse cognitive function in the elderly [15–18]. Therefore, we wondered whether asymptomatic (non-demented non-stroke) SVD plays a role in PCDS, a phenotype of accelerated functional decline or accelerated aging. The present study cross-sectionally analyzed the high resolution 3T brain MRI imagings of a community-based population aged ≥ 50 years and aimed to evaluate the associations between SVD and PCDS.

2. Methods

2.1. Study population

The I-Lan Longitudinal Aging Study (ILAS) is a community-based aging cohort study in I-Lan County, Taiwan, that aims to evaluate the mechanisms of unhealthy aging at an early, preclinical stage [19]. Community-dwelling adults aged ≥50 years from Yuanshan Township in I-Lan County were invited to participate. The initial wave of participants was recruited between August 2011 and July 2014. The inclusion criteria of the ILAS were as follows: (1) inhabitants of I-Lan County who were not planning to move soon and (2) aged ≥50 years. In addition, participants who met any of the following conditions were excluded: (1) inability to communicate and complete an interview; (2) inability to complete a simple motor task (for example, a 6-m walk) due to functional disability, (3) presence of any major illness with associated decreased life expectancy (less than 6 months), (4) presence of any contraindication for MRI (such as metal implants), and (5) institutionalization for any reason. In addition, participants diagnosed with neuropsychiatric diseases, such as dementia, stroke, brain tumor, or major depression, were excluded from the present study.

A questionnaire that included information on demographics, educational years, smoking habits, and medical history was assessed. The presence of vascular risk factors such as hypertension, diabetes mellitus, dyslipidemia, and smoking habit were determined by history taking or laboratory investigation. Hypertension was defined as a self-report of a current antihypertensive medication prescription, or as a measurement of systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. Diabetes mellitus was defined as a self-report of current diabetes treatment, or a measurement of HgbA1c ≥ 6.5%. Dyslipidemia was recorded if there was a self-report of the use of statins, or a blood level of total cholesterol ≥ 240 mg/dL.

2.2. Standard protocol approval, registration, and patient consent

The study was approved by the Institutional Review Board of the National Yang-Ming University, Taipei, Taiwan (IRB no. YM109161F). All participants provided written informed consent. All methods were carried out in accordance with relevant guidelines and regulations.

2.3. Physical assessment

Handgrip strength of the dominant hand was measured using digital dynamometry (Smedlay's Dynamo Meter; TTM, Tokyo, Japan); participants sat with their arms by their sides and the best of three readings was used for analysis. The 6-m usual walking speed during dynamic walking and without deceleration was used to assess the gait speed and to define slowness.

2.4. Cognitive assessment

All participants received a face-to-face neuropsychological assessment administered by trained interviewers at baseline and follow-up, including the Mini–Mental State Examination (MMSE) and neuropsychological tests of different cognitive domains:

- Verbal memory: delayed recall in the Chinese Version Verbal Learning Test
- Language: Boston Naming Test, and category (animal) Verbal Fluency Test
- Visuospatial function: Taylor Complex Figure Test
- Executive function: Backward Digit and Clock Drawing Test

2.5. Definitions of PCDS

Mobility impairment was defined as gait slowness and/or handgrip weakness (by cut-offs from the 2019 consensus update of the Asian Working Group for Sarcopenia) [20]. Cognitive impairment was defined as cognitive performance ≥1.5 SD below the mean for age-, sex-, and education-matched controls in any of cognitive domains assessed by our comprehensive objective neuropsychological tests. PCDS was defined as concurrent mobility and cognitive impairments [8]. Participants with isolated mobility impairment would be classified as mobility impairment without disable (MIND) while participants with isolated cognitive impairment would be classified as cognitive impairment without dementia (CIND). Thus, study population would be stratified into four groups, e.g. robust, CIND, MIND and PCDS groups.

2.6. Brain MRI acquisitions

Multimodal neuroimaging acquisition was performed at the National Yang-Ming University to obtain CSVD markers for each participant, including WMH, lacunes, and CMBs. All MRI scans were collected on a single 3Tesla Siemens MRI scanner (Siemens Magnetom Tim Trio, Erlangen, Germany) with a vendor-supplied 12-channel phased-array head coil. All acquired whole-brain MRI scans were without inter-slice gap and interpolation. The following imaging sequences were used. First, T1-weighted images were acquired using a three-dimensional T1-weighted magnetisation-prepared rapid-acquisition gradient echo sequence (repetition time [TR]/echo time [TE]/inversion time [TI] = 3500/3.5/1100 ms; flip angle = 7°; number of excitations (NEX) = 1; field of view (FOV) = 256 × 256 mm; matrix size = 256 × 256; 192 sagittal slices; and voxel size = 1.0 mm^3). Second, T2-weighted fluid-attenuated inversion recovery (FLAIR) images were acquired using a two-dimensional T2-weighted FLAIR multishot turbo-spin-echo sequence (TR/TE/TI = 9000/143/2500 ms; flip angle = 130°; NEX = 1; FOV = 220 × 220 mm; matrix size= 320 × 320, echo train length= 35; 63 axial slices; and voxel size = 0.69 mm × 0.69 mm × 2.0 mm). Third, susceptibility-weighted images (SWI) were acquired using a three-dimensional SWI sequence (TR/TE = 28/21 ms; flip angle = 15°, FOV = 256 × 224 mm; matrix size = 256 × 224; 88 axial slices; bandwidth =120 Hz/Px; and voxel size = 1.0 × 1.0 × 2.0 mm). Before the

image pre-processing, all the acquired MRI scans were visually examined by an experienced neuroradiologist to exclude any data with severe motion artifacts or gross brain abnormalities including trauma, tumor, and intracerebral hemorrhagic or territorial infarct lesions (in the territory of large arteries or their branches but not of a perforating artery).

2.7. Volume quantification of WMH

We applied the previously established analytical framework to estimate volumetric information of multiple tissue types for each individual [18]. All the following analyses were conducted with Statistical Parametric Mapping (SPM12, version 7487, Wellcome Institute of Neurology, University College London, UK, http://www.fil.ion.ucl.ac.uk/spm/) and Matlab R2016a (The Mathworks, Inc., Natick, MA, USA) using default settings. First, individual T2-weighted FLAIR scan was affine-registered to the corresponding T1-weighted scan, and then served as the inputs for generating a native T1 space WMH probability map and lesion-filled T1 images using the Lesion Segmentation Toolbox (LST, version 3.0.0, https://www.applied-statistics.de/lst.html) (Fig. 1). Second, all the lesion-filled T1 anatomical scans were processed using the standard Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra–voxel based morphometry (DARTEL-VBM) approach to obtain the corresponding deformation field for each individual. Finally, all the native T1 space tissue probability maps (including grey matter, white matter, cerebrospinal fluid and WMH) were spatial transformed into the standard Montreal neurological institute (MNI) space using subject-specific deformation field and then modulated to obtain absolute volumetric information of total intracranial volume (TIV, summation of grey matter volume, white matter volume and cerebrospinal fluid volume) and WMH volume simultaneously.

2.8. Detection and assessment of other SVD MRI markers [17]

Lacunes were assessed using T2-weighted FLAIR anatomical scans. Lacunes are defined as small (<15 mm in diameter) cerebrospinal fluid-containing cavities, located in the deep gray or white matter, with adjacent WMH. CMBs were defined as small, rounded or circular, well-defined, hypointense lesions within the brain parenchyma with clear margins and ≤10 mm in size on SWI. Microbleed mimics, such as vessels, calcification, partial volume, air-bone interfaces, and hemorrhages

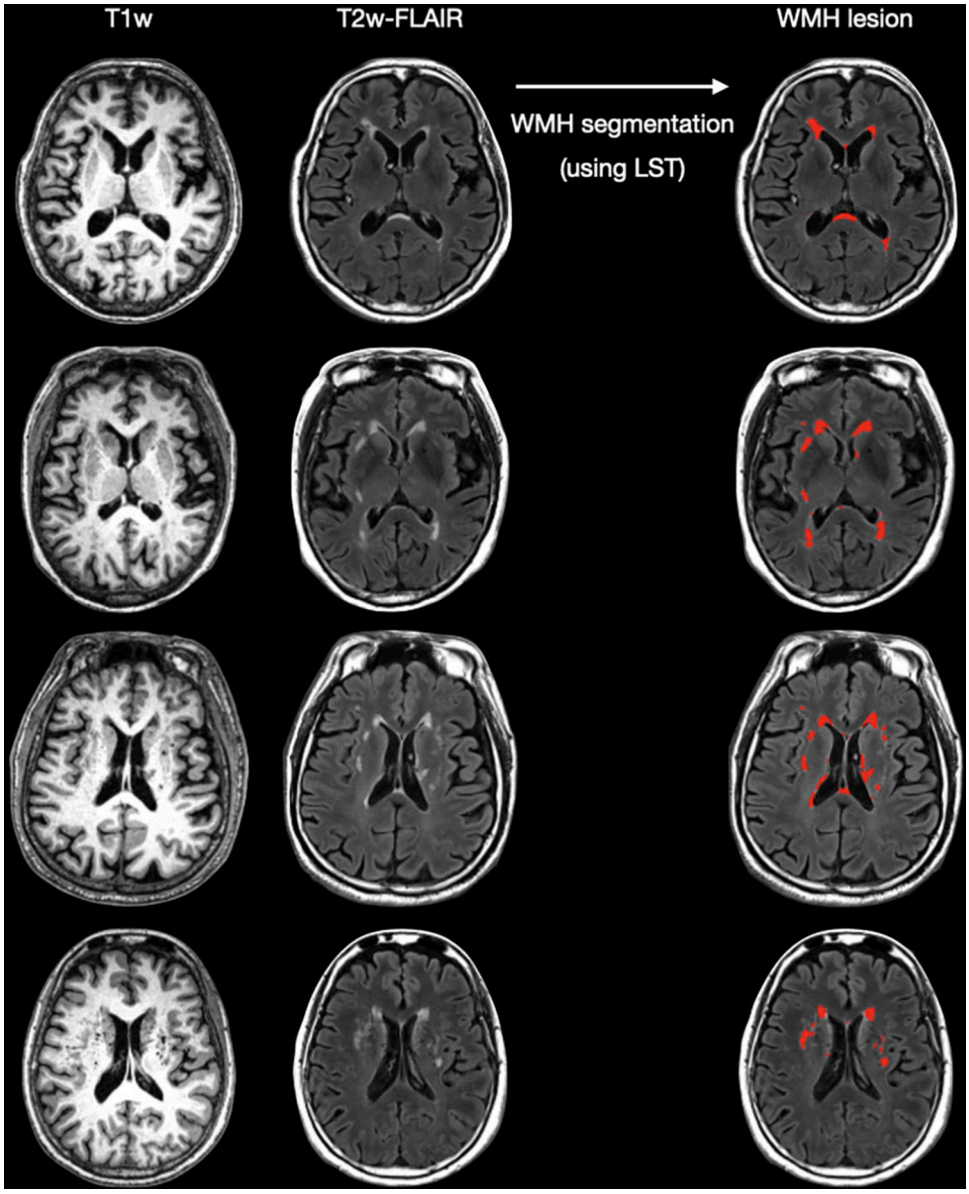

Fig. 1. Example of white matter hyperintensity segmentation.

within or adjacent to an infarct, were carefully excluded. Intra-rater reliability was assessed by evaluating CMBs in 20 randomly sampled images at a separate time (K, 0.83; 95% confidence interval [CI], 0.79–0.90). We also reassessed CMBs in the 25 randomly sampled images previously assessed by Dr. Chung and another investigator (K, 0.82; 95% CI, 0.79−0.88). CMBs were classified into deep, infratentorial, and lobar categories. Individuals with CMBs were divided into two types according to the CMB topography: strictly lobar (CMB exclusively located in lobar regions) and mixed CMB (deep and/or infratentorial CMB with or without lobar CMB).

2.9. Definition of SVD

We used a simple SVD score to represent the SVD burden [21]. One point was given for the presence of any lacune, severe WMH (defined as $>50^{th}$ percentile of WMH volume/TIV ratio [0.07%]), and CMB; thus, the simple SVD score ranged from 0 to 3. We defined participants of SVD as having SVD score ≥ 2.

3. Statistical analyses

Analyses were performed using SPSS version 22.0. (IBM, Armonk, NY, USA). All data are presented as mean (standard deviation, SD) or median (range) for continuous variables and number (percentage) for discrete variables. Group comparisons were made using the nonparametric Kruskal-Wallis test with post-hoc analyses. When appropriate, chi-square or Fisher's exact tests were performed for categorical variables. Multivariate regression analyses were performed to evaluate the independent associations between SVD and PCDS. The covariates included the age, sex, vascular risk factors (presence of hypertension, diabetes mellitus, dyslipidemia and cigarette smoking habits) or/and each SVD marker. Odds-ratios (ORs) with 95% CIs would be provided. *P* value < 0.05 was considered statistically significant. SVD population attributable risk fraction of PCDS was measured as (observed case number of PCDS with SVD exposure minus estimated (expected) case number of PCDS with no SVD exposure)/case number of PCDS.

4. Results

Among the initial sampling population of the ILAS recruited between August 2011 and July 2014, 760 individuals without stroke and dementia had received comprehensive MRI modalities for SVD detection and evaluation. We excluded nine individuals with incidentally found brain tumors, 16 individuals with problematic images due to head motion and 26 individuals without sufficient physical and cognitive assessments. There were 709 participants' data and neuroimagings eventually included in the analyses. A flow chart of the study population is illustrated in Fig. 2**.** There were 317 (44.7%) classified as robust group, 212 (29.9%) as CIND group, 117 (16.5%) as MIND group and 63 (8.9%) as PCDS group.

Demographic and clinical data of the study population are demonstrated in Table 1. PCDS and MIND groups had the oldest ages; these two groups, respectively, were older than the robust and the CIND groups revealed by *post-hoc* analyses. Four groups had similar sex distributions. As to the frequency of vascular risk factors, PCDS had more prevalent hypertension, diabetes mellitus and dyslipidemia with statistical significance in the frequency of diabetes mellitus. There was also significant difference in the frequency of cigarette smoking habits between groups; MIND had the most prevalent cigarette smoking habits. *Post-hoc* analyses showed that PCDS and MIND, respectively, had slower gait and weaker handgrip strength than CIND and the robust. In group comparisons of cognitive functional tests with *post-hoc* analyses, PCDS had lower scores than MIND and than robust in all cognitive domains. The results also showed that PCDS had lower scores than the CIND in all cognitive tests except in clock drawing test.

4.1. SVD profiles in four groups

Table 2 shows the details and comparisons of SVD profiles among four groups. The results showed a significant difference of SVD severity (SVD score) among four groups. PCDS group had the least proportion of people with SVD score zero (28.2% versus 42.9-52.4% in the other three groups) and the most proportion of people with severer SVD (SVD score ≥ 2; 33.3% versus 11.3-19.1% in the other three groups) (Table 2; Fig. 3**A**). We also tested whether there were group differences in the profiles of each SVD marker (Table 2; Fig. 3**B-E**). The results showed significant differences in the frequencies of severe WMH ($> 50^{th}$ percentile of WMHV/TIV ratio) and lacune(s) among groups. As to the CMB profiles, the results depended on their topographic characteristics; group differences only showed significance in the frequencies of mixed

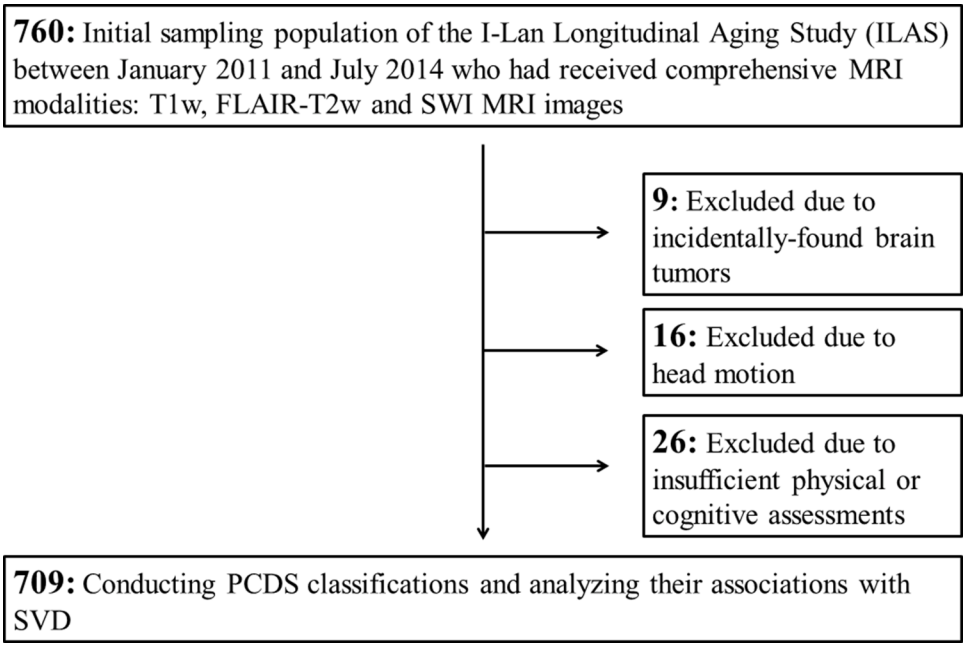

Fig. 2. Flow chart of study population recruitment.

Table 1
Demographic and clinical data in four groups: robust, isolated cognitive impairment no dementia, isolated mobility impairment no disable, and physio-cognitive decline syndrome groups.

	Robust	CIND	MIND	PCDS	*p* value
Population number (%)	317 (44.7)	212 (29.9)	63 (8.9)	117 (16.5)	–
Age, years, mean (SD)	60.7 (7.6)	61.5 (8.1)	64.7 (9.7)	65.8 (9.2)	< 0.001[a]
Sex, men, number (%)	146 (46.1)	86 (40.6)	33 (52.4)	52 (44.4)	0.361
Education, years, mean (SD)	8.1 (5.1)	6.9 (5.1)	6.9 (5.4)	5.0 (4.7)	<0.001[b]
Vascular risk factors, number (%)					
Hypertension	97 (30.6)	73 (34.4)	16 (25.4)	49 (41.9)	0.078
Diabetes mellitus	38 (12.0)	24 (11.3)	7 (11.1)	27 (23.1)	0.012
Dyslipidemia	14 (4.4)	9 (4.2)	4 (6.3)	12 (10.3)	0.088
Cigarette smoking	82 (25.9)	44 (20.8)	20 (31.8)	33 (28.2)	0.046
Physical mobility functions, mean (SD)					
Gait speed, m/s	1.8 (0.4)	1.7 (0.4)	1.4 (0.4)	1.4 (0.4)	<0.001[a]
Handgrip strength, kgw	31.5 (9.0)	30.4 (8.6)	23.6 (7.8)	22.1 (7.5)	<0.001[a]
Cognitive functions, score, mean (SD)					
Chinese Version Verbal Learning Test	7.3 (1.4)	6.2 (1.9)	6.6 (1.8)	5.3 (2.3)	<0.001[c]
Boston naming test	13.1 (2.1)	12.1 (2.5)	12.2 (2.2)	11.2 (2.7)	<0.001[d]
Verbal fluency test	16.4 (5.1)	14.3 (4.6)	14.9 (3.9)	12.0 (3.9)	<0.001[e]
Taylor complex figure test	33.1 (3.7)	30.0 (6.8)	32.0 (4.6)	27.0 (9.1)	<0.001[f]
Backward digit test	4.6 (1.5)	3.2 (2.2)	4.0 (1.5)	2.4 (2.1)	<0.001[d]
Clock drawing test	8.7 (1.7)	7.3 (2.5)	8.4 (2.1)	6.8 (2.6)	<0.001[g]

Post-hoc analyses: [a]PCDS and MIND, respectively, were significantly different than robust and CIND. [b]PCDS was significantly different than robust and CIND. [c]PCDS, MIND and CIND, respectively, were significantly different than robust; PCDS was significantly different than the other three groups. [d]PCDS and CIND, respectively, were significantly different than MIND and the robust; PCDS was significantly different than the other three groups. [e]PCDS and CIND, respectively, were significantly different than robust; PCDS was significantly different than the other three groups. [f]CIND was significantly different than robust; PCDS was significantly different than the other three groups. [g]PCDS and CIND, respectively, were significantly different than MIND and the robust.
Abbreviations: CIND = cognitive impairment no dementia; MIND = mobility impairment no disable; PCDS = physio-cognitive decline syndrome.

CMB but not of strictly lobar CMB. Among four groups, PCDS group had the most severe WMH and the most people with lacune(s) and mixed CMB(s).

We also measured the SVD attributable risk fraction of PCDS (Fig. 4). The results showed that about 21.1% of PCDS were attributable to SVD.

4.2. Multivariate analyses of associations between SVD (SVD score ≥ 2) and PCDS

To validate the independent association between SVD and PCDS, we performed multivariate analyses adjusting for age, sex and vascular risk factors (Table 3). The results showed that SVD (SVD score ≥ 2) was significantly associated with PCDS, concurrent mobility physical and cognitive impairments, but not with isolated mobility physical impairment (MIND) or isolated cognitive impairment (CIND). People of SVD had an OR of 2.3 developing PCDS compared with people of non-SVD, which was independent of age, sex and vascular risk factors.

Table 2
The presence and severity of cerebral small vessel disease on neuroimaging markers in four groups: robust, isolated cognitive impairment no dementia, isolated mobility impairment no disable, and physio-cognitive decline syndrome groups.

	Robust	CIND	MIND	PCDS	*p* value
Population number (%)	317 (44.7)	212 (29.9)	63 (8.9)	117 (16.5)	–
SVD score category, number (%)					<0.001[a]
0	166 (52.4)	98 (46.2)	27 (42.9)	33 (28.2)	
1	112 (35.3)	90 (42.5)	24 (38.1)	45 (38.5)	
2	31 (9.8)	20 (9.4)	9 (14.3)	28 (23.9)	
3	8 (2.5)	4 (1.9)	3 (4.8)	11 (9.4)	
WMHV/TIV ratio, %, median (range)	0.05 (0-2)	0.07 (0-1)	0.09 (0-1)	0.14 (0-3)	<0.001[b]
Lacune amount category, number (%)					<0.001
No lacune	294 (92.7)	194 (91.5)	55 (87.3)	90 (76.9)	
1-3 lacune(s)	23 (7.3)	18 (8.5)	8 (12.7)	24 (20.5)	
4-5 lacunes	0	0	0	3 (2.6)	
CMB amount category, number (%)					0.137
No CMB	277 (87.4)	193 (91.0)	53 (84.1)	93 (79.5)	
1-5 CMB	38 (12.0)	18 (8.5)	10 (15.9)	20 (17.1)	
> 5 CMB	2 (0.6)	2 (0.9)	0	4 (3.4)	
CMB location, number (%)					
Mixed CMB	21 (6.6)	11 (5.2)	7 (11.1)	18 (15.4)	0.006
Strictly lobar CMB	18 (5.7)	8 (3.8)	3 (4.8)	6 (5.1)	0.802

[a] Fisher's exact tests. [b]*Post-hoc* analyses showed that PCDS had significantly higher WMHV/TIV ratio than the robust, CIND and MIND respectively. Abbreviations: CIND = cognitive impairment no dementia; MIND = mobility impairment no disable; PCDS = physio-cognitive decline syndrome; SVD = cerebral small vessel disease; WMHV = white matter hyperintensities volume; TIV = total intracranial volume; CMB = cerebral microbleed.

4.3. Multivariate analyses of associations between each SVD marker and PCDS

We further explored which SVD marker was the potential contributor to the significant association between SVD and PCDS with multivariate analyses (Table 4). After adjusting for age, sex and vascular risk factors (model 1 in Table 4), PCDS was significantly associated with WMH and lacune, respectively, and borderline-significantly associated with mixed CMB. The significance remained in the association between PCDS and lacune after simultaneously adding the other SVD markers into adjustment (model 2 in Table 4).

5. Discussion

The main finding is that, at an early, preclinical stage, SVD (SVD score ≥ 2) was significantly associated with PCDS, a phenotype of concurrent physical and cognitive impairment, but not isolated physical or cognitive impairment. In addition, among three common SVD markers (WMH, lacune and CMB), the presence of lacune and severe WMH, respectively, were significantly correlated with PCDS. These significant associations were independent of age, sex and vascular risk factors.

SVD is the primary cause of vascular cognitive impairment/dementia

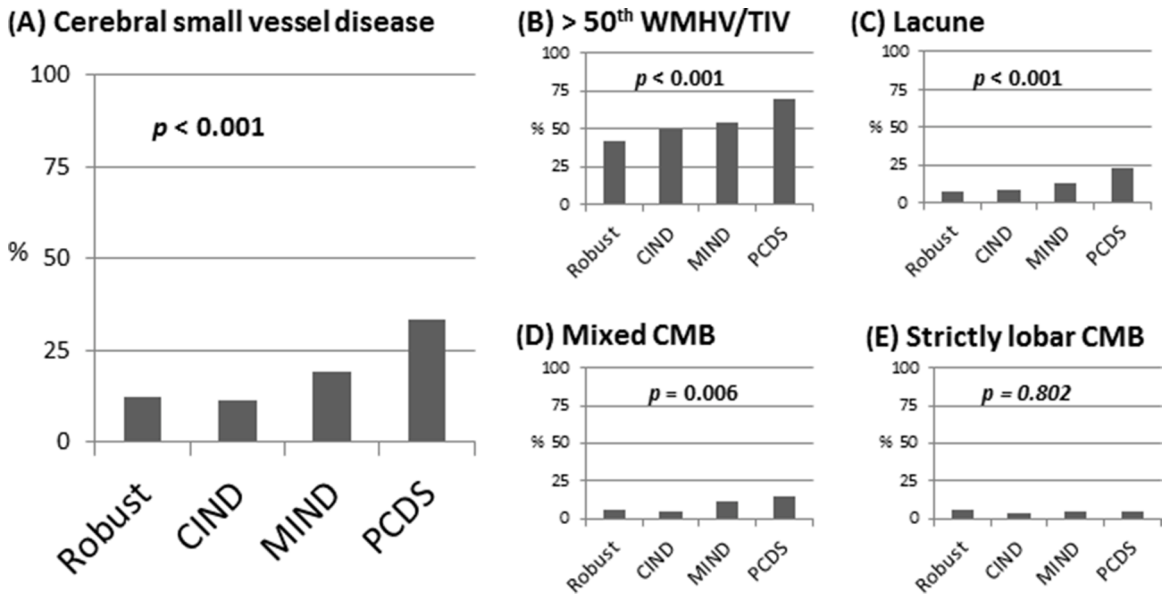

Fig. 3. Frequency of cerebral small vessel disease (SVD score $\geq$ 2) and each SVD marker in four groups and group comparisons with chi-square tests.

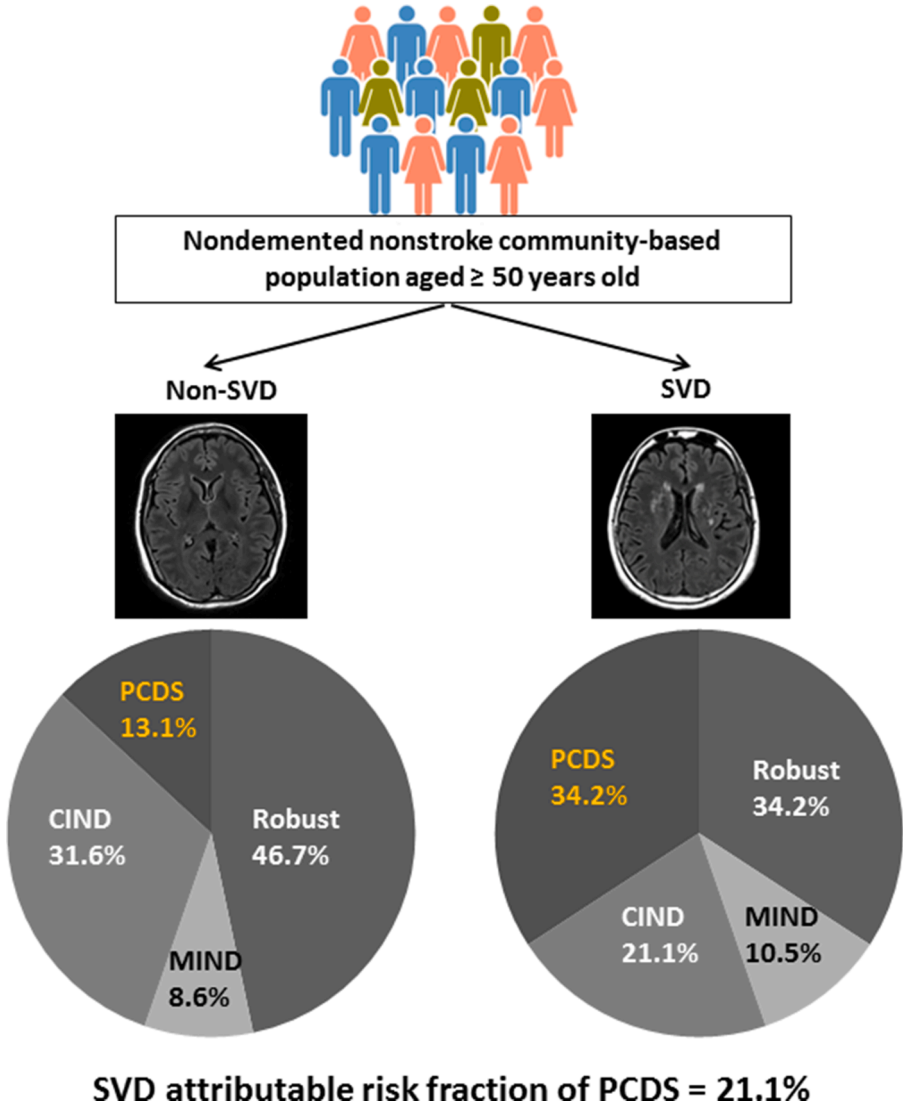

Fig. 4. The proportion of PCDS attributable to SVD.

Table 3
Multivariate analyses of associations between cerebral small vessel disease (SVD score ≥ 2) and physio-cognitive decline syndrome.

	Model 1			Model 2		
SVD versus non-SVD	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**
Robust	Ref.	–	–	Ref.	–	–
CIND	0.8	0.5-1.5	0.543	0.8	0.5-1.5	0.515
MIND	1.2	0.6-2.5	0.666	1.2	0.6-2.6	0.640
PCDS	2.5	1.4-4.3	0.001	2.3	1.3-4.0	0.003

Model 1: adjusted for age and sex; model 2: adjusted for age, sex and vascular risk factors (hypertension, diabetes mellitus, dyslipidemia and cigarette smoking).
Abbreviations: CIND = cognitive impairment no dementia; MIND = mobility impairment no disable; PCDS = physio-cognitive decline syndrome; SVD = cerebral small vessel disease; OR = odds ratio; 95% CI = 95% confidence interval.

Table 4
Multivariate analyses of associations between each cerebral small vessel disease marker and physio-cognitive decline syndrome.

	Model 1			Model 2		
Severe WMHV/TIV ratio	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**
Robust	Ref.	–	–	Ref.	–	–
CIND	1.4	1.0-2.1	0.121	1.4	0.9-2.2	0.113
MIND	1.1	0.5-1.9	0.929	0.9	0.5-1.8	0.812
PCDS	1.9	1.1-3.2	0.023	1.6	0.9-2.8	0.086
The presence of lacune	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**
Robust	Ref.	–	–	Ref.	–	–
CIND	1.1	0.6-2.2	0.742	1.1	0.6-2.2	0.753
MIND	1.4	0.6-3.3	0.501	1.3	0.5-3.4	0.608
PCDS	2.5	1.3-4.8	0.005	2.1	1.1-4.1	0.036
The presence of mixed CMB	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**
Robust	Ref.	–	–	Ref.	–	–
CIND	0.7	0.3-1.6	0.446	0.7	0.3-1.4	0.297
MIND	1.4	0.5-3.5	0.489	1.3	0.5-3.4	0.626
PCDS	2.0	1.0-4.1	0.058	1.4	0.7-3.1	0.349
The presence of strictly lobar CMB	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**
Robust	Ref.	–	–	Ref.	–	–
CIND	0.6	0.3-1.5	0.295	0.6	0.3-1.5	0.269
MIND	0.7	0.2-2.5	0.575	0.7	0.2-2.6	0.602
PCDS	0.7	0.3-1.9	0.519	0.8	0.3-2.1	0.638

Model 1: adjusted for age, sex and vascular risk factors (hypertension, diabetes mellitus, dyslipidemia and cigarette smoking); model 2: adjusted for age, sex, vascular risk factors and other SVD markers (the presence of severe WMHV/TIV ratio, lacune, mixed CMB and strictly lobar CMB).
Abbreviations: CIND = cognitive impairment no dementia; MIND = mobility impairment no disable; PCDS = physio-cognitive decline syndrome; SVD = cerebral small vessel disease; CMB = cerebral microbleed; OR = odds ratio; 95% CI = 95% confidence interval.

[22] and also associated with Alzheimer's dementia [23]. However, the nature or characteristics of impaired cognitive profile in SVD has not been determined. A recent systemic-review and meta-analysis shows that SVD is not only affected executive function and processing speed as previously thought, but also other cognitive domains [24]. Therefore, it is recommended the use of comprehensive neuropsychological tests for SVD research and clinical applications. We have used neuropsychological tests covering several cognitive domains to define cognitive impairment in PCDS. Notably, in our population, PCDS group who was identified with concurrent mobility and cognitive impairments had worse cognitive performances than isolated cognitive impairment group (CIND). The present study revealing significant associations between SVD with PCDS but not isolated cognitive or physical impairments have provided insights into the clinical manifestations of asymptomatic SVD; our results indicate that cognitive impairment in early stage of SVD is accompanied with concurrent physical impairment. Therefore, we suggest that, in addition to comprehensive neuropsychological tests of multiple domains, physical evaluations (particularly gait speed and handgrip strength) are also needed to capture the thorough clinical pictures of SVD.

Previous epidemiological studies have found that frailty is a risk factor of both vascular dementia and Alzheimer's dementia [1–7]. An autopsy study recently published also revealed that frailty was associated with global cognitive function and dementia independent of Alzheimer's and neurovascular neuropathological burdens [25]. The present study showed that 21.1% of PCDS were attributable to the presence of SVD; this fraction of PCDS population might be prevented when SVD lesions were reversed or mitigated. These results indicate that PCDS might be a multiply determined condition, and thus the evaluation and management strategy for PCDS should be multifactorial.

The operational definition of PCDS efficiently identifies the elderly who are at higher risk of accelerating aging [8–13]. Most importantly, functional declines in people with PCDS are potentially reversible or being slowed down. The Taiwan Health promotion Intervention Study for Community Elders (THISCE), a cluster-randomized controlled trial, evaluated a participatory multidomain intervention in community-dwelling ≥65-year-olds, which integrated physical exercise, cognitive training, nutrition advice, and disease management education [26]. A secondary THISCE sub-analysis showed that the multidomain intervention significantly improved cognitive dysfunction in older people with PCDS [27]. Elderly with PCDS seem to be at a critical point toward unhealthy aging. In addition to serving as a phenotype to be identified and to intervene for public health use, we have used PCDS as a study target to evaluate the pathophysiology of and develop the mechanism-based management strategy [8,28]. The present study showed that neurovascular aging, e.g. SVD, is involved in this specific geriatric manifestation of concurrent physical and cognitive impairments. We also demonstrated the relationship between each SVD marker and PCDS. The results suggest that (1) ischemic SVD (lacune with WMH) instead of bleeding SVD (CMB) and (2) hypertensive vasculopathy (presented with mixed CMB) instead of cerebral amyloid angiopathy (presented with strictly lobar CMB), [18,29] are more relevant to the development of PCDS. Therefore, interventions to prevent SVD such as hypertension control might also reverse or prevent further functional declines in the elderly with PCDS.

There are method issues needed to be concerned. We assessed the severity of WMH using semiautomatic volumetric measurement since it offers a more reliable, sensitive, and objective alternative to visual rating scales [30]. The present study defined the presence of severe WMH as $> 50^{th}$ percentile of WMH/total intracranial volume ratio in our study population. The cut-off point of the WMH volume ratio for defining severe WMH might differ between populations. Secondly, since we wanted to elucidate the pathophysiology at the earlier, preclinical stage of unhealthy aging, the present findings were from the community-based community who had no stroke or dementia. Whether the present results of associated clinical features in SVD could be generalized to other population with evident clinical events needs more validation studies. Last, we would need longitudinal studies to validate the causal role of SVD in PCDS.

Conclusion

In non-demented non-stroke adults aged 50 and older, SVD was associated with PCDS, a phenotype with concurrent physical mobility and cognitive impairments. The present study revealed the clinical features related to early stage of SVD and also has provided clues to the pathophysiology and future management strategy of accelerated functional declines in the elderly.

Funding

This work was funded by the Ministry of Science and Technology, Taiwan (MOST 109-2314-B-075-048-MY2, MOST 109-2314-B-075-084- to Chung; MOST 108-2634-F-010-001, MOST 109-2321-B-009-007 to Chen; MOST 108-2321-B-010-013-MY2, MOST 110-2321-B-010-007 to Wang) and Taipei Veterans General Hospital (107 VACS-001 to Chen; V110C-044, V109D52-003-MY3-2 to Chung)

Declaration of Competing Interest

There is no conflict of interest to be disclosed by any of the authors.

References

[1] T Hedden, JD. Gabrieli, Insights into the ageing mind: a view from cognitive neuroscience, Nat. Rev. Neurosci. 5 (2004) 87–96, https://doi.org/10.1038/nrn1323.
[2] JE. Morley, The new geriatric giants, Clin. Geriatr. Med. 33 (2017) xi–xii, https://doi.org/10.1016/j.cger.2017.05.001.
[3] F Panza, M Lozupone, V Solfrizzi, R Sardone, V Dibello, L Di Lena, F D'Urso, R Stallone, M Petruzzi, G Giannelli, N Quaranta, A Bellomo, A Greco, A Daniele, D Seripa, G Logroscino, Different cognitive frailty models and health- and cognitive-related outcomes in older age: from epidemiology to prevention, J. Alzheimers Dis. 62 (2018) 993–1012, https://doi.org/10.3233/JAD-170963.
[4] DA Robertson, GM Savva, RA. Kenny, Frailty and cognitive impairment—a review of the evidence and causal mechanisms, Ageing Res. Rev. 12 (2013) 840–851, https://doi.org/10.1016/j.arr.2013.06.004.
[5] F Panza, V Solfrizzi, MR Barulli, A Santamato, D Seripa, A Pilotto, G. Logroscino, Cognitive frailty: a systematic review of epidemiological and neurobiological evidence of an age-related clinical condition, Rejuvenation Res. 18 (2015) 389–412, https://doi.org/10.1089/rej.2014.1637.
[6] G Kojima, Y Taniguchi, S Iliffe, K. Walters, Frailty as a predictor of Alzheimer disease, vascular dementia, and all dementia among community-dwelling older people: a systematic review and meta-analysis, J. Am. Med. Dir. Assoc. 17 (2016) 881–888, https://doi.org/10.1016/j.jamda.2016.05.013.
[7] L Zheng, G Li, D Gao, S Wang, X Meng, C Wang, H Yuan, L. Chen, Cognitive frailty as a predictor of dementia among older adults: a systematic review and meta-analysis, Arch. Gerontol. Geriatr. 87 (2020), 103997, https://doi.org/10.1016/j.archger.2019.103997.
[8] CP Chung, WJ Lee, LN Peng, H Shimada, TF Tsai, CP Lin, H Arai, LK. Chen, Physio-cognitive decline syndrome as the phenotype and treatment target of unhealthy aging, J. Nutr. Health Aging 25 (10) (2021) 1179–1189, https://doi.org/10.1007/s12603-021-1693-4.
[9] WJ Lee, LN Peng, CK Liang, CH Loh, LK. Chen, Cognitive frailty predicting all-cause mortality among community-living older adults in Taiwan: A 4-year nationwide population-based cohort study, PLoS One 13 (2018), e0200447, https://doi.org/10.1371/journal.pone.0200447.
[10] LK Liu, CH Chen, WJ Lee, YH Wu, AC Hwang, MH Lin, H Shimada, LN Peng, CH Loh, H Arai, LK. Chen, Cognitive frailty and its association with all-cause mortality among community-dwelling older adults in Taiwan: results from I-Lan longitudinal aging study, Rejuvenat. Res. 21 (2018) 510–517, https://doi.org/10.1089/rej.2017.2038.
[11] H Shimada, H Makizako, T Doi, D Yoshida, K Tsutsumimoto, Y Anan, K Uemura, T Ito, S Lee, H Park, T Suzuki, Combined prevalence of frailty and mild cognitive impairment in a population of elderly Japanese people, J. Am. Med. Dir. Assoc. 14 (2013) 518–524, https://doi.org/10.1016/j.jamda.2013.03.010.
[12] H Shimada, T Doi, S Lee, H Makizako, LK Chen, H. Arai, Cognitive frailty predicts incident dementia among community-dwelling older people, J. Clin. Med. 7 (2018) 250, https://doi.org/10.3390/jcm7090250.
[13] K Tsutsumimoto, T Doi, S Nakakubo, M Kim, S Kurita, H Ishii, H. Shimada, Cognitive frailty as a risk factor for incident disability during late life: a 24-month follow-up longitudinal study, J. Nutr. Health Aging 24 (2020) 494–499, https://doi.org/10.1007/s12603-020-1365-9.
[14] LK Chen, H. Arai, Physio-cognitive decline as the accelerated aging phenotype, Arch. Gerontol. Geriatr. 88 (2020), 104051, https://doi.org/10.1016/j.archger.2020.104051.
[15] JM Wardlaw, C Smith, M. Dichgans, Small vessel disease: mechanisms and clinical implications, Lancet Neurol. 18 (7) (2019 Jul) 684–696, https://doi.org/10.1016/S1474-4422(19)30079-1.
[16] L. Pantoni, Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges, Lancet Neurol. 9 (2010) 689–701, https://doi.org/10.1016/S1474-4422(10)70104-6.
[17] JM Wardlaw, EE Smith, GJ Biessels, C Cordonnier, F Fazekas, R Frayne, RI Lindley, JT O'Brien, F Barkhof, OR Benavente, SE Black, C Brayne, M Breteler, H Chabriat, C Decarli, FE de Leeuw, F Doubal, M Duering, NC Fox, S Greenberg, V Hachinski, I Kilimann, V Mok, Oostenbrugge Rv, L Pantoni, O Speck, BC Stephan, S Teipel, A Viswanathan, D Werring, C Chen, C Smith, M van Buchem, B Norrving, PB Gorelick, M Dichgans, STandards for ReportIng Vascular changes on nEuroimaging (STRIVE v1), Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration, Lancet Neurol. 12 (8) (2013 Aug) 822–838, https://doi.org/10.1016/S1474-4422(13)70124-8.
[18] KH Chou, PL Lee, LN Peng, WJ Lee, PN Wang, LK Chen, CP Lin, CP. Chung, Classification differentiates clinical and neuroanatomic features of cerebral small vessel disease, Brain Commun. 3 (2021) fcab107, https://doi.org/10.1093/braincomms/fcab107.
[19] WJ Lee, LK Liu, LN Peng, MH Lin, LK Chen, ILAS Research Group, Comparisons of sarcopenia defined by IWGS and EWGSOP criteria among older people: results from the I-Lan longitudinal aging study, J. Am. Med. Dir. Assoc. 14 (2013) 528, https://doi.org/10.1016/j.jamda.2013.03.019, e1-7.
[20] LK Chen, J Woo, P Assantachai, TW Auyeung, MY Chou, K Iijima, HC Jang, L Kang, M Kim, S Kim, T Kojima, M Kuzuya, JSW Lee, SY Lee, WJ Lee, Y Lee, CK Liang, JY Lim, WS Lim, LN Peng, K Sugimoto, T Tanaka, CW Won, M Yamada, T Zhang, M Akishita, H. Arai, Asian working group for sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment, J. Am. Med. Dir. Assoc. 21 (2020) 300–307, https://doi.org/10.1016/j.jamda.2019.12.012, e2.
[21] A Amin Al Olama, JMS Wason, AM Tuladhar, EMC van Leijsen, M Koini, E Hofer, RG Morris, R Schmidt, FE de Leeuw, HS Markus, Simple MRI score aids prediction of dementia in cerebral small vessel disease, Neurology 94 (2020) e1294–e1302, https://doi.org/10.1212/WNL.0000000000009141.
[22] OA Skrobot, SE Black, C Chen, C DeCarli, T Erkinjuntti, GA Ford, RN Kalaria, J O'Brien, L Pantoni, F Pasquier, GC Roman, A Wallin, P Sachdev, I Skoog, , VICCCS group, Y Ben-Shlomo, AP Passmore, S Love, PG. Kehoe, Progress toward standardized diagnosis of vascular cognitive impairment: guidelines from the vascular impairment of cognition classification consensus study, Alzheimers Dement 14 (2018) 280–292, https://doi.org/10.1016/j.jalz.2017.09.007.
[23] HW Kim, J Hong, JC. Jeon, Cerebral small vessel disease and Alzheimer's disease: a review, Front. Neurol. 11 (2020) 927, https://doi.org/10.3389/fneur.2020.00927.
[24] OKL Hamilton, EV Backhouse, E Janssen, ACC Jochems, C Maher, TE Ritakari, AJ Stevenson, L Xia, IJ Deary, JM. Wardlaw, Cognitive impairment in sporadic cerebral small vessel disease: A systematic review and meta-analysis, Alzheimers Dement 17 (2021) 665–685, https://doi.org/10.1002/alz.12221.
[25] LMK Wallace, O Theou, S Darvesh, DA Bennett, AS Buchman, MK Andrew, SA Kirkland, JD Fisk, K. Rockwood, Neuropathologic burden and the degree of frailty in relation to global cognition and dementia, Neurology 95 (2020) e3269–e3279, https://doi.org/10.1212/WNL.0000000000010944.
[26] LK Chen, AC Hwang, WJ Lee, LN Peng, MH Lin, DL Neil, SF Shih, CH Loh, ST Chiou, Taiwan Health Promotion Intervention Study for Elders research group. Efficacy of multidomain interventions to improve physical frailty, depression and cognition: data from cluster-randomized controlled trials, J. Cachexia Sarcopenia Muscle 11 (2020) 650–662, https://doi.org/10.1002/jcsm.12534.
[27] CK Liang, WJ Lee, AC Hwang, CS Lin, MY Chou, LN Peng, MH Lin, LK. Chen, Efficacy of multidomain intervention against physio-cognitive decline syndrome: a cluster-randomized trial, Arch. Gerontol. Geriatr. 95 (2021), 104392, https://doi.org/10.1016/j.archger.2021.104392.
[28] LK Liu, KH Chou, CCH Hsu, LN Peng, WJ Lee, WT Chen, CP Lin, CP Chung, PN Wang, LK. Chen, Cerebellar-limbic neuro-circuit is the novel bio-signature of physio-cognitive decline syndrome, Aging. (Albany NY) 12 (2020) 25319–25336, https://doi.org/10.18632/aging.104135.
[29] L Puy, M Pasi, M Rodrigues, SJ van Veluw, G Tsivgoulis, A Shoamanesh, C. Cordonnier, Cerebral microbleeds: from depiction to interpretation, J. Neurol. Neurosurg. Psychiatry (2021), https://doi.org/10.1136/jnnp-2020-323951 jnnp-2020-323951.
[30] DM van den Heuvel, VH ten Dam, AJ de Craen, F Admiraal-Behloul, AC van Es, WM Palm, A Spilt, EL Bollen, GJ Blauw, L Launer, RG Westendorp, MA van Buchem, PROSPER Study Group, Measuring longitudinal white matter changes: comparison of a visual rating scale with a volumetric measurement, AJNR Am. J. Neuroradiol. 27 (2006) 875–878.