White Matter Changes and Cognitive Impairment

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DECLARATION OF ORIGINALITY

I hereby declare that all studies that are contained in this thesis are original research carried out by the author in the Division of Neurology, Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong. No part of the thesis has been submitted to other universities or institutions for a degree or diploma.

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LIST OF ABBREVIATIONS

ACA	Anterior cerebral artery
AD	Alzheimer's disease
ADAS	Alzheimer's Disease Assessment Scale
ADC	Apparent diffusion coefficient
ADDTC	State of California Alzheimer's Disease Diagnostic and Treatment Centers
ApoE	Apolipoprotein E
ARWMC	Age-related white matter changes scale
ASPS	Austrian Stroke Prevention Study
AUC	Area under curve
BA	Basilar artery
BP	Blood pressure
C/T	Cytosine/thymine
CBF	Cerebral blood flow
CC	Cognitive complaints
CDR	Clinical dementia rating
CE	Cardioembolism
cGM	Cortical gray matter
CI	Confidence interval
CRP	C-reactive protein
CT	Computed tomography
DM	Diabetes mellitus
DSM-IV	Diagnostic and statistical manual of mental disorders (4th edition)

DTI	Diffusion tensor imaging
DWI	Diffusion weighted imaging
DWMC	Deep white matter changes
FA	Fractional anisotropy
FLAIR	Fluid-attenuated inversion recovery
GDS	Geriatric depression scale
I/D	Insertion/deletion
ICA	Internal carotid artery
ICAM-1	Intercellular adhesion molecule-1
ICC	Intraclass correlation coefficient
ICD-10	The tenth revision International Classification of Diseases and Related Health Problems
IL	Interleukin
IQR	Interquartile range
LAA	Large artery atherosclerosis
MCA	Middle cerebral artery
MCI	Mild cognitive impairment
MDRS I/P	Mattis dementia rating scale-initiation/perseveration
MMSE	Mini-mental state examination
MoCA	Montreal cognitive assessment
MRI	Magnetic resonance imaging
NIHSS	National Institute of Health Stroke Scale
NINDS-AIREN	The National Institute for Neurological Disorders and Stroke with the Association Internationale pour la Recherche et l'Enseignement en

	Neurosciences
NPV	Negative predicting value
OA	Ophthalmic artery
OR	Odds ratio
PCA	Posterior cerebral artery
PET	Positron emission tomography
PI	Pulsatility index
PIB	Pittsburgh compound B
PPV	Positive predicting value
PROGRESS	Perindopril Protection Against Recurrent Stroke Study
PROSPER	Prospective Study of Pravastatin in Elderly at Risk
PVWMC	Periventricular white matter changes
ROCAS	Regression of Cerebral Artery Stenosis
RR	Relative risk
SAO	Small artery occlusion
SMC	Subjective memory complaints
SSVD	Stroke associated with Small Vessel Disease
SUV	Standardized uptake value
SVD	Small vessel disease
TCD	Transcranial Doppler ultrasonography
TIA	Transient ischemic attack
VA	Vertebral artery
VaD	Vascular dementia
VB	Vertebrobasilar

VCI	Vascular cognitive impairment
VISP	Vitamin Intervention for Stroke Prevention
VITATOPS	VITAmins TO Prevent Stroke
WMC	White matter changes

ABSTRACT

Abstract of thesis entitled

White Matter Changes and Cognitive Impairment

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With an aging population, prevalence of dementia is expected to escalate in the coming decades. The burden is especially great in developing countries like China. Similar to Alzheimer's pathology (e.g. amyloid plaque), age- related white matter changes (WMC) are important substrates of dementia. Since WMC are considered to be of ischemic origin, dementia related to WMC is believed to be more preventable than Alzheimer's disease. Yet, studies focusing on WMC have been relatively few. The thesis will cover 4 aspects of WMC and cognitive impairment.

I. Detection of WMC

We hypothesized that pulsatility index (PI) in transcranial Doppler ultrasonography correlates with severity of WMC and it may be used to differentiate WMC patients from normal subjects.

Among 100 stroke patients with WMC and 50 controls without WMC, we found mean bilateral middle cerebral artery (MCA) and vertebrobasilar (VB) PI were higher in patients with WMC (1.53 and 1.23, respectively) than in controls (0.88 and 0.91, respectively; $p<0.001$). Multivariate linear regressions found that mean MCA PI and mean VB PI were independent predictors for total WMC volume (beta=0.43, $p<0.001$ and beta=0.37, $p<0.001$, respectively). (Xiong et al., 2010. Seoul, Korea.)

II. Cognitive impact of WMC

We hypothesized that subjective cognitive complaints are related to severity of WMC.

Seventy-five consecutive lacunar stroke patients without major depression were recruited for the study. At 3 months after stroke, WMC volume, objective psychometric performance, depressive symptoms, and infarct measures were assessed. Thirty-two (42.7%) patients had post-stroke cognitive complaints. In the multivariate logistic regression model, only the severity of depressive symptoms but not WMC was independently associated with post-stroke cognitive complaints.(Xiong et al., 2010)

III. Evaluation of WMC severity

The Age-related WMC (ARWMC) scale has been advocated to be applicable to both MRI and CT. It has been widely used to grade WMC severity. However, the correlation between this scale and cognitive impairment is unknown and the inter-rater reliability of this scale is fair when used in CT. We hypothesized that (a) the total score of ARWMC correlates with cognitive impairment and (b) the inter-rater reliability of the scale can be improved by operationalized the scoring definitions.

We found that even after adjusting for other clinical variables, total score of ARWMC scale were independently associated with Mattis dementia rating scale-initiation/perseveration (MDRS I/P) subset (beta = 0.248,P = 0.001) and mini-mental state examination (MMSE) (adjusted odds ratio 1.181, 95%CI

[1.038–1.343]).(Xiong et al., 2010) Interrater reliability of the operationalized ARWMC scale on CT (0.874, 95% confidence interval [0.780-0.934]) was better than the original scale (0.569, 95% confidence interval [0.247-0.775]). Its intrarater reliability on CT (0.869) and reliability on MRI (interrater: 0.860; intrarater: 0.838) was comparable with the original scale (CT intrarater: 0.750 and on MRI interrater: 0.845; intrarater: 0.853). The original scale and operationalized scale also significantly correlated with WMC volume (operationalized scale rho=0.613, p<0.001, original scale rho=0.638, p<0.001).(Xiong et al., 2010)

IV. Mechanisms for cognitive impairment in WMC

Albeit age-related confluent WMC is an important substrate for cognitive impairment, the mechanisms whereby WMC induce cognitive impairment are uncertain. We hypothesized that WMC volume and regional brain atrophy may predict cognitive impairment and subsequent cognitive decline. We investigated predictors for (a) cognitive impairment and (b) subsequent cognitive decline in 100 ischemic stroke patients with confluent WMC.

In the first cross-sectional study, we found that cortical gray matter (cGM) volume independently accounted for performance on both the MDRS I/P (β=0.241, p=0.045) and MMSE (β=0.243, p=0.032). Models examining frontal subregions revealed that volumes of both left (β=0.424, p<0.001) and right (β=0.219, p=0.045) lateral frontal orbital gyri predicted MDRS I/P whereas education (β=0.385, p<0.001) and left

lateral frontal orbital gyrus (β=0.222, p=0.037) predicted MMSE. Since volumes of WMC and global and frontal cortical gray matter (cGM) were also significantly associated, hence cognitive impairment in patients with confluent WMC was probably mediated by global and frontal cortical atrophy.(Xiong et al., 2009. Singapore.; Mok et al., 2010) In the second longitudinal study, we followed-up the same cohort over 2 years. We found that 33 patients (33%) had cognitive decline. The cognitive decline was associated with cGM atrophy, absence of hyperlipidemia, and low diastolic blood pressure (BP) at baseline. Deterioration in scores of MMSE and MDRS I/P was associated with cGM atrophy, absence of hyperlipidemia, and low baseline scores. (Xiong et al., 2010. Bali, Indonesia.)

The conclusion of the studies reported herein can be summarized as follows: (1) PI in TCD correlates well with WMC volume and helps to differentiate those with and without WMC in stroke patients. (2) Post-stroke cognitive complaints are not related to severity of WMC among lacunar stroke patients. (3) The ARWMC scale correlates with objective cognitive performances and the operational definitions of ARWMC scale improves inter-rater reliability on CT. (4) Cognitive impairment in patients with confluent WMC is mediated by global and frontal cortical atrophy. Predictors for cognitive progression are cortical atrophy, absence of hyperlipidemia, low BP, and low cognitive scores.

論文摘要

隨著人口老齡化的發展，癡呆的患病率在未來十年將逐步上升，其負擔在發展中國家例如中國尤其艱巨。與阿爾茨海默病的病理特徵（老年斑和神經纖維纏結）類似，年齡相關性腦白質病變（WMC）是癡呆的重要底物之一。WMC 主要是由不完全性缺血造成的，因此，WMC 所致的癡呆普遍被認爲比阿爾茨海默病更易於預防。然而，以 WMC 爲重點的研究相對較少。該論文研究了 WMC 與認知功能障礙的四個方面。

I. 檢測 WMC

假設：經顱多普勒超聲波（TCD）中的搏動指數（PI）與 WMC 的嚴重程度相關。PI 值可能可以用於分辨 WMC 病人與正常人。

該研究入組了 100 名中風患者和 50 名對照，測量了他們各血管的搏動指數，包括雙側大腦中動脈（MCA），雙側椎動脈（VA）及基底動脈（BA）。WMC 體積測量運用了半自動分割的方法。該研究發現 WMC 患者的雙側 MCA 平均搏動指數及平均椎基底動脈搏動指數（分別爲 1.53 和 1.23）均比對照（分別爲 0.88 和 0.91）高並具有顯著統計學差異（$p<0.001$）。多因素線性回歸分析發現總 WMC 體積是雙側 MCA 平均搏動指數及平均椎基底動脈搏動指數的獨立預測因數（分別爲 beta=0.43，p<0.001 和 beta=0.37，p<0.001）。搏動指數有助於在中風患者中篩查 WMC。

II. WMC 對認知功能的影響

假設：認知主訴與 WMC 的嚴重程度相關。

該研究連續入組了 75 位腔隙性腦梗死但未合併抑鬱症的患者。在中風 3 個月後，評估客觀神經心理測驗、抑鬱症狀評分、WMC 與腔隙性腦梗死體積。結

果發現 32 位（42.7%）患者主訴中風後認知功能減退。經多因素回歸分析後， 只有抑鬱症狀的嚴重程度是中風後認知功能減退主訴的獨立預測因數。

III. WMC 嚴重程度的評估

血管性認知功能統一標準推薦使用年齡相關性腦白質病變量表（ARWMC）用於評估 WMC 的嚴重程度。它不僅適用於 MRI，而且適用於 CT。但是，該量表與認知功能的關係並不清楚，而且，它在 CT 上的評判間信度只是一般。

假設：（a）ARWMC 量表總分與認知功能損害相關；（b）細化 ARWMC 量表的評分系統可以提高 CT 上的評判間信度。

我們的研究發現在平衡了其他臨床變數後，ARWMC 量表總分與 Mattis 癡呆量表-啓動與保存（MDRS I/P）相關(beta=0.248，p=0.001)，與簡易智能量表（MMSE）亦相關【比值比 1.181，95%可信區間（1.038-1.343）】。細化後的 ARWMC 量表在 CT 上的評判間信度比原始的 ARWMC 量表高，分別爲【0.874，95%可信區間（0.780-0.934）】和【0.569（0.247-0.775）】。它在 CT 及 MRI 上的評判內信度與原始的 ARWMC 量表具有可比性。原始的及細化後的 ARWMC 量表總分都和 WMC 體積顯著相關 （原始量表 rho=0.638，p<0.001；細化後的量表 rho=0.613，p<0.001）。

IV. WMC 致認知功能損害的機制

雖然融合性 WMC 是認知功能損害的重要底物，但是其機制並不清楚。我們假設 WMC 體積和腦區域性萎縮可能預示著認知功能損害及下降。 我們在 100 例缺血性中風合併融合性 WMC 的患者中研究了（a）認知功能損害的預測因數，（b）隨之發生的認知功能下降的預測因數。

首先，在橫斷面研究中，我們發現皮層灰質萎縮（cGM）是 MDRS

I/P(β=0.241，p=0.045)和 MMSE(β=0.243，p=0.032)損害的獨立預測因數。額葉區域中，左(β=0.424，p<0.001)及右(β=0.219，p=0.045)外側額眶葉萎縮預測著 MDRS I/P 損害然而受教育程度(β=0.385，p<0.001)及左外側額眶葉萎縮(β=0.222，p=0.037)預測著 MMSE 損害。由於 WMC 體積和 cGM 體積及額葉體積呈高度負相關，因此，融合性 WMC 患者出現認知功能損害很有可能是由 cGM 和額葉萎縮所介導的。在隨後的前瞻性研究中，我們隨訪了該 100 名患者 2 年。研究發現 33 例(33%)患者出現了認知功能下降。認知功能下降與基線期的 cGM 萎縮，無高血脂，低舒張壓有關。MMSE 和 MDRS I/P 分值的下降與基線期 cGM 萎縮，無高血脂和低基線期分值有關。

本論文的研究結論歸納如下：(1) 搏動指數與 WMC 體積高度相關，它有助於分別中風患者中是否合併 WMC。(2) 在腔隙性梗死患者中，中風後認知障礙主訴與 WMC 嚴重程度無關。(3) ARWMC 量表分值低與客觀認知功能損害有關，細化後的 ARWMC 量表提高了 CT 上的評判間信度。(4) 皮層灰質和額葉萎縮介導了融合性 WMC 患者中的認知功能損害。皮層萎縮，無高血脂，低舒張期血壓及低認知分值預示著認知功能的下降。

PART I LITERATURE REVIEW

Chapter 1 White Matter Changes

1.1 History

In 1894, Otto Binswanger described one case of a syphilitic man in mid-fifties who had developed a progressive decline in mental functions characterized by speech and memory disorders, depression, and personality changes, accompanied by diminished motor power in the lower extremities and slight hand tremor. (Binswanger, 1894; Blass et al., 1991) At autopsy, the dura mater at the base of the skull showed granular deposits, minimal intracranial atherosclerosis, considerable enlargement of the lateral ventricles, marked atrophy of the cerebral white matter, and multiple ependymal thickenings. (Binswanger, 1894; Blass et al., 1991) In 1902, Alzheimer referred to the case described by Otto Binswanger, in an analogous case, he attributed the white matter changes to arteriosclerosis of the long penetrating vessels after a short histological description. (Alzheimer, 1902; Pantoni and Garcia, 1995) However, in 1962, Olszewski suggested that Binswanger's case was neurosyphilis and proposed the term subcortical arteriosclerotic encephalopathy to describe "a form of cerebral arteriosclerosis in which vessels of the white matter and subcortical grey matter are affected predominantly. (Olszewski, 1962) In 1987, Babikian and Ropper's review showed that the pathological diagnosis of Binswanger's disease or subcortical arteriosclerotic encephalopathy was rare and only less than 50 cases were reported till then. (Babikian and Ropper, 1987) In the same year, Hachinski et al introduced the term leukoaraiosis (from the Greek *leuko* [white] and *araiosis* [rarefaction]) to designate periventricular or subcortical (Centrum semi vale) areas of hypodensity on

CT or hyperintensity on T_2-weighted MRI. (Hachinski et al., 1987) The term leukoaraiosis refers to both CT- and MRI-detectable alterations, although these lesions are not completely superimposable as to number, site, and extension. With the development of MRI, leukoaraiosis was also termed white matter hyperintensities because of their appearance as hyperintensities on T2, proton density and fluid-attenuated inversion recovery sequences (FLAIR). (Fazekas et al., 2002) Several other terms are used to describe leukoaraiosis, such as white matter changes (WMC), white matter lesions, and age-related white matter changes. For consistency, we use the term WMC throughout this article.

1.2 Prevalence

WMC is very common in elderly with prevalence ranging from 15% to 98%. (Skoog et al., 1994; Jorgensen et al., 1995; Liao et al., 1996; Longstreth et al., 1996; Liao et al., 1997; Mantyla et al., 1999; de Leeuw et al., 2001; Launer et al., 2006; Wen et al., 2008) The prevalence varies from studies, which mainly depends on the subjects, study design and neuroimaging modalities. The older the subjects are, the higher the prevalence of WMC is. MRI is more sensitive than CT for detecting the WMC. The comparisons between large sample-sized epidemiological studies on prevalence of WMC are summarized in table 1-1.

Table 1-1 Epidemiological studies on prevalence of WMC

Authors	Year	Subjects	Age	Study design	Sample size	Neuroimaging modality	Overall Prevalence	PVWMC prevalence	DWMC prevalence
Skoog, I, et al. (Skoog et al., 1994)	1994	Dementia patients and no dementia subjects	85 years old	Cross-sectional population-based study	236	CT	49.15%	Not given	Not given
Jorgensen, H.S, et al. The Copenhagen Stroke Study (Jorgensen et al., 1995)	1995	Acute TIA and stroke patients	Mean age with WMC: 79 years old; Without WMC: 72 years old	Prospective hospital-based study	1084	CT	15%	Not given	Not given
Longstreth, W.T., et al. The Cardiovascular Health Study (Longstreth et al., 1996)	1996	Community residents	65 years or older	Prospective population-based study	3301	MRI	95.6%	Not given	Not given
Liao, D, et al. The ARIC Study (Liao et al., 1996)	1996	Community residents	55-72 years	Prospective population-based study	1920	MRI	97%	Not given	Not given
Mantyla, R, et al. (Mantyla et al., 1999)	1999	Stroke patients	55-85 years	Cross-sectional Hospital-based study	395	MRI	Not given	98.2%	95.7%
de Leeuw, F.E, et al. The Rotterdam Scan Study (de Leeuw et al., 2001)	2001	Community residents	60-90 years	Prospective population-based study	1077	MRI	95%	80%	92%
Wen, W, et al.(Wen et al., 2008)	2005	Community residents	44-48 years	Cross-sectional population-based study	428	MRI	50.9%	29.4%	34.1%
Launer, LJ, et al (Launer et al., 2006)	2006	Community residents	65-75 years	Cross-sectional population-based study	1805	MRI	Not given	75.9%	92%

* The prevalence was based on proton density. TIA: transient ischemic stroke; PVWMC: periventricular WMC; DWMC: deep WMC.

1.3 Progression of WMC

Many studies have reported longitudinal data on the progression of white matter lesions. Table 1-2 compares the longitudinal studies on WMC progression. The progression rate varies among studies, mainly attributed to the study subjects, follow-up duration, assessment method and baseline severity of WMC. Patients with punctate WMC usually had small increase of WMC, but those with early confluent and confluent WMC at baseline predicted future rapid increase of WMC.(Schmidt et al., 2004) Diastolic blood pressure and presence of diabetes mellitus were also reported to be predictors for WMC progression.(Veldink et al., 1998; Taylor et al., 2003)

Table 1-2 The longitudinal studies on WMC progression

Year and authors	Sample size	Subjects	Follow-up duration	Imaging modality	WMC assessment	Results
1996, Wahlund LO, et al (Wahlund et al., 1996)	13	80 to 90-year old subjects	5 years	0.02 T and 0.5 T MRI	Scheltens scale (Scheltens et al., 1993)	A mild increase.
1998, Veldink JH, et al (Veldink et al., 1998)	14	Community residents	2 years	0.6 T MRI	Scheltens scale	57% (8/14) subjects had increase.
1999, Schmidt R, et al (Schmidt et al., 1999)	273	Community-dwelling elderly without neuropsychiatric disease	3 years	1.5 T MRI	Austrian Stroke Prevention Study visual rating scheme	A progression of WMC in 17.9% of subjects and 8.1% showed marked lesion progression.
2001, Whitman GT, et al (Whitman et al., 2001)	70	Healthy elders with gait dysfunction	4 years	MRI	Volume estimation was done with a point grid and restricted to three consecutive slices	An increase in WMC volume of 1.1 cm^3 over 4 years.
2003, Schmidt R, et al (Schmidt et al., 2003)	296	Community-dwelling elderly without neuropsychiatric disease	6 years	1.5 T MRI	Volumetry	After 3 and 6 years, the total median (interquartile range) volume increase was 0 (0-0.3) and 0.1 (0-0.7) cm^3, and the median (interquartile range) volume increase over the 6-year period was 2.7 (0.5-5.9) cm^3 in subjects with early confluent lesions and 9.3 (7.1-21.0) cm^3 for individuals with confluent WMC at baseline.
2003, Taylor WD, et al (Taylor et al., 2003)	117	Community-dwelling elderly	2 years	MRI	Semi-automated volumetry	1.51 cm^3, approximately a 27% increase in lesion volume.
2003, Streifler JY, et al (Streifler et al., 2003)	596	Patients with brain ischemia and carotid artery disease, but without WMC	6 years	CT	Van Swieten JC visual rating scale (van Swieten et al., 1990)	107 (18.0%) developed restricted WMC and 18 (3.0%) developed widespread WMC.
2007, Sachdev P, et al (Sachdev et al., 2007)	51	Healthy elders	3 years	MRI	Automated volumetry	Total WMC volume had increased by 39.6% (mean 6.48 cm3), i.e., 13.2% per year, with the change in DWMC being 43.8% and 29.7% in PVWMC.
2007, Podewils LJ, et al (Podewils et al., 2007)	179	AD, MCI and cognitive stable subjects	5 years	MRI	Scheltens scale	WMC increased significantly.
2008, Gouw AA, et al (Gouw et al., 2008)	396	Nondisabled participants	3 years	MRI	Modified Rotterdam Progression scale (Prins et al., 2004)	WMC progressed (mean score 1.9) mostly in the subcortical white matter.
2009, Mok V, et al (Mok et al., 2009)	208	Stroke free patients with middle cerebral artery stenosis	2 years	MRI	Semi-automated volumetry	Total patients with severe WMC at baseline had WMC volume increase of 2.4cm^3.

1.4 Risk Factors

Considering the high prevalence of WMC, the epidemiological studies concerned on risk factors for WMC which may be helpful for early prevention of this disease. Age and hypertension were well-known risk factors for WMC, other factors such as female, diabetes mellitus, homocysteinemia, genetics were also reported to increase the risk for WMC. In this thesis, I mainly focus on the well-known risk factors, and briefly introduce other risk factors.

1.4.1 Age

Studies consistently found that age was a prominent risk factor for WMC. (Jorgensen et al., 1995; Henon et al., 1996; Longstreth et al., 1996; Liao et al., 1997; de Leeuw et al., 2001; Basile et al., 2006; Launer et al., 2006) In the Rotterdam Scan study, among subjects aged between 60–70 years, about 87% had DWMC and 78% had PVWMC, whereas in subjects aged between 80–90 years these percentages were 100% and 95%, respectively. And the mean volume of DWMC increased from 0.6 ml for subjects between 60–70 years of age to 3.2 ml for subjects aged between 80–90 years ($p<0.01$). (de Leeuw et al., 2001) Jorgensen study in stroke patients, age was the only factor that significantly increased the risk of leukoaraiosis (odds ratio [OR] per 10-year increase, 2.4; 95% confidence interval [CI]: 1.8-3.1). (Jorgensen et al., 1995) In the Cardiovascular Health Study, 1919 participants had extensive initial and follow-up evaluations, including 2 MRI scans separated by 5 years. It also found that in the initial low grade participants, increased age was associated with increased risk of worsening WMC (OR per year increase, 1.05; 95% CI: 1.01-1.10). (Longstreth et al., 2005) Hence, WMC was also named age-related WMC nowadays.

1.4.2 Hypertension

Besides age, hypertension is constantly reported to be the main risk factor for WMC. Large amounts of cross-sectional and prospective studies had consistently shown that hypertension contributed independently to WMC and their progression. (van Swieten et al., 1991; Liao et al., 1996; Liao et al., 1997; Dufouil et al., 2001; Sierra, 2001; de Leeuw et al., 2002; Jeerakathil et al., 2004; van Dijk et al., 2004; Park et al., 2005; Basile et al., 2006; Choi et al., 2009; Kuller et al., 2010) Recent studies found that mainly high systolic blood pressure (BP) was related to WMC, (Liao et al., 1996; Longstreth et al., 1996; Liao et al., 1997; Goldstein et al., 1998; Park et al., 2005; Kuller et al., 2010) and some studies also indicated that diastolic BP was also associated with WMC. (Karsidag et al., 1995; Liao et al., 1997; Goldstein et al., 1998; Longstreth et al., 2005) Furthermore, de Leeuw FE study found that long-standing hypertension increased the risk of both PVWMC and DWMC. For the participants with more than 20 years hypertension and aged 60-70, the relative risk (RR) for PVWMC and DWMC were 15.8 (95% CI: 3.4-73.5) and 24.3 (95% CI:5.1-114.8), respectively, compared with normotensive subjects. (de Leeuw et al., 2002) And poor control of BP increased the risks of 5.8 (95% CI: 2.1-16.0) and 8.4 (95% CI: 3.1-22.6), respectively. (de Leeuw et al., 2002) The ARIC study also indicated that treated uncontrolled hypertensive subjects have greater odds of WMC than those with treated controlled hypertension, multivariable adjusted OR for WMC grade > or = 3 relative to normotensive subjects was 1.94 (95% CI: 1.32-2.85) for treated controlled hypertensives, and 3.40 (95% CI: 2.30-5.03) for treated uncontrolled hypertensives. (Liao et al., 1996) Moreover, a recent Manhattan study in community elderly found that compared with individuals with low BP and low fluctuations in BP, the risk of WMC increased with higher BP and BP fluctuations. (Brickman et al., 2010) It

suggested that interventions should focus on long-term fluctuating BP and elevated BP. (Brickman et al., 2010)

The main hypothesis regarding the association between high BP and WMC was that long-standing hypertension caused lipohyalinosis of the media and thickening of the vessel walls, which attributed to narrowing of the lumen of the small perforating arteries and arterioles nourishing the deep white matter. (Pantoni and Garcia, 1995) The perforating vessels, which originate from cortical and leptomeningeal arteries, have a relatively poor anastomotic system, which makes the white matter vulnerable to cerebral ischemia. In this sense, low BP has also been reported to be a risk factor for WMC. (Pantoni and Garcia, 1995) Kario, et al study found that nocturnal BP dipping was associated with WMC. (Kario et al., 1996) Hypertension might also cause disturbances in the blood-brain barrier, which might cause lesions in the white matter by cerebral edema, activation of astrocytes, or destructive enzymes or other poisons which pass through the damaged vessel walls. (Pantoni and Garcia, 1995)

1.4.3 Female

Cross-sectional studies have reported that a higher prevalence or higher degree of WMC among women than men. (Henon et al., 1996; Longstreth et al., 1996; de Leeuw et al., 2001; Choi et al., 2009) A longitudinal study in 554 elders (313 men, 241 women) aged 70 to 82 years indicated that women had significantly higher DWMC volume than men at baseline, after 3 years follow-up, they had accumulated approximately twice as much DWMC as men whereas their progression of PVWMC was as same as men. (van den Heuvel et al., 2004)

1.4.4 Diabetes mellitus (DM)

Manschot, et al study showed that patients with type 2 DM had more WMC than controls. (Manschot et al., 2008) It indicated that diabetes altered the glucose and insulin transfer across the blood-brain barrier, thus affected regional metabolism and microcirculation. Chronic hyperglycemia, which further altered membrane permeability and decreased regional blood flow, might lead to permanent cell damage. Therefore, DM seems to be associated with progressive metabolic disturbance in the cerebrovascular bed that may affect blood flow and accelerate the white matter ischemia. (Novak et al., 2006; Manschot et al., 2008) However, many other epidemiological studies found that DM was not associated with WMC, (Jorgensen et al., 1995; Karsidag et al., 1995; Longstreth et al., 1996; Liao et al., 1997) nor did the post-mortem Honolulu-Asian Aging study. (Korf et al., 2006) DM, hypertension, obesity and hyperlipidemia are always treated as metabolic syndrome, the interactions among these factors are complex. Choi HS, et al study has indicated that WMC was associated with mainly hypertension in the metabolic syndrome. (Choi et al., 2009) Whether DM is a risk factor for WMC still needs more exploration.

1.4.5 Cigarette smoking

Cigarette smoking independently predicted WMC severity in some epidemiological studies. (Longstreth et al., 1996; Liao et al., 1997; Jeerakathil et al., 2004; Park et al., 2005; Pu et al., 2009) In the Ansan study, cigarette smoking (OR=1.10; 95% CI: 1.03-1.18) were significantly related to the presence and severity of WMC. (Park et al., 2005) In the Framingham study, number of cigarette per day (OR=1.021, 95% CI: 1.009-1.034) was an independent predictor for WMC volume after controlling for age and sex. (Jeerakathil et al., 2004) However, a recent diffusion tensor imaging (DTI)

study in 10 chronic smokers and 10 nonsmokers further found that lower exposure to cigarette smoking was associated with increased microstructural integrity of the white matter compared with either no exposure or higher exposure. (Paul et al., 2008) But this study was limited by its small sample size and cautions should be paid to interpret the result.

1.4.6 Genetics

WMC were thought to be highly heritable and associated with small artery ischemic stroke. (Atwood et al., 2004; Paternoster et al., 2009) Many studies have attempted to find associations between WMC and polymorphisms in various candidate genes (representing mainly lipid metabolism, vascular tone, and blood pressure regulation pathways). Among all the genes, apolipoprotein E (ApoE) εe4 allells was mostly investigated. A recent meta-analysis evaluated polymorphisms in the ApoE, (Bornebroek et al., 1997; Barber et al., 1999; Bronge et al., 1999; DeCarli et al., 1999; Hirono et al., 2000; Sawada et al., 2000; Bartres-Faz et al., 2001; Nebes et al., 2001; de Leeuw et al., 2004; Szolnoki et al., 2004; Wen et al., 2006; Teodorczuk et al., 2007) angiotensin converting enzyme, (Sierra et al., 2002; Henskens et al., 2005; Purandare et al., 2006) methylenetetrahydrofolate reductase, (Kohara et al., 2003) and angiotensinogen genes which had been studied in more than 2000 subjects. (Paternoster et al., 2009) The meta-analysis found no evidence for an association between ApoE (ε4+/-), methylenetetrahydrofolate reductase (677 cytosine/thymine polymorphism [C/T]), or angiotensinogen (Met235Thr) and WMC. (Paternoster et al., 2009) For the angiotensin-converting enzyme insertion/deletion polymorphism (I/D) there appeared to be a significant association (OR=1.95; 95% CI, 1.09–3.48), but this may be partly attributable to the small study (mainly publication) and other

biases.(Paternoster et al., 2009) So currently, no genetic polymorphism showed convincing evidence for an association with WMC. Larger studies are needed to identify the association between genes and WMC.

1.4.7 Others

Some studies found other factors might increase the risk of WMC. One of the prominent factors is hyperhomocysteinaemia, the details will be addressed in the biomarkers of WMC. Other non-traditional factors are listed in table 1-3.

Table 1-3 Non-traditional factors for WMC

Factors
Alcohol intake (Henon et al., 1996; Liao et al., 1997)
Lower education (Liao et al., 1997)
Left ventricular hypertrophy (Jeerakathil et al., 2004)
History of cardiovascular disease (Jeerakathil et al., 2004)
Hepatocyte growth factor (Anan et al., 2010)
Atrial fibrillation (Henon et al., 1996)
Absence of hyperlipidemia (Henon et al., 1996; Jimenez-Conde et al., 2010)
Fibrinogen (Marti-Fabregas et al., 2002) and Alpha-tocopherol (Schmidt et al., 1996)
Lower forced expiratory volume in 1 second (Longstreth et al., 1996; Guo et al., 2006)
Low income (Longstreth et al., 1996)
Pulse pressure (Lee et al., 2006)

1.5 Pathophysiology

The pathophysiology of WMC is still a matter of investigation. WMC was characterized by partial loss of myelin, axons, and oligodendroglial cells; mild reactive astrocytic gliosis; and sparsely distributed macrophages as well as stenosis resulting from hyaline fibrosis of arterioles and smaller vessels. (Brun and Englund, 1986) The mechanisms hypothesized to be involved in the pathophysiology of WMC include ischemia, dysfunction of autoregulation, blood-brain barrier alterations, chronic edema, apoptosis, genetic factors, combination of the above and unknown.

1.5.1 Ischemia

Nowadays, the most accepted opinion is that WMC represent a vascular process mainly related to cerebral small vessel changes. Alterations of deep small vessels, such as atherosclerosis, were considered to play a central role in the development of WMC. (Pantoni, 2002) Stenosis or occlusion of small vessels might cause sudden or more chronic ischemia resulting in small areas of necrosis (lacunar infarction) or diffuse alterations consistent with the definition of white matter incomplete infarct. (Pantoni, 2002) The clues that support ischemia for WMC are: (1) Epidemiological studies found vascular risk factors were predictors for WMC, especially hypertension. (Longstreth et al., 1996; Liao et al., 1997) (2) Animal studies showed high susceptibility of oligodendrocytes and myelinated axons were ischemic white matter components. (Pantoni et al., 1996; Petito et al., 1998) (3) Pathological study indicated that arteriolosclerosis was frequently found in areas corresponding to radiologically detected WMC; Furthermore, these areas were characterized by a rarefied appearance of white matter similar to that found at the border of true infarcts. (Brun and Englund, 1986) In Rotterdam study, atherosclerosis, indicated by increased common carotid

intima to media thickness, carotid plaques, and a lower arm systolic BP ratio, was related to WMC. (Bots et al., 1993) (4) Functional examinations using positron emission tomography (PET) showed cerebral blood flow and oxygen metabolism were markedly reduced in the white matter as well as an increased oxygen extraction rate in WMC area. (Yao et al., 1990; Yao et al., 1992) (5) Longitudinal studies found that WMC increased the risk of stroke, and vascular death. (Inzitari et al., 1995; Inzitari et al., 1997; Vermeer et al., 2003; Bokura et al., 2006; Buyck et al., 2009; Oksala et al., 2009)

1.5.2 Dysfunction of vasomotor reactivity and autoregulation

The vasomotor reactivity and autoregulation are two elements to keep constant cerebral blood flow. The vasomotor reactivity was the compensatory dilatory mechanism to a vasodilatory stimulus of the intracerebral arterioles. (Bakker et al., 1999) The cerebral autoregulation included static and dynamic autoregulation. (Dawson et al., 2000) The static autoregulation was the adjustments in response to prolonged BP changes, and the dynamic autoregulation was the ability to maintain cerebral blood flow in face of BP changes occurring within seconds. (Dawson et al., 2000) The vasomotor reactivity might be due to loss of neurogenic control or endothelium-dependent dilatation of the cerebral vessels. (Immink et al., 2006) The autoregulation was related to metabolic, myogenic, and possibly endothelium-related mechanisms. (Tiecks et al., 1995) Previous studies supported that these two processes were distinct, having separate effector mechanisms, and interacting in a complex way. (Birns et al., 2009)

Some studies had shown that dysfunction of vasomotor reactivity and autoregulation

were associated with WMC and might be an important factor in the development of WMC. (Isaka et al., 1994; Matsushita et al., 1994; Bakker et al., 1999; Ohtani et al., 2003; Fu et al., 2006; Kozera et al., 2010; Kozera et al., 2010) It was hypothesized that small vessel stenosis impaired the vessel dilation which caused the vessel dilate not enough in response to the changes of systolic BP and consequent cerebral blood flow fluctuations. Inzitari et al study suggested that recurrent transient decrease of cerebral blood flow (hypoperfusion) producing incomplete infarction in the white matter was the basis of WMC. (Inzitari et al., 1997) However, data is lacking on the integrity of cerebral autoregulation and vasomotor reactivity in patients with small vessel disease (SVD) but no concomitant large vessel disease. A recent study in hypertensive patients with SVD without large artery disease found that vasomotor reactivity and autoregulation were related to blood pressure levels and duration of hypertension other than WMC. (Birns et al., 2009) However, a study in 52 middle-aged hypertensive men with no to mild WMC found that the cerebral vasomotor reactivity was impaired in patients with WMC. (Kozera et al., 2010) Whether vasomotor reactivity and autoregulation is impaired in WMC is still controversial. The related studies are listed in table 1-4. Previous studies are of small sample size, either without control, with concomitant large artery disease, or using visual rating scale to rate WMC. Hence, larger studies in pure small vessel disease are needed to investigate the relation of WMC to vasomotor reactivity and autoregulation.

Table 1- 4 Studies on relation of WMC to vasomotor reactivity and autoregulation

Author	Year	Subjects	Sample size	Mean age	Method	WMC assessment	Conclusion	Shortcoming
Yoshinari Isaka, et al	1994	Stroke free high risk population	28	67.8	Acetazolamide	A 4-point visual rating scale with total score 54	Inverse association	Rating PVWMC on T2-weighted images
Matsushita K, et al	1994	Lacunar infarction and hemorrhage patients	51	59.4	Postural changes	Hijdra PVWMC visual rating scale on CT	Inverse association	WMC rating on CT, no exclusion of large artery disease
Bakker SLM, et al	1999	Community residents	73	70.2	CO_2 inhalation	Rotterdam visual rating scale	Inverse association	Not determine systemic blood pressure or large artery disease
Ryo Ohtani, et al	2003	SVD without large artery disease	28	61-78	Postural changes	Schmidt scale	Inverse association	Small sample size
Fu JH, et al	2006	Asymptomatic elderly subjects without large artery occlusive disease	33	76.2	Acetazolamide	Fazekas scale	Inverse association	Small sample size
Birns J,et al	2009	SVD without large artery disease	64	63.7	Thigh cuff release (depressor) and CO_2 inhalation	Volumetric measurement	No association with WMC	Small sample size, lack of control group
Kozera GM, et al	2010	Asymptomatic middle-aged individuals with HT	51	60	Breath holding and hyperventilation tests	Fazekas modified scale	Inverse association	Small sample size and no normal tensive controls

1.5.3 Dysfunction of blood-brain barrier and cerebral edema

Small vessel alterations could lead to damage of the blood-brain barrier and chronic leakage of fluid and macromolecules in the white matter. (Pantoni, 2002) Animal studies also found that chronic ischemic blood-brain barrier insufficiency might be responsible for the development of WMC. (Ueno et al., 2002; Pluta et al., 2008) Increased concentration of cerebrospinal fluid proteins was found in patients with CT detected WMC. (Pantoni et al., 1993; Wallin et al., 2000) A recent MRI study even found that blood-brain barrier permeability increased in normal-appearing white matter in patients with WMC and its presence in normal-appearing white matter would be consistent with it playing a causal role in disease pathophysiology. (Topakian et al., 2010) Moreover, a pathological study showed that Albumin extravasation was widespread in the ageing brain and enhanced in WMC, suggesting dysfunction of the blood-brain barrier might contribute to the pathogenesis of WMC. (Simpson et al., 2010)

White matter diseases similar to WMC (pallor of the WM sparing the U-fibers, accompanied by reactive astrogliosis and small vessel thickening) have been described in conditions in which brain edema might have preceded the appearance of WMC. (Feigin and Popoff, 1963) It suggested that transient cerebral edema might be an added cause of WMC. Arterial hypertension could result in increased interstitial fluid concentration in abnormal white matter and consequent blood-brain barrier alterations, the increased vascular permeability also leads to chronic edema in chronic hypertension. (Nag, 1984; Kobayashi et al., 1985) Apart from the effects of chronic hypertension, hypertensive bouts of short duration could cause fluid transudation and protein leakage. (Inzitari et al., 1997)

Another important cause of interstitial white matter edema was impaired venous return in the deep white matter. Changes in periventricular venules which were characterized by deposition of collagen fibers in the vessel wall, might be responsible for narrowing the venular lumen. This might disrupt the blood brain barrier at the venular level and might increase the perfusion pressure on the arterial side of the capillary bed. (Pantoni and Garcia, 1997) In additional to central impaired venous return, Chung suggested that internal jugular vein might play a key role in the pathogenesis of WMC through a sustained or long-term repetitive retrograde-transmitted cerebral venous pressure and venous outflow insufficiency, which might lead to chronic cerebral venous hypertensions, abnormal cerebral venules structural changes, decreased cerebral blood flow, endothelial dysfunction, and vasogenic edema in cerebral white matter. (Chung and Hu, 2010)

1.5.4 Apoptosis

Apoptosis was the process of programmed cell death without necrotic aspects and with cell shrinkage, nuclear fragmentation, chromatin condensation, and chromosomal DNA fragmentation. (Cummings et al., 1997) Brown et al study had proposed that apoptosis, predominantly of oligodendrocytes, might play a role in the pathogenesis of the WMC. (Brown et al., 2000) The study reported that in the neuropil, the number of cells showing DNA fragmentation was 2.5 times as great in the area of WMC as in the adjacent white matter and 25 times as great as in the nearby cortex. (Brown et al., 2000) Within the area of WMC, they also found numerous small veins that were partially occluded by severe collagenous thickening of the vessel walls. This collagenosis might have contributed to or resulted from chronic ischemia in that area.

(Brown et al., 2000) This case report could be consider as preliminary, but it warrants further investigation. (Pantoni, 2002; Black et al., 2009)

1.5.5 Genetic

Genetically determined factors could play an important role in the development of WMC, although currently no gene was confirmed to be responsible for WMC. (Paternoster et al., 2009) It is possible that other genetic factors contribute, by interaction with conventional risk factors, to the development of WMC. (Pantoni, 2002)

1.6 Clinical Features

WMC were considered silent or benign before, however, in the recent 20 years, a large amount of studies indicated that WMC were predictors for poor outcome. They were reported to be associated with cognitive impairment and decline, gait disturbance, urinary incontinence, depression, stroke and increased risk of death. However, some inconsistent results still exist, part of the discrepancies stem from different sensitivities of rating scales for WMC, small sample size of patients, and using of different neuropsychological tests. (Pantoni and Garcia, 1995)

1.6.1 Cognitive impairment and decline

This is the focus of this thesis, previous studies found WMC was associated with cognitive impairment (executive function, global cognition, mental processing speed, etc) and long-term cognitive decline in both community residents and stroke patients. (Debette and Markus, 2010) The details will be addressed in chapter 2.

1.6.2 Gait disturbance

Abnormal gait in high-functioning elders, such as slow walking speed, deficiency in balance, short-stepped gait, may indicate underlying subtle structural brain abnormalities. The WMC had been postulated to increase the risk of gait disturbance and falls possibly by affecting motor control. (Kuo and Lipsitz, 2004) Previous cross-sectional studies found that the WMC were associated with gait disorder and falls. (Briley et al., 1997; Maki, 1997; Camicioli et al., 1999; Guttmann et al., 2000; Rosano et al., 2006; Rosano et al., 2007; Baezner et al., 2008) Two longitudinal studies also confirmed that some older people developed gait and balance dysfunction that was associated with gradual onset of cerebral white matter disease. (Whitman et al., 2001; Srikanth et al., 2009) Srikanth study showed that the risk of incident falls was doubled in people with WMC volume in the highest quintile of its distribution compared with the lowest (adjusted RR 2.32, 95% CI:1.28–4.14). Greater lesion volume was also associated with poorer gait and greater gait variability. And the effect of WMC volume on the risk of falls was magnified in people with poorer quadriceps muscle strength and greater gait variability. (Srikanth et al., 2009)

Regarding to the WMC location on gait, Srikanth study applied partial least squares regression in brain MRI and DTI. (Srikanth et al., 2010) In this study, bilateral frontal and periventricular WMC-affected voxels corresponding to major anterior projection fibers (thalamic radiations, corticofugal motor tracts) and adjacent association fibers (corpus callosum, superior fronto-occipital fasciculus and short association fibers) showed the greatest covariance with poorer gait. (Srikanth et al., 2010) So WMC probably contribute to gait decline by disconnecting motor networks served by these tracts. (Srikanth et al., 2010) Bhadelia DTI study also found white matter integrity in

the genu of corpus callosum was an important marker of gait in the elderly. (Bhadelia et al., 2009) Iseki study using single photon emission computed tomography suggested that abnormalities in the basal ganglia-thalamo-cortical loops partly explained gait disturbance in WMC. (Iseki et al., 2010)

1.6.3 Urinary incontinence

The WMC was associated with urgency urinary incontinence. (Kuo and Lipsitz, 2004; Sitoh et al., 2004; Poggesi et al., 2008; Sonohara et al., 2008; Kuchel et al., 2009) Kuchel study found in community, among 100 residents, 64% of them had urinary incontinence. The presence of WMC in right inferior frontal regions and selected WM tracts predicts incontinence, incontinence severity, and degree of bother. The study confirmed a critical role for the cingulum in bladder control, and suggested potential involvement of anterior corona radiata and superior fronto-occipital fasciculus. (Kuchel et al., 2009) Tadic study in old women indicated that the presence of WMC in anterior thalamic radiation and superior longitudinal fasciculus might affect continence control. (Tadic et al., 2010)

1.6.4 Depression

Late life depression is a common and heterogeneous disease. Lines of evidence found that WMC was associated with late life depression. (Lesser et al., 1993; Nebes et al., 2002; Steffens et al., 2002; Taylor et al., 2003; Firbank et al., 2005; Godin et al., 2008; Herrmann et al., 2008; Olesen et al., 2010; Vattakatuchery and Joy, 2010) In post-stroke patients, severe deep WMC predicted post-stroke depression. (Tang et al., 2010) To date, the link between WMC and depression remains unclear. Herrmann suggested the vascular depression hypothesis, which held that WMC were caused by

cerebrovascular disease disrupting fiber tracts within frontostriatal circuits. (Herrmann et al., 2008) Because of their involvement in the regulation of mood, disruption of frontostriatal circuits might lead to a disconnection syndrome that corresponded to the clinical and neuropsychological profile of depression. (Herrmann et al., 2008) A DTI study also found that frontolimbic neural pathways might contribute to the pathophysiology of depression. (Cullen et al., 2010)

1.6.5 Stroke and death

The WMC can not only contribute to the development of cognitive impairment, gait disorder, urinary symptoms and depression, but also increase the risk for stroke (Vermeer et al., 2003; Fu et al., 2005; Bokura et al., 2006; Buyck et al., 2009) and death. (Inzitari et al., 1997; Bokura et al., 2006; Oksala et al., 2009) Debette S and Markus H's meta-analysis revealed that stroke yielded a significant association of WMC with incident stroke (HR 3.5; 95%CI: 2.5-4.9, P<0.001) and with death (HR 2.0; 95%CI:1.6-2.7, P<0.001). (Debette and Markus, 2010)

All in all, WMC, especially confluent WMC, predict poor functional outcome and should be emphasized on in future studies. The European Task Force on Age-related WMC also recommended that clinical trials on cerebral SVD should target those with severe WMC and to use its progression as surrogate marker. (Schmidt et al., 2004)

1.7 Neuroimaging

1.7.1 Computed tomography and magnetic resonance imaging

The CT is widely used in clinical practice. WMC appear as hypodensities on CT, with vague borders. Soon after the development of MRI, MRI was found to be more

sensitive than CT in detection of WMC. (Barkhof and Scheltens, 2002) WMC were hypointensities on T1-weighted imaging, and hyperintensities on T2-weight imaging, proton-density sequence, and FLAIR. The FLAIR sequence is desirable because it can suppress the signal of CSF and show the border of WMC clearer.

According to the Rotterdam Scan study, lesions were defined as PVWMC when their largest diameter was adjacent to the ventricle otherwise they were defined as DWMC. (de Groot et al., 2000) Figure 1-1 shows the WMC on CT and MRI. There is controversy as to whether PVWMC and DWMC are distinct in their etiologies, rates of progression, clinical demonstrations and whether these two should be studied independently. A pathological study has shown that smooth periventricular hyperintensities, including caps around ventricular horns, had to be differentiated from subcortical white matter abnormalities as they were related to disruption of the ependymal lining with subependymal widening of the extracellular space without representing a vascular etiology. (Fazekas et al., 1993)

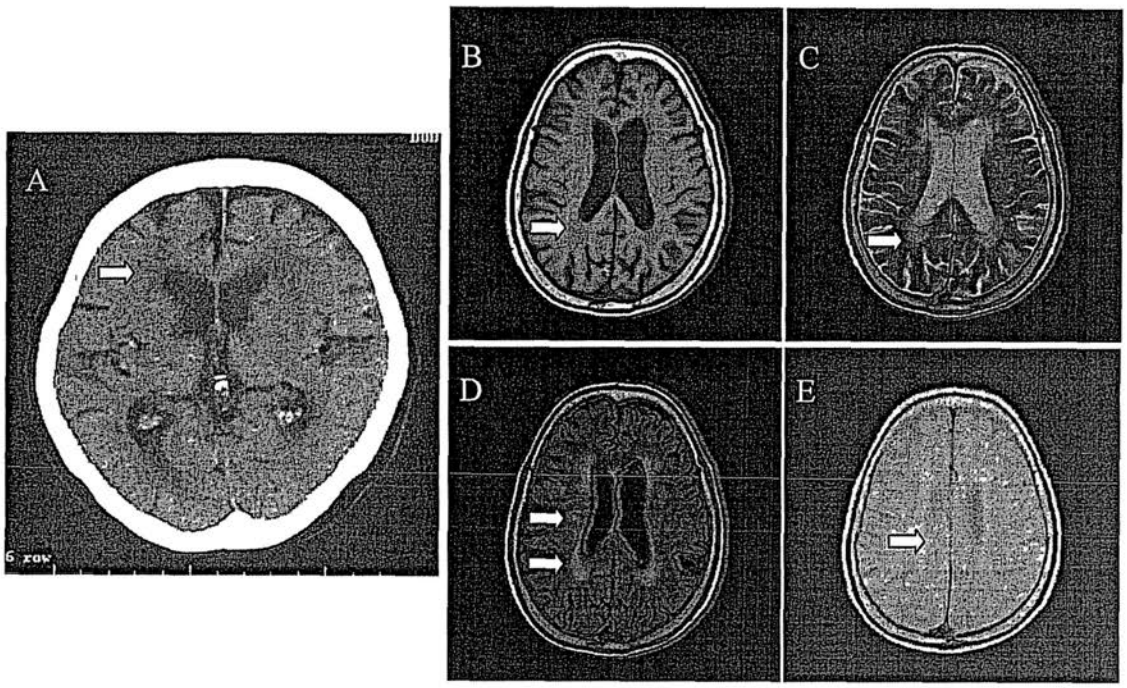

Figure 1-1 WMC on CT and MRI. A: hypodensities on CT; B: hypointensities on T1-weighted MRI; C, D, E: hyperintensities on T2-weighted MRI, proton-density and FLAIR sequences, respectively. D: the lower arrow shows the PVWMC, the upper one shows the DWMC.

1.7.1.1 Visual ratings scales and volumetric measurement

Visual rating scales and volumetric measurement are two methods to assess the severity of WMC. A large amount of visual rating scales on CT and/or MRI have been proposed, each had its own merits and shortcomings. (Scheltens et al., 1998) The visual rating scales were quick and easy to perform on different quality of scans, but they varied from each other. (Fazekas et al., 2002) The data is not quantitative, and has ceiling effect. In addition, discrepancies between the various scales may lead to inconsistent findings. Table 1-5 lists the most popularly used visual rating scales in research. The details of these scales are attached in the appendix.

Table 1-5 Common visual rating scales

Scale	Total score	Anatomical distinction	PVWMC and DWMC	Lesion size	Reliability	Strength	Shortcoming
Scheltens scale (Scheltens et al., 1993)	0 to 84	4 regions and basal ganglia	Yes	Yes	Good	Detail, good reliability	Complex, for MRI use only
Modified Fazekas scale (Fazekas et al., 1987)	0 to 3	No	Yes	Yes	Poor to good (Kozachuk et al., 1990; Leys et al., 1990; Scheltens et al., 1993)	Validated histopathologically (Fazekas et al., 1993)	For MRI use, PVWMC and WMC were rated separately, but no guidelines were offered when both scores are high, causing the same phenomena to be rated twice.(Leys et al., 1990) Some studies only used the DWMC rating as the final score. (Basile et al., 2006; Fu et al., 2006; Kozera et al., 2010)
Rotterdam scan study scale (de Leeuw et al., 2001)	0 to 9 for PVWMC, three categories of DWMC	No	Yes	Yes	Good (de Leeuw et al., 2001)	Detail	For MRI use only
ARWMC scale (Wahlund et al., 2001)	0 to 30	Frontal, temporal, parietal-occipital lobes, basal ganglia and infratentorial regions	No	No	Moderate to good (Wahlund et al., 2001; Xiong et al., 2010)	Applicable to MRI and CT	The inter-rater reliability on CT was fair

With the development of computer science and MRI, volumetric measurement becomes feasible and is favored by research institutes. The volumetry provides continuous data and make studies more comparable. It is more useful for longitudinal studies to assess WMC change than visual ratings scales. However, the assessment relies mainly on manual tracing techniques or semi-automated segmentation methods. These techniques are labor intensive and time consuming. (Tiehuis et al., 2008) Although some automated measurements (Wu et al., 2006; Jongen et al., 2007; Herskovits et al., 2008; Maillard et al., 2008; Tiehuis et al., 2008) have been proposed, these techniques are not popularly used in clinical practice and institutions.

1.7.1.2 Infarct

The cerebral infarct is seen as rounded well-circumscribed hypodensity on CT, hypointensity like CSF on T1-weighted MRI, hyperintensity on T2-weighted MRI, and hypointensity surrounding by a bright rim on FLAIR. (Figure 1-2) Acute infarct appears as hyperintensity on diffusion weighted imaging (DWI) and hypointensity on apparent diffusion coefficient (ADC). Usually the diameter of infarct ranges from 3 to 15 or 20 mm. (Fu et al., 2005; Mok et al., 2005) Volume of infarct can be measured by computerized program. Furthermore, location of infarct is an important aspect for cognitive impairment. Infarct located in strategic sites (e.g. thalamus, genu of internal capsule) might account for the cognitive impairment. (O'Brien et al., 2003; Mok et al., 2005)

1.7.1.3 Perivascular spaces

Perivascular spaces are more visible on MRI than on CT because of the better resolution. They are commonly located in the basal ganglia and centrum semiovale. It

also shows as hypointensity on T1-weighted MRI just like infarct. They can be punctate or linear. In general, the perivascular spaces were found to be <3 mm in diameter except around the anterior commissure where perivascular spaces could be large. (Bokura et al., 1998)

1.7.1.4 Intracerebral hemorrhage

The intracerebral hemorrhage appears as hyperdensity on CT and hyperintensity on T1-weighted MRI. Cortical hemorrhage may be related to cerebral amyloid angiography, and WMC were associated with intracerebral hemorrhage and increase risk of recurrent hemorrhage. (Smith et al., 2004; Lee et al., 2010)

1.7.1.5 Microbleed

The brain microbleed was rounded areas of signal loss, 2 to10 mm in diameter on gradient-echo T2*-weighted MRI. (Schneider, 2007; Yakushiji et al., 2008) (Figure 1-2) It was characterized histologically by the presence of hemosiderin around small vessels, display several presentations, mainly as hypertensive arteriopathy or amyloid angiopathy. (Fazekas et al., 1999) Some studies indicated that the microbleed was associated with WMC and cognitive impairment. (Schneider, 2007; Pettersen et al., 2008; Yakushiji et al., 2008; Nishikawa et al., 2009)

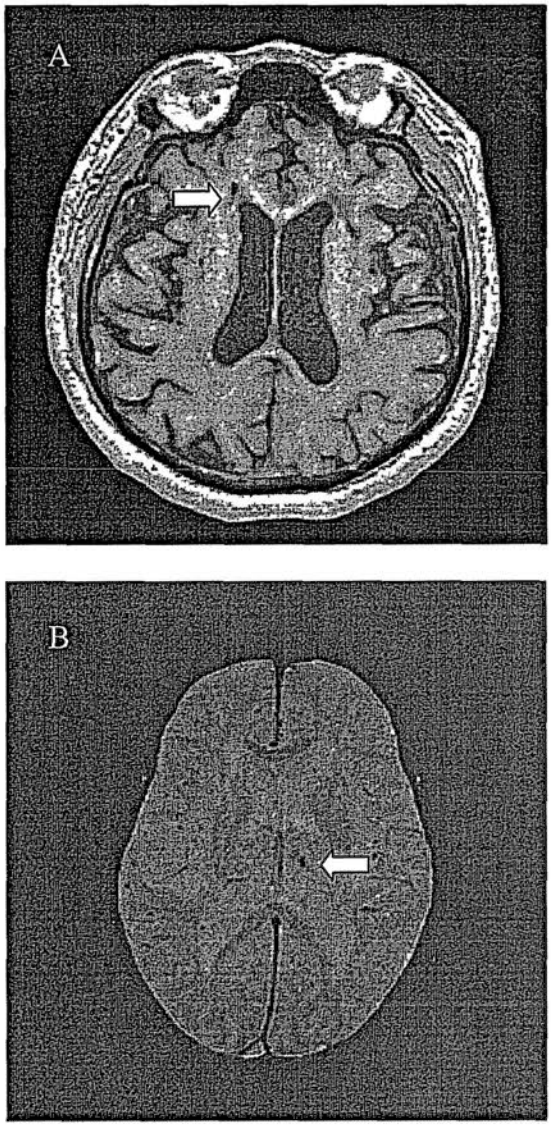

Figure 1-2 Lacunar infarct and microbleed on MRI. A: Right frontal lacunar infarct on T1-weighted imaging; B: Left thalamic microbleed on gradient-echo T2*-weighted MRI.

1.7.2 Diffusion tensor imaging

DTI is a new powerful clinical neuroimaging technique that is sensitive to alterations in cerebral white matter microstructure. In the cerebral spinal fluid and gray matter, diffusion is "isotropic", water molecules can diffuse equally and easily in every direction, while in white matter myelinated fiber, the diffusion was "anisotropic"-restricted along the fiber rather than perpendicular to it. The DTI could provide information on the integrity of white matter tracts by estimation of the diffusion trace (mean diffusivity) and the directionality-fractional anisotropy (FA). (Mok et al., 2008) Reduced FA was associated with WMC pathology: change in the axon's cytoskeleton, reduction in axon density, decline in number and length of myelinated fibers, breakdown in the myelin sheaths, trapping of fluid between thin or lysed sheaths, or bulbous swelling of oligodendrocytes. (Voineskos et al., 2010) Jones et al also found that in WMC, mean diffusivity was elevated and FA was reduced. (Jones et al., 1999) These findings were consistent with axonal loss and gliosis as loss of axons would result in increased diffusion, and loss of ordered axonal tracts and the accompanying non-directionally orientated gliosis might result in marked loss of FA. (Mok et al., 2008)

1.7.3 Positron Emission Tomography (PET)

The PET provides information on cerebral perfusion and metabolism which is different from structural CT and MRI. The PET is the most comprehensive but expensive functional imaging. It can determine quantitatively regional CBF, oxygen metabolism, oxygen extraction fraction, and/or glucose metabolism. (Hachinski et al., 1974) In AD patients with WMC, cerebral blood flow and oxygen metabolism

decreased. (Yamaji et al., 1997) And Tohgi study indicated that WMC significantly decreased CBF in the parietal cortex and in the frontal white matter area. (Tohgi et al., 1998) DeCarli study in 51 healthy individual suggested severe WMC was accompanied by significantly reduced frontal lobe metabolism. (DeCarli et al., 1995) Tullberg study also found that regardless of WMC location, WMC were associated with frontal hypometabolism and executive dysfunction. (Tullberg et al., 2004) These studies provide evidence for the ischemic origin of WMC and further confirm that WMC mainly affect the frontal lobe function.

The Alzheimer's disease and WMC related vascular dementia always interplay and are difficult to differentiate. The ^{11}C Pittsburg compound B (PIB) PET could detect the amyloid burden in the brain, which might be helpful for determining WMC predominant or Alzheimer predominant cognitive impairment. (Archer et al., 2006; Koivunen et al., 2008) PIB had been shown to be more specific than other radiotracers at binding to Aβ at the concentrations achieved during a PET scan. PIB uptake had been shown to be 50–90% higher in cortical brain regions (frontal, precuneus, parietal and temporal cortices) and significant higher retention in striatum (caudate nucleus and putamen), anterior and posterior cingulate gyrus in AD patients compared to controls. (Engler et al., 2006; Fripp et al., 2008; Koivunen et al., 2008)

1.7.4 Single Photon Emission Computed Tomography

Single photon emission computed tomography was less sensitive yet less costly and could provide regional cerebral semi-quantitative assessment on cerebral blood flow. (Ohtani et al., 2003; Caroli et al., 2007; Mok et al., 2008)Different from PET, it only provided the ratios of perfusion at region of interest compared to another brain region,

the absolute CBF could not be obtained. (Mok et al., 2008) $^{99}Tc^{m}$ labeled derivative of hexamethyl propylene amine oxime is the most frequently used tracer for study on WMC. Caroli study using SPECT found that WMC were associated with gray matter hypoperfusion in areas of the insula and temporal neocortex which suggested that WMC might be associated with remote brain cortical dysfunction. (Caroli et al., 2007)

1.7.5 Transcranial Doppler ultrasonography

1.7.5.1 Vascular anatomy

The vascular anatomy is the basis of performing transcranial Doppler ultrasonography (TCD). The brain includes arteries and venous, in this section, we mainly focus on the arteries.

The internal carotid artery (ICA) plays the key role in forming the anterior circulation. The ICA firstly branches off the ophthalmic artery (OA), which is served as an important collateral flow between ICA and external carotid artery. When it enters into skull, it forms S-double curve— the siphon artery. Then it terminates at anterior cerebral artery (ACA) which courses anteromedially and middle cerebral artery (MCA) which courses laterally. The ICA and ACA forms the anterior portion of circle of Willis.

The MCA is the most popular examined artery in TCD research. It originates from the intracranial portion of the ICA and may rarely originate from the A1 segment of the ACA. The MCA is divided into four segments by angiographers based on its relationship to anatomical landmarks: M1 (sphenoidal), M2 (insular), M3 (Opercular) and M4 (Cortical) segments. Since the course of MCA is stable, we usually choose

MCA for TCD monitoring.

The posterior circulation mainly includes bilateral vertebral arteries (VA), basilar artery (BA) and bilateral posterior cerebral artery (PCA). The VAs arise from the subclavian arteries and pass cephalad in the neck to enter the bony canal at the C6 vertebrae. (Ribo and Alexandrov, 2010) They go through the transverse processes of the vertebrae, and enter into the skull through the foramen magnum. At the point, bilateral VAs converge into the BA. The BA courses about 3 cm or more and then terminates in right and left PCA. The PCA forms the posterior portion of circle of Willis. (Ribo and Alexandrov, 2010)

1.7.5.2 Guideline for TCD in intracranial arteries

The examiners usually insonate the intracranial arteries through temporal, occipital and orbital windows. Table 1-6 shows the guideline for TCD in intracranial arteries.

Table 1-6 The guideline for TCD in intracranial arteries (Ribo and Alexandrov, 2010)

Artery	Window	Depth	Direction	Mean velocity
MCA	Temporal	45-65	Toward	32-82 cm/s
ACA	Temporal	62-75	Away	18-82 cm/s
PCA	Temporal	60-68	Bidirectional	20-77 cm/s
Siphon	Orbital	60 to 68	Bidirectional	20-77 cm/s
OA	Orbital	50-62	Toward	Wild range
VA	Occipital	45-80	Away	12-66 cm/s
BA	Occipital	80-100+	Away	12-66 cm/s

1.7.5.3 WMC and TCD

TCD was mostly used for screening large artery disease and monitoring for emboli in clinical practice. Since WMC was considered to be atherosclerotic SVD, on TCD, the velocities of the intracranial large arteries were in normal range, while pulsatility index (PI), which reflected downstream resistance, was reported to be high in WMC. (Kidwell et al., 2001) The PI is calculated from the flow velocities according to this formula: PI = (peak systolic velocity-end diastolic velocity)/mean flow velocity. Other factors such as hypertension, (Cho et al., 1997) diabetes mellitus, (Lee et al., 2000; Tkac et al., 2001; Petrica et al., 2007) lacunar infarcts, (Kidwell et al., 2001; Lee et al., 2007) and high intracranial pressure (Hassler et al., 1988) were also reported to be associated with high PI.

Kidwell study (Kidwell et al., 2001) investigated the association between PI and SVD (WMC and lacunar infarcts) in 55 ischemic stroke patients. The study used the modified Fazekas scale to rate the severity of WMC, and found that PI was an independent predictor of WMC. Receiver operator curve analyses identified PI cut points (1.17 for PVWMC and 0.96 for DWMC) that allowed discrimination of PVWMC with 89% sensitivity and 86% specificity and discrimination of DWMC with 70% sensitivity and 73% specificity. (Kidwell et al., 2001) However, this study had relatively small sample size and WMC was rated by visual rating scales, larger studies with WMC are in need. A recent study examined the PI and WMC in 54 hypertensive mid-aged stroke-free men, they found no consistent association between PI and WMC. (Kozera et al., 2010) That may be due to mild WMC in this study and no enough power to detect the association. Thus, more studies are needed to confirm or refute the association between WMC and PI.

1.8 Chemical Biomarkers

1.8.1 Homocysteine

Homocysteine was a dietary sulphur-containing amino acid derived as an intermediate during the metabolism of methionine. (Hankey and Eikelboom, 1999) It was reported to be a risk factor for stroke, (Perry et al., 1995; Sacco et al., 1998; Bots et al., 1999) myocardial infarction, (Bots et al., 1999; Eikelboom et al., 1999) brain atrophy, (Sachdev, 2005) dementia (Clarke et al., 1998; Sachdev, 2005) and cognitive impairment. (Lehmann et al., 1999; Dufouil et al., 2003; Sachdev, 2005) Nutritional deficiencies in the vitamin cofactors (folate, vitamin B_{12}, and vitamin B_6) required for homocysteine metabolism might promote hyperhomocyst(e)inemia. (Welch and Loscalzo, 1998)

Pathophysiologically, excessive amount of total plasma homocysteine (tHcy)—hyperhomocysteinemia, impaired endothelial function and nitric oxide regulation, smooth muscle cell proliferation, and increased platelet adherence and coagulation that subsequently predisposed to atherosclerosis. (Harker et al., 1974; Wall et al., 1980; Nishinaga et al., 1993; Stamler et al., 1993; Tsai et al., 1996; Welch and Loscalzo, 1998) It was also excitotoxic, increased oxidative stress, promoted apoptosis, promoted the pathophysiological processes of Alzheimer's disease (AD). (Sachdev, 2005)

Perini study found that the hyperhomocysteinemia in acute stoke stage was associated with higher risk of small artery disease subtype of stroke. (Perini et al., 2005)Many studies had indicated that hyperhomocysteinemia was an independent predictor for

WMC even after adjusted by smoking, hypertension, or age. (Vermeer et al., 2002; Dufouil et al., 2003; Hassan et al., 2004; Longstreth et al., 2004; Sachdev et al., 2004; Scott et al., 2004; Wright et al., 2005; Wong et al., 2006; Censori et al., 2007; Seshadri et al., 2008; Anan et al., 2009; Tseng et al., 2009; Fuh, 2010) Homocysteine-lowing therapy was proposed to treat WMC, although the effect is still uncertain.

1.8.2 Inflammatory biomarkers

Atherosclerosis was an important etiology for ischemia which leaded to SVD, while inflammatory processes were involved in the pathogenesis of atherosclerosis. Adhesion molecules mediate attachment and transendothelial migration of leukocytes as a critical step in pathogenesis of atherosclerosis. (Fassbender et al., 1999)

Intercellular adhesion molecule-1 (ICAM-1) and E-selection were expressed by endothelial cells. ICAM-1 was only minimally expressed on resting endothelial cells, but their expression could be increased by cytokines and LPS (endotoxin) activation. In contrast to ICAM-1, which could also be expressed on leukocytes, fibroblasts, or epithelial cells, E-selectin was exclusively expressed on endothelial cells. (Galley and Webster, 2004)

The endothelial cells could also produce a variety of cytokines in response to stimulation with cytokines, bacterial products, hypoxaemia and other mediators. IL-6 was one of its products. (Galley and Webster, 2004) It was also proposed to be involved in the inflammatory process of WMC. (Fornage et al., 2008)

The C-reactive protein (CRP) was a sensitive systemic marker of inflammation and

involved in the endothelial inflammatory response. (Ridker et al., 2000; Khreiss et al., 2004) In the Rotterdam study, CRP level was assessed by high-sensitive assay, they found that higher high-sensitive CRP level has been associated with presence and progression of WMC. (van Dijk et al., 2005)

Table 1-7 summarizes the studies on biomarkers for WMC. Although results are not consistent, in general, soluble ICAM-1 and high-sensitive CRP are two most recommended biomarkers. Longitudinal studies are in need to study the relationship between progression of ICAM-1 and high-sensitive CRP with progression of WMC.

Table 1-7 The comparisons of studies on biomarkers for WMC

Year	Author	Sample Size	Study Design	WMC assessment	Inflammatory Factors	Meaningful Biomarkers
1999	Klaus Fassbender, et al (Fassbender et al., 1999)	64	Case-control	Not mentioned	Soluble endothelial-leukocyte adhesion molecule (sE-selectin), soluble vascular-leukocyte adhesion molecule-1, and soluble intercellular adhesion molecule-1 (sICAM-1)	sE-selectin and sICAM-1
2003	Ahamad Hassan, et al (Hassan et al., 2003)	110	Case-control	Fazekas scale	ICAM1, thrombomodulin, tissue factor and tissue factor pathway inhibitor	ICAM1, thrombomodulin, and tissue factor pathway inhibitor
2005	The Rotterdam Study (van Dijk et al., 2005)	1033	Longitudinal	Rotterdam scale	High-sensitive CRP levels	Higher CRP levels
2005	Hugh S.Markus, et al (Markus et al., 2005)	296	Longitudinal	Volumetry	ICAM, thrombomodulin, tissue factor plasma inhibitor, prothrombin fragments 1 and 2, and D-dimers	ICAM levels
2006	Reinhold Schmidt, et al (Schmidt et al., 2006)	505	Longitudinal	Volumetry	CRP	No association between CRP and WMC volume.
2008	The Cardiovascular Health Study (Fornage et al., 2008)	3644	Cross-sectional, blacks and whites	Presence or not	CRP and IL-6	Plasma IL-6 and CRP levels
2008	Manabu Wada, et al (Wada et al., 2008)	689	Cross-sectional, Japanese	Fazekas scale	CRP and Thrombomodulin	No significant factors
2009	Jinghao Han, et al (Han et al., 2009)	175	Cross-sectional	Fazekas scale	sICAM-1	sICAM-1

Chapter 2 Vascular Cognitive Impairment and White Matter Changes

2.1 Concept of vascular cognitive impairment

The vascular cognitive impairment (VCI) was a heterogeneous group of cognitive disorder that shared a presumed vascular cause. (Moorhouse and Rockwood, 2008) It includes VCI–no dementia, VaD, and mixed dementia (Alzheimer's disease and VaD).

The idea of VCI grew from dissatisfaction with the term multi-infarct dementia. Multi-infarct dementia was originally diagnosed by neuropsychological tests on the basis of the Alzheimer's disease paradigm, and no or only rudimentary neuroimaging. (Moorhouse and Rockwood, 2008) It was sometimes incorrectly used interchangeably with the broader concept of VaD. (Moorhouse and Rockwood, 2008) The concept of VaD was introduced to further refine the description of dementias caused by infarcts of varying sizes including the smaller lacunar infarcts and microinfarcts. (Erkinjuntti and Gauthier, 2009) However, the definition of VaD did not account for the growing neuropathological evidence that most dementias had both neurodegenerative and vascular features that seemed to act synergistically. (Moorhouse and Rockwood, 2008) Various sets of diagnostic criteria for VaD had been proposed over the decades, including the Hachinski Ischemic Score, (Hachinski et al., 1975) Diagnostic and statistical manual of mental disorders(4^{th} edition) (DSM-IV), (Association, 1994) the tenth revision International Classification of Diseases and Related Health Problems (ICD-10), (Organization, 1993) State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC), (Chui et al., 1992) and the National Institute for Neurological Disorders and Stroke with the Association Internationale pour la

Recherche et l'Enseignement en Neurosciences (NINDS-AIREN), (Roman et al., 1993) they all required that memory impairment be present for a diagnosis of vascular dementia to be made. Finally, the criteria for VaD were not adequate to fully describe the vascular causes of early cognitive impairments. (Erkinjuntti and Gauthier, 2009)

2.2 Neuropsychological tests for VCI

VCI might affect several cognitive domains including executive function, memory, psychomotor processing speed and so on, and it typically showed as executive dysfunction. (Nyenhuis et al., 2004; Sachdev et al., 2004) The executive dysfunction referred to a set of loosely related cognitive functions that served the purpose of coordinating higher level cognitive function and emotion and regulating behavioral responses to environmental demands. (Royall et al., 2002) Features of executive dysfunction might include impaired decision making, poor judgment, distractibility, emotion instability, failure of set-shifting, perseveration, poor initiation, failure to inhibit inappropriate responses, poor abstraction, abulia, restricted emotion, deficient empathy, lack of planning, or executive memory loss. The executive memory loss was due to defective retrieval mechanism, it was different from the amnesia in AD, which was due to impaired encoding mechanism related to hippocampal atrophy or lesions. The executive memory loss would have intact recognition memory when cues were given whereas the recognition memory remains poor in AD. (Tierney et al., 2001; Mok et al., 2008)

Therefore, neuropsychological tests should be both sensitive to a wide range of abilities and more attuned to executive function. Timed executive function tests might be especially sensitive to VCI because of the slowed information processing speed

noted in this patient sample. (Hachinski et al., 2006)

The National Institute of Neurological Disorders and Stroke–Canadian Stroke Network vascular cognitive impairment harmonization standards (Hachinski et al., 2006) proposed 3 protocols which take 5 min, 30 min, and 60 min, respectively. The 60-minute protocol was developed for studies that required a breakdown of cognitive abilities by domain, it covered 4 domains: executive function, language, visuospatial, and memory. (Hachinski et al., 2006) The 30-minute protocol was selected from within the 60-minute protocol to be used as a clinical screening instrument for patients with suspected VCI. (Hachinski et al., 2006) Finally, a 5-minute protocol was devised for quick screening of VCI. It was derived from Montreal cognitive assessment (MoCA), (Heyman et al., 1998) including 5-word memory task, 6-item orientation and1-letter phonemic fluency. The 5-minute protocol could also be administered by telephone. (Hachinski et al., 2006) In Hong Kong, the1-letter phonemic fluency was not feasible in Chinese because Chinese characters are pictograms, Wong A, et al has validated the MoCA test in Cantonese. (Wong et al., 2009) The details of three protocols are shown in table 2-1.

Table 2-1 VCI harmonization standards: the 60 min Protocol, 30 min protocol and 5min protocol (Hachinski et al., 2006)

60 min protocol	30 min protocol	5 min protocol
Executive/Activation	Semantic Fluency (Animal Naming)	MoCA subtests
Animal Naming (semantic fluency)	Phonemic Fluency (Controlled Oral Word Association Test)	5-Word Memory Task (registration,
Controlled Oral Word	Digit Symbol-Coding from the Wechsler Adult Intelligence Scale,	recall, recognition)
Association Test	Third Edition	6-Item Orientation
WAIS-III Digit Symbol-Coding	Hopkins Verbal Learning Test	1-Letter Phonemic Fluency
Trail making Test	Center for Epidemiologic Studies-Depression Scale	
List Learning Test Strategies	Neuropsychiatric Inventory, Questionnaire Version (NPI-Q)	
Future Use: Simple and Choice Reaction Time	Supplemental: MMSE, Trail Making Test	
Language/Lexical Retrieval		
Boston Naming Test 2nd Edition, Short Form		
Visuospatial		
Rey-Osterrieth Complex Figure Copy		
Supplemental: Complex		
Figure Memory		
Memory		
Hopkins Verbal Learning		
Test-Revised		
Alternate: California Verbal		
Learning Test		
Supplemental: Boston Naming Test Recognition		
Supplemental: Digit Symbol		
Coding Incidental Learning		
Neuropsychiatric/Depressive Symptoms		
Neuropsychiatric Inventory Questionnaire Version		
Center for Epidemiological Studies-Depression Scale		
Other		
Informant Questionnaire Cognitive Decline in the Elderly,		
Short Form		
MMSE		

2.3 The relationship between subjective cognitive complaints and objective cognitive impairment

In clinical practice, stroke patients always complains of memory loss and slow thinking, whether these kind of subjective cognitive complaints reflect objective cognitive impairment is still uncertain. Subjective memory complaints (SMC) has been mostly studied because they have been one type of everyday concerns cited by people with cognitive difficulties as well as some healthy people. SMC were present in 42.8% of those with dementia and 38.2% of those with MCI. Across all levels of cognitive impairments 39.8% of people had SMC compared with 17.4% in healthy elderly controls (Relative Risk 2.3). Examining the diagnostic value of SMC in dementia, the meta-analysis pooled sensitivity 43.0% and specificity 85.8%. The absence of SMC might be a reasonable method of excluding dementia and MCI and could be incorporated into short screening programs for dementia and MCI. (Mitchell, 2008)

Patient who complains poor memory can accompany with or without objective memory impairment by psychometric assessments. Previous studies have indicated that SMC were more closely correlated with depression (Maor et al., 2001; Kim et al., 2003) and personality traits (Hanninen et al., 1994) than the objective cognitive impairment. The relationship between SMC and objective memory impairment was inconsistent, some studies showed weak association (Bassett and Folstein, 1993; Gagnon et al., 1994; Maor et al., 2001; Martinez-Aran et al., 2005), whereas others showed no association (O'Connor et al., 1990; Kim et al., 2003; Jungwirth et al., 2004; Minett et al., 2005).

In WMC patients which typically impaired the executive function, might not have memory complaints, but complained slow thinking, difficulty in problem solving and so on. The Rotterdam Scan study examined the relationship between WMC and subjective cognitive complaints in 1049 community-dwelling subjects. Data on subjective cognitive dysfunction and its progression were derived from a 15-item questionnaire including memory problems, concentration, planning activities, slow thinking, depression and feeling exhausted. They found that WMC were associated with subjective cognitive failures and in particular with reporting progression of these failures, even in the absence of objective cognitive impairment. (de Groot et al., 2001) Data is lacking on whether subjective cognitive complaints predict VCI or not, which warrants further study.

2.4 The Relationship between white matter changes and vascular cognitive impairment

Lines of evidence found that WMC were important imaging determinant for VCI. Certain factors need to be considered in the evaluation of the relationship between WMC and cognitive impairment. Firstly, the relationship between WMC and VCI might not be linear and a threshold effect was proposed. (Boone et al., 1992) Secondly, cognitive impact of WMC might vary with its location. PVWMC may contribute to VCI more than DWMC. Thus, studies evaluating total WMC might dilute the cognitive influence of region specific WMC. Thirdly, the conventional imaging techniques (CT and MRI sequences) varied across studies, which might have different sensitivity for detecting WMC. Fourthly, psychometric tests in studies might not be comprehensive for the assessment of executive function, consequently, the impact of WMC might be underestimated. (Mok et al., 2008) Lastly, silent brain infarcts and microbleeds were reported to be associated with cognitive impairment, (Vermeer et al.,

2003; Schneider, 2007; Vermeer et al., 2007; Pettersen et al., 2008; Yakushiji et al., 2008) and brain atrophy (global atrophy, cortical gray matter [cGM], hippocampus and medial temporal lobe atrophy) was a confounder between WMC and VCI, these neuroimaging measures were not assessed in some of the studies.

2.4.1 Cross-sectional studies

Albeit some studies found negative association, most cross-sectional studies consistently indicated that WMC were associated with cognitive impairment.

In community, several studies found that WMC affected one or several domains of cognition. Ylikoski R, et al study found that WMC were associated with slowing of distinct motor and attention, as well as slowing of mental processing speed. (Ylikoski et al., 1993) Schmidt R, et al study suggested that the presence of WMC exerted a subtle effect on neuropsychological performance of normal elderly individuals, which became particularly evident on tasks measuring the speed of more complex mental processing. (Schmidt et al., 1993) Fukui T, et al study indicated that WMC affected attention and metal processing speed. (Fukui et al., 1994) The Rotterdam study found that WMC tended to be associated with lower scores on tests of cognitive function and were significantly associated with subjective mental decline. (Breteler et al., 1994) DeCarli C, et al study in 51 healthy olders showed that WMC were associated with poorer frontal lobe cognitive function. (DeCarli et al., 1995) Skoog I, et al study found poorer scores on verbal and spatial ability, perceptual speed, secondary memory, arithmetic and MMSE among subjects with WMC. (Skoog et al., 1996) The cardiovascular health study in 3301 elderly people found WMC patients had lower scores on the modified MMSE and on the digit symbol substitution test suggesting

impairment on global cognition and executive function. (Longstreth et al., 1996) In the LADIS study, WMC independently predicted general cognitive impairment which was assessed using MMSE and the modified Alzheimer's Disease Assessment Scale (ADAS). (van der Flier et al., 2005)

In patients with vascular risk factors, Junque C, et al study found that WMC were related to performance on tasks measuring the speed of information processing and, in particular, on those that involve complex processes. (Junque et al., 1990) However, in 89 hypertensive patient, Schmidt R, et al study did not find any difference on neuropsychological measures between hypertensive subjects with and without WMC. (Schmidt et al., 1995) Leys D study indicated WMC contributed to post-stroke dementia. (Leys et al., 1998) In post-stroke patients, Mok V, et al study found that WMC were associated with impaired executive function. (Mok et al., 2004) However, Mungas D, et al study found that cognitive impairment associated with subcortical ischemic vascular disease (silent infarcts and WMC) was primarily a result of associated hippocampal and cortical changes. (Mungas et al., 2001) Similar finding was observed in confluent WMC, the cGM and frontal atrophy predicted executive dysfunction but not WMC. (Mok et al., 2010)

In view of previous studies, a number of unsolved issues are apparent, (1) the threshold of WMC needed to affect cognition, (2) the neuropsychological features for PVWMC and DWMC, (3) the role of concomitant confounders: lacunar infarcts, callosal atrophy, cGM atrophy, global atrophy, medial temporal atrophy, depression and genetic markers. (Ferro and Madureira, 2002) Longitudinal studies are needed to address these questions.

2.4.2 Longitudinal studies

Although cross-sectional studies showed that the severity of WMC was associated with cognitive impairment, particularly in executive dysfunction. More persuasive longitudinal studies identified that WMC progression paralleled cognitive decline. Table 2-2 summarizes the prospective studies relating to WMC and cognitive decline. Baseline WMC contributed to cognitive decline, especially the PVWMC. In summary, compared with baseline WMC, WMC progression was found to be a better predictor. However, if brain atrophy was added into the predicting models, WMC was not significant whereas global and/or regional atrophy (i.e. medial temporal lobe atrophy, cGM and hippocampus atrophy) contributed to the cognitive decline. (Mungas et al., 2002; Mungas et al., 2005; Schmidt et al., 2005) Smith study in community residents also found that WMC progression might predict normal to mild cognitive impairment, whereas global atrophy predicted mild cognitive impairment to dementia.(Smith et al., 2008) Global brain atrophy might result from both Alzheimer's disease and cerebrovascular disease. (Mungas et al., 2002) Neuronal loss in cortical associative areas, as well as cerebrovascular damage to white matter fiber tracts connecting these areas, might explain cognitive decline associated with global atrophy. Mungas study also indicated that WMC might lead to cGM atrophy, and the cGM atrophy might be more directly affect cognition than WMC progression. (Mungas et al., 2002) There were three possible explanations for the association between WMC and cGM atrophy. First, WMC might induce Wallerian degeneration, which impaired the cortical-subcortical connection and causes deafferentaion, subsequently resulting in neuronal loss in cGM. Second, WMC might represent generalized ischemic vascular disease, which correlated with hypoperfusion (Wen et al., 2004) and hypometabolism

(DeCarli et al., 1995; Tullberg et al., 2004) in the cortex so as to exert effect on cGM atrophy. Third, concomitant cortical microinfarcts might be more directly related to neuronal loss in the cortex albeit this process was beyond the resolution of current MR techniques. (Tullberg et al., 2004) Alternately, cortical neuronal loss may secondary lead to downstream demyelination and hence WMC.

Table 2-2 Longitudinal studies on WMC and cognitive decline

Year	Author	sample size	subjects	Mean follow-up time	WMC assessment	Neuropsychological evaluation	Results
Community-based studies							
2003	Vermeerm SE, et al (Vermeer et al., 2003)	1015	Community subjects	3.6 years	Rotterdam Scan Study scale	Memory, attention, executive function and global cognition	Severity of PVWMC (per SD increase) increased the risk for dementia (HR: 1.59 [1.13-2.25]).
2003	Kuller LH, et al (Kuller et al., 2003)	3608	Community subjects	7 years	Visual rating scale	Global cognition and executive function	Marked WMC predicted dementia (HR: 1.8)
2004	Prins ND, et al (Prins et al., 2004)	1077	Community subjects	5.2 years	Rotterdam Scan Study scale	DSM-III R	PVWMC increased dementia risk (HR: 1.67 [1.25-2.24]).
2005	Prins ND, et al (Prins et al., 2005)	832	Community subjects	5.2 years	Rotterdam Scan Study scale	Global cognition, information processing speed, executive function and memory	Stroke played an intermediate role in the relationship between WMC and cognitive decline.
2008	van Dijk EJ, et al (van Dijk et al., 2008)	668	Community subjects	3 years	Rotterdam Scan Study scale	Memory, psychomotor speed, attention and executive function	WMC progression was associated with a paralleled decline in general cognitive function and in particular with a decreased information processing speed.
2009	Silbert LC, et al (Silbert et al., 2009)	98	Community subjects without cognitive impairment	9.5 years	Volumetry	Global cognition and CDR	Increased progression of total WMC volume (HR: 1.84 [1.3–2.7]) and PVWMC volume (HR: 1.94 [1.3–3.1]) conferred higher risk of persistent cognitive impairment.
2005	Schmidt R, et al (Schmidt et al., 2005)	329	Community subjects	6 years	Volumetry	Memory, attention, conceptualization, visuopractical skills	Brain atrophy mediated the association between WMC volume progression and cognitive decline.
2005	Longstreth WT, et al (Longstreth et al., 2005)	1919	Community subjects	5 years	Visual rating scale (Manolio et al., 1994)	Global cognition and executive function	Worsening WMC grade on serial MRI scans in elderly was associated with cognitive decline in global cognition and executive function.

2009	Jokinen, H (Jokinen et al., 2009)	639	Subjects with no to mild disability	3 years	Fazekas scale	Language, psychomotor speed, attention, executive function and global cognition	WMC contributed to incident dementia, cognitive decline in psychomotor speed, executive function and global cognition.
2010	Debette S, et al (Debette et al., 2010)	2013	Community subjects	5.6 years	Volumetry	DSM-IV(Association, 1994)	WMC volume was associated with an increased risk of dementia (HR: 2.22 [1.32- 3.72]) independent of vascular risk factors and interim stroke.
Hospital based studies							
MCI patients							
2002	Mungas D, et al (Mungas et al., 2002)	120	Normal to demented patients	3 years	Volumetry	Global cognition, language and attention/executive function	Cortical gray matter atrophy at baseline but not WMC volume predicted faster cognitive decline.
2004	DeCarli C, et al (DeCarli et al., 2004)	54	MCI patients	3.1 years	Volumetry	Memory and executive function	Baseline cognitive function but not WMC volume predicted dementia progression.
2005	Mungas D, et al (Mungas et al., 2005)	103	Cognitive normal, impaired and demented patients	4.8 years	Volumetry	Global cognition, attention and executive function	Change in memory was related to hippocampus baseline and hippocampus change. Change in executive function was related to baseline cortical gray matter volume and to change in cortical gray matter volume, hippocampus volume, and total lacune volume.
2006	Geroldi C, et al (Geroldi et al., 2006)	117	MCI patients and healthy controls	15.4 months	ARWMC scale	NINCDS-ADRDA criteria, (McKhann et al., 1984) and research criteria of subcortical vascular dementia (Erkinjuntti et al., 2000)	MTA but not WMC predicted dementia conversion.
2007	Meguro K, et al (Meguro et al., 2007)	539	MCI patients and healthy olders	7 years	Visual rating scale	NINCDS-ADRDA, NINDS-AIREN,(Roman et al., 1993) McKeith criteria (McKhann et al., 2001)	WMC predicted progression to VaD whereas generalized atrophy predicted AD.
2008	Smith EE, et al (Smith et al., 2008)	223	MCI patients and normal subjects	6 years	Volumetry	DSM-IV, NINCDS-ADRDA criteria	High WMC was a predictor of progression from normal to MCI (HR: 3.30 [1.33-8.17]) whereas brain parenchymal fraction (BPF) predict conversion to dementia (HR: 1.10 for each 1% decrease in BPF [1.02-1.19]) and conversion to AD.

2008	Tapiola T, et al (Tapiola et al., 2008)	60	MCI patients	34 months	ARWMC scale	Memory, language, attention, visual spatial, executive function and global cognition	Baseline volumes of the right hippocampus, the right entorhinal cortex and CDR sum of boxes predicted the progression of MCI to dementia, only the baseline volumes of entorhinal cortex predicted conversion of MCI to AD. WMC was not significant in the analyses.
2008	Bombois S, et al (Bombois et al., 2008)	170	MCI patients	3.8 years	Scheltens scale	Memory, language, attention, visual spatial, executive function and global cognition	WMC independently increased the risk of vascular or mixed dementia (HR: 1.14 [1.06 to 1.24]).
2008	van Straaten ECW, et al (van Straaten et al., 2008)	152	Amnestic MCI patients	3 years	Scheltens scale	NINCDS-ADRDA criteria	Only PVWMC were related to an increased risk of AD (HR: 1.59 [1.24–2.05])
2009	Kantarci K, et al (Kantarci et al., 2009)	151	MCI patients	2.1 years	Volume estimation	DSM-III R	WMC volume was not associated with MCI conversion to dementia
2009	Staekenborg SS, et al (Staekenborg et al., 2009)	152	MCI patients	2 years	Scheltens scale	NINCDS-ADRDA, NINDS-AIREN, Neary and Snowden criteria, McKeith criteria	WMC predicted progression to non-AD whereas MTA predicted AD.
Stroke patients and others							
2007	Firbank MJ, et al (Firbank et al., 2007)	79	Stroke patients	2 years	Volumetry	Global cognition	14 patients (18%) develop dementia, medial temporal atrophy but not WMC predicted the memory loss.
2006	van den Heuvel, et al (van den Heuvel et al., 2006)	554	High risk population	3 years	Volumetry	Memory, attention and executive function	Baseline PVWMC volume was longitudinally associated with reduced mental processing speed.
2007	Steffens DC, et al (Steffens et al., 2007)	161	Older depressed subjects without dementia	5.4 years	Volumetry	Alzheimer Disease (CERAD) neuropsychological battery, memory, attention and executive function	Change of WMC volume was significantly associated with development of dementia, especially among non-Alzheimer dementias.
2009	Dufouil C, et al (Dufouil et al., 2009)	226	Patients with history of stroke or TIA	3.9 years	Scheltens scale	Global cognition, DSM-IV	Incident severe cognitive deterioration was associated with baseline severe WMC (OR 7.7, P< 0.005).

2.5 White matter changes and AD

WMC were frequently found in AD patients, (Barber et al., 1999) and evidence suggested that these lesions interacted with typical Alzheimer's disease pathology (amyloid plaques and neurofibrillary tangles). (Kalaria, 2002) Kalaria RN indicated that hypertension-related vascular and WMC were causal in AD pathogenesis. (Kalaria, 2002) Populational longitudinal studies also proved that WMC could accelerate the AD progression. In Smith EE, et al study, WMC was associated with the transition of normal to MCI, whereas brain atrophy which determined the transition of MCI to AD. (Smith et al., 2008) Schmidt study indicated that WMC predicted brain atrophy. (Schmidt et al., 2005) Therefore, AD pathology and vascular damage may be a synergistic complex relation. It is possible that prevention and treatment of WMC may retard the progression of AD.

2.6 Treatment of white matter changes and vascular cognitive impairment

WMC were important substrates for VCI, their progression was considered to be a surrogate endpoint for trials in cerebral SVD, emphasis should be put on confluent WMC which progress faster and parallel cognitive decline. (Schmidt et al., 2004)

Despite the importance of WMC on a population basis, no specific therapies are available. Treatment is limited to risk factor control and antiplatelet agents, based on trials that included all stroke subtypes. Only a small number of studies have examined therapy specifically in cerebral small-vessel disease. However, the results of these trials are not consistent, most trails failed to prevent both stroke recurrence and cognitive decline in many patients.

2.6.1 Blood pressure lowing therapy

Apart from age, hypertension was a major risk factor for WMC, and The EVA MRI study had shown a positive linear relationship between blood pressure and severity of WMC. (Dufouil et al., 2001) In 1995, Fukuda H, et al study retrospectively assessed the relationship between hypertension treatment and severity of PVWMC in 238 patients. The PVMMC was rated using a 4-point visual rating scale on T2-weighted 1.0 T MRI. The study found subjects receiving regular treatment of hypertension had less severe PVWMC than those receiving no or irregular treatment of hypertension. Due to its cross-sectional design, the treatment effect of hypertension on WMC progression could not be examined in this study. The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) MRI substudy (Dufouil et al., 2005) was a longitudinal randomized placebo-controlled trail investigating the blood pressure lowing therapy using perindopril or perindopril plus indapamide on WMC progression. 192 participants were followed up for 36 months, the blood pressure reduction in the active arm compared with the placebo arm was 11.2 mm Hg for systolic blood pressure and 4.3 mm Hg for diastolic blood pressure. The study found the mean total volume of new WMC was significantly reduced in the active treatment group compared with the placebo group, this difference was greatest for patients with severe WMC at entry. (Dufouil et al., 2005) However, the volumetric measurement of new WMC in this study was based on T2-weighted MRI, where the PVWMC might not be clearly differentiated from cerebral spinal fluid, or the infarcts might be misclassified as DWMC. Moreover, the whole WMC were assessed by a four-point (no to severe) visual rating scale, which might have ceiling effect for describe the progression of WMC. Other limitations of this study are the selection bias and the small sample size which may limit the power. Albeit a positive finding, it is important

to note that this study was a post-hoc analysis and the result may be hypotheis driven. Larger randomized trails are needed to confirm or refute the conclusion.

2.6.2 Statins

Statins have long been demonstrated to reduce cardiovascular events and ischemic stroke among patients with coronary heart disease. (The Scandinavian Simvastatin Survival Study Group,1994) Imaging studies had shown that statins retard progression of coronary and carotid atherosclerosis. (Brown et al., 1990; Amarenco et al., 2004) Whether statins benefit the WMC or not is still controversial.

The PROSPER (Prospective Study of Pravastatin in Elderly at Risk) Study examined the effect of pravastatin 40 mg daily on the progression of WMC in 270 placebo-treated subjects and 265 active subjects within a period of 33 months. Automated volumetric measurement was used to measure the WMC volume in baseline and follow-up T2-weighted MRI. As addressed before, using T2-weighted MRI may not be accurate for measuring the WMC volume. The study failed to demonstrate an overall beneficial effect of statins upon WMC progression. However, data on proportions of subjects having different WMC severity were lacking and stratified analysis based on WMC severity was not performed in the study. Hence, the effect of statins upon severe WMC in this study is uncertain.

In the Cardiovascular Health Study, 3334 community participants were followed-up over an average observational period of 7 years. (Bernick et al., 2005) Patients treated with statins were observed to have slightly less cognitive decline than untreated subjects. This significant cognitive benefit was associated with reduced progression in

cerebral infarcts among the treated subjects, whereas progression of WMC was not statistically different between these two groups. Although the findings may suggest that statins exert cognitive benefits independent of WMC progression, the visual rating scale used in that study was unlikely to be sensitive in detecting WMC progression. In general, visual rating scales are insensitive for measuring changes in WMC severity with significant ceiling or floor effects. Moreover, stratified analysis based on baseline WMC severity was, again, not performed. More importantly, that study was an observational study that could be greatly confounded by other unrecognized characteristics of the various treatment groups. (Mok et al., 2009)

The ROCAS (Regression of Cerebral Artery Stenosis) study evaluated the simvastatin on WMC progression in patients with asymptomatic middle cerebral artery stenosis. (Mok et al., 2009) Two hundreds and eight randomized subjects were assigned to either placebo (n = 102) or simvastatin 20 mg daily (n = 106) for 2 years. Simvastatin group did not slow the progression of WMC volume compared with the placebo group, however, in severe WMC at baseline, the median volume increase in the simvastatin group (1.9 cm^3) was less compared with that in the placebo group (3.0 cm^3; P = 0.047). It indicated that simvastatin might delay the progression of cerebral WMC. However, in this study, treatment probably prevented WMC progression among those with severe WMC at baseline was based only on subgroup analysis upon a small subset of subjects. Hence, findings of this study required further confirmation from another larger study that aims primarily to investigate the effects of statins upon WMC progression among those who already had severe WMC. Secondary, the subjects of this study belonged to a high risk group in that all our subjects had concurrent MCA stenosis, and a majority had either DM or HT. Hence, the findings

might not be applicable to patients with less vascular burden or to those with WMC but without concurrent MCA stenosis.

2.6.3 Homocysteine lowering therapy

Homocysteine was associated with WMC, brain atrophy, stroke and cognition. (Sacco et al., 1998; Bots et al., 1999; Lehmann et al., 1999; Vermeer et al., 2002; Dufouil et al., 2003; Hassan et al., 2004; Sachdev, 2005; Wright et al., 2005; Wong et al., 2006; Seshadri et al., 2008; Anan et al., 2009; Fuh, 2010) Two clinical trails investigated the homocysteine lowering therapy on stroke prevention and cognition. The Vitamin Intervention for Stroke Prevention (VISP) study recruited 1827 participants receiving 25 mg of pyridoxine, 0.4 mg of cobalamin, and 1853 participant receiving 2.5 mg of folic acid 200 μg of pyridoxine, 6 μg of cobalamin, and 20 μg of folic acid. In this study, moderate reduction of total homocysteine after nondisabling cerebral infarction had no effect on vascular outcomes during the 2 years of follow-up. (Toole et al., 2004) Its subanalysis on 150 participants in each group, treatment with high dose vitamins did not, however, influence plasma levels of Aβ, despite their effect on lowering total homocysteine. Furthermore, Aβ measures were not associated with cognitive change which was assessed using MMSE. (Viswanathan et al., 2009) However, whether homocysteine lowering therapy was associated with cognitive changes or WMC progression is not examined in this study. And the follow-up duration in VISP study may be too short to assess the homocysteine-lowering effect on stroke and cognition.

The other randomized double-blind, parallel, placebo-controlled trial is the VITAmins TO Prevent Stroke (VITATOPS) study. 8164 Patients with recent stroke or transient

ischaemic attack (within the past 7 months) received one tablet daily of placebo (n=4089) or B vitamins (2 mg folic acid, 25 mg vitamin B6, and 0.5 mg vitamin B12, n=4075)) with a median followed up duration of 3.4 years. Although the vitamin combination used in the VITATOPS trial resulted in a reduction in homocysteine (an estimated 2% [95% CI –0.5 to 4.3] reduction in the risk of the primary outcome for each 1 μmol/L decrease in homocysteine), vitamin treatment was not significantly more effective than placebo in reducing the incidence of the composite primary endpoint of stroke, myocardial infarction, or vascular death. In the subgroup analyses, homocysteine lowering might have preferential benefit in small vessel disease patients (risk ratio 0.80 [95%CI: 0.67–0.96]). (VITATOPS Trial Study Group., 2010) Whether B vitamins can slow the WMC progression or cognitive decline is still unknown. Analysis of the VITATOPS MRI substudy is ongoing to answer this question.

2.6.4 Acetylcholinesterase inhibitors and *N*-methyl-D-aspartate (NMDA) receptor antagonists

WMC were important substrates for VaD, the treatments for VaD may be beneficial to WMC theoretically. Acetylcholinesterase inhibitors (donepezil, galantamine, and rivastigmine) and *N*-methyl-D-aspartate (NMDA) receptor antagonists (memantine) have been approved for treatment of AD. Donepezil, galantamine, and rivastigmine, have also been considered for treatment of VaD.(Erkinjuntti et al., 2004) The rationale behind its use was because neurodegenerative and vascular processes were interactive to each other, and the serotonin metabolism was severely reduced and so was the activity of choline acetyltransferase in VaD, independent of any concomitant AD pathology.(Gottfries et al., 1994) Cholinergic structures in the brain were vulnerable to ischemic damage.(Jellinger, 2001)

Glutamate was an important excitatory amino acid neurotransmitter in cortical and hippocampal neurons. The cortical neuronal loss might be related to an increased sensitivity to glutamate and/or sustained elevations of glutamate levels.(Cacabelos et al., 1999) Increased glutamate levels leaded to a cumulative influx of calcium into neurons, impaired homeostasis, and eventually neurodegeneration, resulting in cell death. One of the receptors activated by glutamate was the *N*-methyl-D-aspartate (NMDA) receptor (Danysz and Parsons, 1998), agents that block pathologic stimulation of NMDA receptors might prevent further cortical neurodegeneration in VaD.(Kornhuber et al., 1994; Heim and Sontag, 1995) Memantine is an NMDA receptor antagonist and may be a new approach to treat VCI.(Mobius and Stoffler, 2002)

Kavirajan H reviewed three donepezil, two galantamine, one rivastigmine, and two memantine placebo-controlled, randomized, double blinded trails, it showed that cognitive effects on the ADAS were significant for all drugs, and post-hoc analyses of donepezil tails suggested greater improvement in patients with cortical and territorial lesions compared with those with predominantly subcortical lesions. By contrast, cognitive effects in the memantine trials derived largely from worsening in patients in the placebo- treated groups who predominantly had small vessel disease. (Kavirajan and Schneider, 2007) It also revealed that the interpretation was difficult due to the insensitive vascular dementia assessment instruments, not enough follow-up duration, and the variety of cerebrovascular lesions and clinical presentations, diagnostic imaging modalities and the extent of comorbid AD pathology. Thus, data is insufficient to support the widespread use of acetylcholinesterase inhibitors (donepezil,

galantamine, and rivastigmine) and memantine in patients with vascular dementia.(Kavirajan and Schneider, 2007)

A recent multicentre, 18-week, placebo-controlled, double-blind, randomized parallel-group trial using donepezil in 168 CADASIL patients revealed that Donepezil had no effect on the Vascular ADAS-cog score in CADASIL patients with cognitive impairment. Improvements were noted on several measures of executive function, which might suggest that cholinergic pathways were involved in the executive function. (Dichgans et al., 2008) Another randomized, international, multicenter, 24-week trial in 974 probable or possible VaD patients who received donepezil 5 mg/d or placebo, found that donepezil improved the vascular ADAS-cog score in the patients.(Roman et al., 2010) Patients with hippocampal atrophy who were treated with donepezil demonstrated stable cognition versus a decline in the placebo-treated group; in those without atrophy, cognition improved with donepezil versus relative stability with placebo.(Roman et al., 2010) The comorbid AD pathology in VaD might explain the differential treatment response of VaD patients by hippocampal size, and the large proportion of patients aged ≥75 years probably increased the overall admixture of other potential sources of cognitive impairment. This was the largest clinical trail focusing on donepezil for VaD, a limitation of this study was the substantial variability in imaging information resulted from using both CT and MRI images and site-based image-acquisition procedures.(Roman et al., 2010)

Regarding to the memantine, a recent meta-analysis indicated that memantine might have a role in managing behavioral and psychological symptoms related to dementia, however, many limitations were found in the studies and the effect size was relatively

small, and whether memantine produced significant clinical benefit was not clear. (Maidment et al., 2008)

With regards to the safety of these drugs, adverse events (anorexia, nausea, vomiting, diarrhea, and insomnia) were observed in cholinesterase inhibitors, while memantine was found to be well-tolerate and safe.

In summary, there is no approved treatment for WMC yet. Large randomized trails with WMC progression as primary outcome are in need, and emphasis should be put on patients with confluent WMC. Schmidt R suggested that if one focuses on subjects with confluent abnormalities alone, which was the most likely scenario in a subcortical VaD trial, a 30 and 20% therapeutic effect could be detected with 87 and 195 patients per arm, respectively. (Schmidt et al., 2004)

PART II STUDIES ON WHITE MATTER CHANGES AND VASCULAR COGNITIVE IMPAIRMENT

I Detection of WMC

Chapter 3 Evaluation of Age-Related White Matter Changes using Transcranial Doppler Ultrasonography

3.1 Introduction

Although age-related WMC are often subclinical, its presence increases risk of future dementia and disability. (Inzitari et al., 2007) Ideally, preventive trials should target those having WMC at the subclinical phase. Although MRI is commonly used for detection of WMC, it is not cost effective for screening purpose. To date, methods that guide selective scanning are lacking.

TCD is a non-invasive, easily administered, and relatively inexpensive test that has traditionally been used to detect intracranial large artery disease. It has also been suggested that the arterial PI, which is derived from the flow velocity of large arteries, reflects the vascular resistance distal to the examined artery. (Kidwell et al., 2001) SVD is believed to play a central role in the development of WMC. (Pantoni, 2002; Roman et al., 2002) A previous study among a small cohort of stroke patients with or without WMC suggested that PI correlated with severity of WMC, as determined by a visual rating scale. (Kidwell et al., 2001) In the present study, we investigated the association between PI and volume of WMC in stroke patients. We hypothesized that PI is associated with the volume of WMC.

3.2 Methods

3.2.1 Subjects and TCD examination

Eighty- six lacunar stroke and 14 TIA patients with WMC on MRI were recruited for this study. They were included retrospectively from our acute stroke unit registry from

2002 to 2009 if they fulfilled all of the following criteria: (1) aged over 50 years old; (2) lacunar stroke or TIA; (3) presence of WMC on MRI as defined by hyperintensities ≥5 mm on coronal and axial-FLAIR sequence;(4) presence of good temporal window at least in one side; (5) no significant extracranial large artery stenosis (>50%) on carotid duplex ultrasound or intracranial large artery stenosis (>50%) on MRA; and (6) no atrial fibrillation. We excluded patients with atrial fibrillation because irregular rhythm interferes with systolic and diastolic velocity interpretation on TCD, leading to incorrect PI. All the TCD examinations were performed by experienced sonographers using a standard protocol. (Wong et al., 2002) In brief, a 2-MHz pulsed Doppler hand-held probe insonated the MCA through temporal window above the zygomatic arch at a depth of 52-56 mm, and the BA and VA though occipital window at a depth of 86 mm and 64 mm, respectively. We measured the proximal large arteries (MCA, VA and BA) other than small penetrating arteries because distal high resistance can be reflected to the proximal arteries. The PI was automatically calculated by the TCD machine according to the formula: PI = (peak systolic flow velocity-end diastolic flow velocity)/mean flow velocity. Then a mean MCA PI was calculated by averaging bilateral MCA PI, and mean VB PI was calculated by averaging bilateral VA PI and BA PI. If the subject only had good temporal window in one side, then unilateral MCA PI was considered as mean MCA PI.

In order to investigate the differences between patients with WMC and those without, we also recruited 50 elderly subjects without WMC as control group. These 50 subjects consisted of 25 stroke-free community residents and 25 patients who were admitted to our acute stroke unit with suspected TIA. These 25 patients all had normal

brain MRI and MRA, and had no WMC, infarct, and hemorrhage. The 25 community residents were recruited by means of recruitment notice placed in community centers and all had no WMC on MRI. All these 50 subjects were aged over 50, with good temporal window and had no atrial fibrillation. For each subject, we collected demography (age and gender) and vascular risk profile including hypertension, diabetes mellitus, hyperlipidemia, ischemic heart disease, history of smoking and history of drinking. Among these 50 controls, the 25 TIA patients and 25 stroke-free healthy controls did not differ in terms of age, cardiovascular risk factors and PI values of all examined arteries.

3.2.2 Neuroimaging measures

All subjects' MRI examinations were performed within one week after admission on a 1.5 T Scanner (Sonata, Siemens Medical System, Erlangen, Germany) with T1-weighed, T2-weighed, DWI, coronal and axial FLAIR and gradient echo sequences.

WMC were defined as hyperintensities ≥5 mm on coronal and axial FLAIR sequence. Lesions were defined as PVWMC when their largest diameter was adjacent to the ventricle, otherwise they were defined as DWMC. (de Groot et al., 2000) Total WMC volume, PVWMC volume and DWMC volume were measured using semi-automated "seeding method" by easy vision software (Philips Medical Best, the Netherlands) on coronal or axial FLAIR sequences by a neurologist Y.X.. (Wen et al., 2004) In brief, WMC region was first identified by threshold and a "seed" was dropped on that region. The "seed" would grow automatically to include all connected pixels until that region was outlined; and volume of outlined region would be generated automatically.

We also rated the WMC severity using age-related white matter changes scale (ARWMC) (Wahlund et al., 2001) and recorded the total ARWMC scores.

Lacunar infarcts were defined as well-defined hypointensities with diameter 3-15 mm on T1-weighted images and hyperintensities on T2-weighted images. If the lesion appeared as hyperintensity on DWI and hypointensity on ADC, then it was considered as acute lacunar infarct. We defined microbleed as a circular area of marked and homogeneous signal loss on gradient recall echo T2-weighted MRI, of size ranges from 2-10 mm, that was not located in sulcal areas to avoid confusion with flow void from cerebral vessels. (Mok et al., 2004) Presence of acute lacunar infarct, presence of total lacunar infarcts, presence of infratentorial infarct and presence of microbleed were recorded by Y.X.. We also measured total lacunar infarcts volume using semi-automated segmentation method on T1-weighted images.

3.3 Statistics

Independent-Samples T Tests for normally distributed data (age) and Mann-Whitney U tests for skewed data (mean MCA PI and mean VB PI) and χ^2 tests for categorical data were used to test the differences between cases and controls. Analysis of covariance was performed to identify the WMC effect on the mean MCA PI and mean VB PI separately with significant different variables between both groups as covariates.

In the case group, the mean MCA PI, the mean VB PI, total WMC volume, PVWMC volume and DWMC volume were transformed into normal distribution using natural Log transformation. Univariate analyses using Pearson and Spearman rank correlation

were performed to test the association between the mean MCA PI and demography, cardiovascular profile and neuroimaging variables according to normality of the data. Then Multivariate linear regression model was performed to determine the independent predictors for mean MCA PI after adjusting for those factors with $p<0.05$ in the univariate analyses. We used the same statistical method to identify the independent predictors for mean VB PI and total WMC volume.

Taking all subjects as a whole, receiver operator curve (ROC) analyses were performed to identify PI cut points that yielded the greatest sensitivity and specificity in discriminating patients with WMC from those without WMC. To consider some imbalanced factors between cases and controls, we performed further analysis wherein we reconstructed the ROC after controlling for the imbalanced factors.

3.4 Results

Subjects' characteristics are presented in table 3-1. Compared with controls, cases were older, with higher proportion of hypertension, hyperlipidemia and diabetes mellitus. Regarding to the TCD measures, mean flow velocities of all examined arteries were lower in cases than in controls, whereas PI values were higher in cases than in controls. To determine whether the case and control groups have significant different PI but not affected by the imbalance age and vascular risk factors, we found that the case/control group (presence of WMC) was significantly associated with mean MCA PI and mean VB PI ($F=19.14$, $p<0.001$and $F=16.70$, $p<0.001$, respectively) after adjusting for age, hypertension, hyperlipidemia and diabetes mellitus using analysis of covariance. Majority (84%) of cases had a score of $\geqslant 2$ in at least one brain region.

Table 3- 1 Characteristics of case and control groups

	Case (N=100)	Control (N=50)	*p*
Clinical characteristics			
Age, mean±SD, y	70.39±7.23	59.34±11.44	<0.001*
Male (%)	65 (65.00%)	29 (58.00%)	1.000
History of smoking (%)	44 (44.00%)	16 (32.00%)	0.194
History of drinking (%)	12 (12.00%)	6 (12.00%)	1.000
Hypertension (%)	77 (77.00%)	24 (48.00%)	<0.001*
Hyperlipidemia (%)	55 (55.00%)	15 (30.00%)	0.004*
Diabetes mellitus (%)	32 (32.00%)	8 (16.00%)	0.037*
Ischemic heart disease (%)	10 (10.00%)	3 (6.00%)	0.545
Neuroimaging variables			
Total ARWMC score, median (IQR)	7 (4-9)		
Total WMC volume, median (IQR), cm^3	10.47 (2.74-25.70)		
PVWMC volume, median (IQR), cm^3	8.24 (2.32-22.93)		
DWMC volume, median (IQR) , cm^3	1.17 (0.34-4.10)		
Presence of acute lacunar infarct	23 (23.00%)		
Presence of total lacunar infarcts	87 (87.00%)		
Total lacunar infarcts volume, median (IQR), cm^3	0.33 (0.07-0.78)		
Presence of microbleed	30 (30.00%)		
TCD measures			
Left MCA SV, median (IQR), cm/s	75 (60-90)	74 (60-86)	0.488
Left MCA MFV, median (IQR), cm/s	30 (25-40)	47.5 (36.5-55.5)	<0.001*
Right MCA SV, median (IQR), cm/s	70 (60-88)	71 (57-93)	0.696
Right MCA MFV, median (IQR), cm/s	30 (25-40)	45 (36-57)	<0.001*
Left VA SV, median (IQR), cm/s	46 (37-55)	44 (35-55)	0.577
Left VA MFV, median (IQR), cm/s	20 (15-25)	31 (24-34)	<0.001*
Right VA SV, median (IQR), cm/s	46 (35.8-53.5)	46 (37-51)	0.906
Right VA MFV, median (IQR), cm/s	20 (15-25)	28 (25-35)	<0.001*
BA SV, median (IQR), cm/s	50 (41-60)	50 (41-60)	0.471
BA MFV, median (IQR), cm/s	22 (20-28)	32 (24-39)	<0.001*
Left MCA PI, median (IQR)	1.55 (1.10-2.46)	0.88 (0.78-1.10)	<0.001*
Right MCA PI, median (IQR)	1.50 (1.08-2.39)	0.90 (0.79-1.09)	<0.001*
Left VA PI, median (IQR)	1.43 (0.92-2.25)	0.88 (0.73-1.10)	<0.001*
Right VA PI, median (IQR)	1.50 (0.95-2.25)	0.91 (0.70-1.14)	<0.001*
BA PI, median (IQR)	1.33 (1.00-2.25)	0.84 (0.75-1.06)	<0.001*
Mean MCA PI, median (IQR)	1.53 (1.09-2.48)	0.88 (0.79-1.07)	<0.001*
Mean VB PI, median (IQR)	1.23 (0.96-2.27)	0.91 (0.74-1.07)	<0.001*

*p<0.05; IQR: interquartile range; MFV: mean flow velocity; SV: systolic velocity

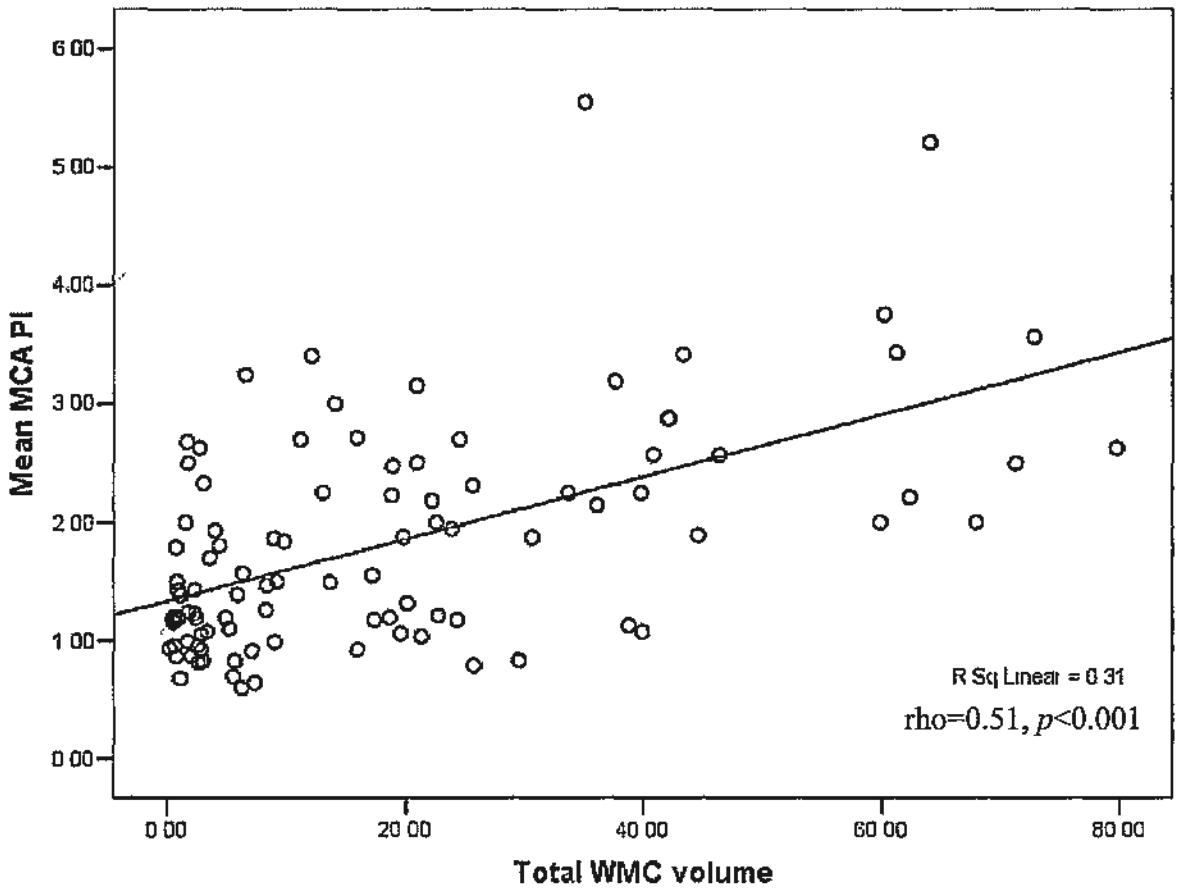

Figure 3-1 The association between mean MCA PI and total WMC volume. MCA: middle cerebral artery; PI: pulsatility index; WMC: white matter changes.

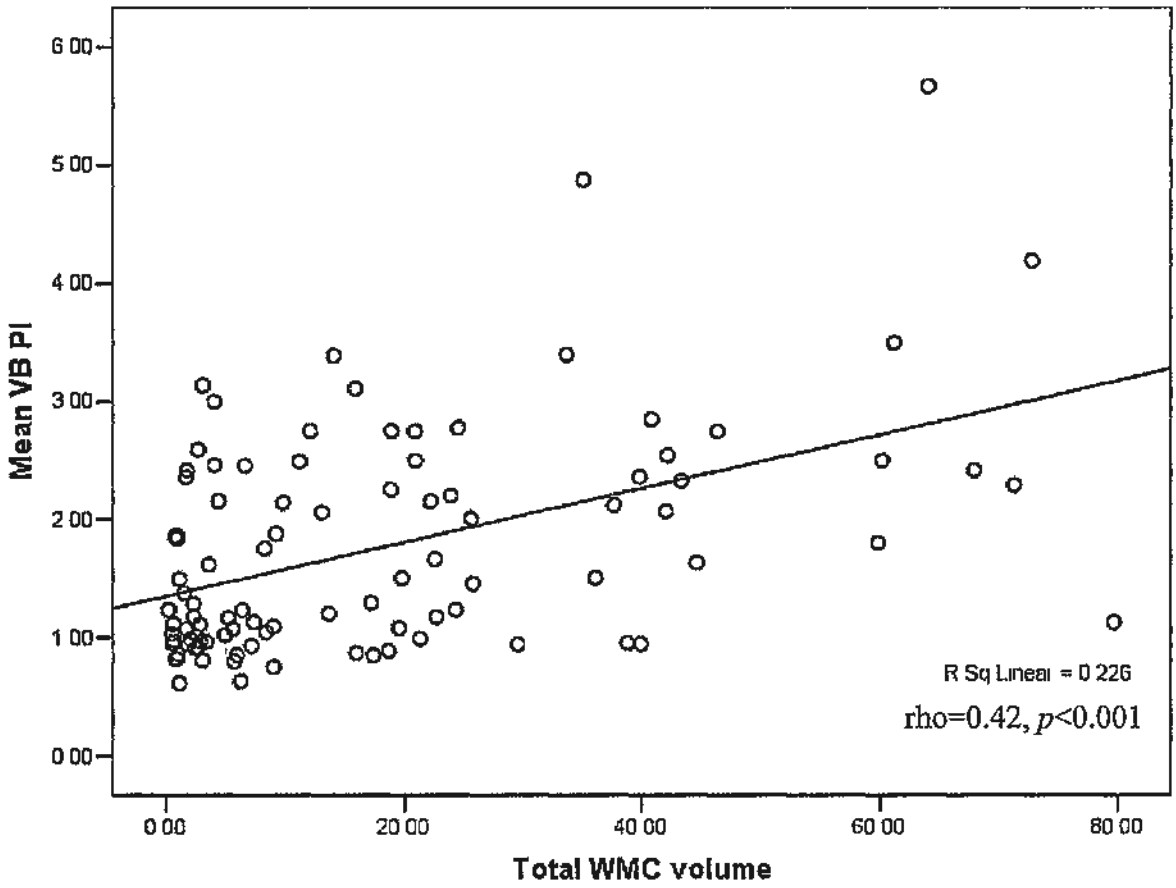

Figure 3-2 The correlation between mean VB PI and total WMC volume. VB: vertebrobasilar artery.

In patients with WMC, the results of univariate analyses are summarized in table 2. Figure 1 and 2 shows the correlation between total WMC volume and mean MCA PI and mean VB PI, respectively. Total WMC volume, PVWMC volume and DWMC volume were positively whereas presence of acute lacunar infarct were negatively associated with mean MCA PI and mean VB PI ($p<0.05$). Since total WMC volume, PVWMC volume and DWMC volume were closely correlated with each other ($r>0.7$, $p<0.001$), we only used total WMC volume in the multivariate linear regression. Multivariate linear regression models found that total WMC volume was a robust predictor for mean MCA PI and mean VB PI (beta=0.39, $p<0.001$and beta=0.32, $p<0.001$, respectively). Presence of acute lacunar infarct had a trend for lowering mean MCA PI and mean VB PI (beta=-0.17, $p=0.095$ and beta=-0.22, $p=0.053$, respectively).

Regarding predictors for WMC volume, univariate analyses found that age ($r=0.35$, $p=0.001$), mean MCA PI ($r=0.51$, $p<0.001$), mean VB PI ($r=0.42$, $p<0.001$) and hyperlipidemia ($r=0.21$, $p=0.034$) were significantly associated with total WMC volume. Separate multivariate linear regression models with age and hyperlipidemia as covariates found that mean MCA PI and mean VB PI were independent predictors for total WMC volume (beta=0.43, $p<0.001$and beta=0.37, $p<0.001$, respectively). Age was a robust independent predictor for total WMC volume whereas hyperlipidemia was not significant in both models.

Table 3-2 Univariate results for PI of all examined arteries

Variables	Mean MCA PI		Mean VB PI	
	coefficient	*p*	coefficient	*p*
Age	0.25	0.013	0.11	0.348
Sex	0.07	0.468	0.01	0.917
History of smoking	0.01	0.932	0.01	0.922
History of drinking	-0.15	0.133	-0.20	0.076
Hypertension	0.05	0.636	-0.02	0.885
Hyperlipidemia	0.15	0.131	0.12	0.277
Diabetes mellitus	0.09	0.384	0.09	0.447
Ischemic heart disease	0.10	0.350	0.10	0.385
Total WMC volume	0.51	<0.001	0.42	<0.001
PVWMC volume	0.52	<0.001	0.43	<0.001
DWMC volume	0.43	<0.001	0.34	<0.001
Presence of microbleed	0.19	0.059	0.01	0.950
Presence of total lacunar infarcts	-0.09	0.377	-0.09	0.403
presence of infratentorial infarct	-0.20	0.055	-0.14	0.228
Presence of acute lacunar infarct	-0.34	0.001	-0.30	0.006
Total lacunar infarcts volume	-0.14	0.180	-0.18	0.122

The ROC results are shown in table 3. Mean MCA PI and mean VB PI identified cut-offs for distinguishing cases from controls. The AUC, sensitivity and specificity of mean MCA PI were higher than that of mean VB PI. Further analysis showed that after adjusting for age, hypertension, hyperlipidemia and diabetes mellitus, the AUC for mean MCA PI and mean VB PI were 0.877 (95% CI: 0.882-0.932) and 0.876 (95% CI: 0.821-0.931), respectively, which slightly improved the overall accuracy.

Table 3-3 ROC results of WMC

	AUC (95% CI)	Cut-off	Sensitivity	Specificity	PPV	NPV
Mean MCA PI	0.85 (0.78-0.91)	1.15	73.70%	82.00%	80.37%	75.72%
Mean VB PI	0.81 (0.74-0.88)	1.06	70.00%	75.00%	73.68%	71.43%

AUC: area under curve; PPV: positive predicting value; NPV: negative predicting value

3.5 Discussion

Our study showed that PI values had significant independent correlation with volume of WMC .We observed that that mean MCA PI and mean VB PI were higher in patients with WMC than controls. The AUC of MCA PI for detection of WMC was good (0.85) and at an optimal cut-off of 1.15, a good sensitivity (73.70%) and specificity (82.00%) could be obtained.

Such strong association between WMC and PI is consistent with our current understanding on the pathophysiology of WMC, in which cerebral SVD is thought to play an important role. (Pantoni, 2002; Roman et al., 2002) It is possible that the process of arteriosclerosis narrows the lumen of small penetrating arteries. The thickened fibrotic vessels lose its elasticity and vasomotor reactivity, resulting in an increase in vascular resistance of the small vessels and hence a high PI. (Kidwell et al., 2001) Although a recent study failed to show an association between PI and WMC severity, (Kozera et al., 2010) this recent study was performed among middle-aged hypertensive stroke-free men having no to mild WMC. Our cohort consisted of stroke patients with more severe WMC. These differences in cohort characteristics may account for the different findings. A recent study indicated that the combination low MFV (<30 cm/s)/ high PI (>1.2) predicted diffuse intracranial large artery disease by TCD. (Sharma et al., 2007) Note our study showed high PI was associated with WMC with relatively low to normal MFV in small vessel disease patients without large artery disease.

Consistent with the study of Kidwell CS, et al, (Kidwell et al., 2001) we found that the mean MCA PI was associated with either PVWMC or DWMC. Noteworthy is that

the mean VB PI was also associated with PVWMC and DWMC, even though the dominant arterial supply to periventricular and deep white matter region is not the VB artery. This association suggests that WMC represent diffuse SVD and is again consistent with our current understanding on the pathophysiology of WMC. (Roman et al., 2002) Since TCD examination is reported to be unsuccessful due to poor temporal window in around 35% Asian population, (Kwon et al., 2006) a practical application of our finding is that in cases with poor or no temporal window, the mean VB PI can also be used as an indicator for subcortical WMC. Note however that the AUC for VB PI in detecting WMC is slightly lower than that for MCA PI.

The presence of acute lacunar infarct was negatively associated with PI of all examined arteries. We hypothesized that the reason behind this finding is because in response to acute ischemic injury, distal small vessels dilate and vascular resistance decreases, so as to increase cerebral perfusion to the ischemic areas. Our finding is contrary to other studies, where lacunar infarct was associated with high PI. (Kidwell et al., 2001; Lee et al., 2007) This is probably because the subjects of other studies were either stroke-free (Lee et al., 2007) or the TCD was performed among stroke patients after the acute phase. (Kidwell et al., 2001)

The strengths of our study are its relatively large sample size compared with similar studies and the severity of WMC was quantified by a semi-automated method. Several limitations should also be addressed. First, the patients with WMC were older with higher proportion of hypertension, hyperlipidemia and diabetes mellitus compared to subjects without WMC. Furthermore, the WMC is mostly related to patient age and hypertension, these two factors also affect PI. The difference in the PI noted in the

case and control groups could be due to the inherent differences in the composition of these two groups. Hence, our results regarding the good ability of PI in differentiating subjects with and without WMC need to be interpreted with caution. Note however that the difference in PI values between those with and without WMC remained significant even after adjusted for age and other vascular risk factors using analysis of covariance. Second, we included stroke patients and TCD was performed during the first few days poststroke. Since PI may vary during the acute stroke phase, our results may not be applicable to stroke-free subclinical elderly or to stroke patients who already passed the acute phase. Third, other factors such as intracranial hypertension, hemodynamic (including decreased cardiac output, heart rate and pulse pressure), respiratory, hematologic parameters (including hemoglobin and homocysteine levels) and migraine that might affect PI had not been investigated in our study, further studies considering all these minor but significant factors are warranted. Finally, potential TCD limitations should be considered in the calculation of PI including incorrect angle and suboptimal temporal window. (Alexandrov et al., 2010)

In conclusion, our study supports the hypothesis that PI is associated with volume of WMC. Further study evaluating the clinical utility of TCD in screening for subclinical WMC among community elderly is warranted. Availability of a simple screening tool that can guide selective MRI scanning will promote early detection and management of WMC and also cost effective recruitment into clinical trials for subclinical WMC.

II. Cognitive impact of WMC

Chapter 4 Frequency and predictors of proxy-confirmed post-stroke cognitive complaints in lacunar stroke patients without major depression

4.1 Introduction

In clinical practice it is common to hear complaints of cognitive decline in elder patients. The prognostic value of these cognitive complaints in predicting unfavorable future cognitive outcome had attracted attention during the past decade. In non-stroke populations, it has been argued that subjective memory complaints represent the earliest sign of an underlying degenerative dementing process before objective cognitive deficits manifest. (Geerlings et al., 1999) Some studies lent support to this hypothesis by showing that patients with cognitive complaints were more prone to develop incident dementia, mostly being Alzheimer's disease (AD). (Schmand et al., 1996; Schofield et al., 1997; Jorm et al., 2001; Glodzik-Sobanska et al., 2007) Due to its potential clinical application, the diagnosis of mild cognitive impairment requires the presence of subjective memory complaints in addition to the evidence of objective neuropsychological impairment. (Petersen, 2003)

Depending on the defining criteria, cognitive impairment can be as frequent as 75% among lacunar stroke patients, (Mok et al., 2004; Grau-Olivares et al., 2007; Rasquin et al., 2007) and those with WMC and co-existing degenerative neuropathology may be particularly susceptible to amplified cognitive symptoms. (Snowdon et al., 1997; Zekry et al., 2002; Schmidt et al., 2004; Debette and Markus, 2010) When faced with lacunar stroke patients and their caregivers complaining of post-stroke cognitive decline, can clinicians assume genuine cognitive problems in these patients? Or are there any other clinical or neuroimaging parameters (such as WMC) to be considered

as well? There is actually a lack of information on how post-stroke cognitive complaints relate to other common clinical measures relevant in the stroke context, such as objective neuropsychological performance, mood, physical impairment and imaging markers of cerebrovascular disease. In previous cross-sectional studies among non-stroke samples, it was generally shown that factors other than objective cognitive performance, notably depression, best explained the presence of subjective memory complaints. (Derouesne et al., 1989; Minett et al., 2005) It is not clear whether these results equally apply to post-stroke cognitive complaints in patients without major depression. Furthermore, there appeared to be a complex interaction between post-stroke cognitive complaints, depression and radiological features of cerebrovascular disease such as severity of SVD, in particular WMC, and infarct location. (Spalletta et al., 2002; Minett et al., 2005) A better understanding of the determinants of post-stroke cognitive complaints is crucial for devising a more comprehensive management plan for these patients. We hypothesized that WMC may be related to the post-stroke cognitive complaints.

4.2 Materials and Methods

This is part of a larger project aimed to evaluate cognitive impairment in patients with lacunar stroke associated with SVD. (Mok et al., 2004) Between January to June in year 2002 we prospectively screened all patients admitted to the acute stroke unit at the Prince of Wales Hospital in Hong Kong. Each stroke patient received cranial CT examination and clinical assessment by neurologists and specialist stroke nurse within 24 hours of admission. MRI was performed within three days of admission. Stroke etiology of each patient is classified using radiological, neurosonological and clinical information. Diagnosis of lacunar stroke required radiological evidence of lacunar

infarct with relevant clinical presentations. (Mok et al., 2004) A lacunar infarct was defined as a well-circumscribed lesion appearing as hyperintense on T2 and hypointense on T1 weighted MRI of size 3-20 mm that is located in the subcortical white and gray matter, cerebellar white matter and brainstem. We classified each lacunar infarct as relevant or non-relevant based on its feature on diffusion-weighted MRI and clinical findings. One-hundred and six patients of the total of 294 admissions had relevant lacunar infarcts. We further excluded patients with infarcts due to relevant intracranial large artery disease (n=14) or unknown vascular etiology (n=6). Intracranial large artery disease was determined if MRA or TCD showing moderate stenosis as defined by ≥ 50% supplying the relevant territory. (Mok et al., 2003)

Out of these 86 patients, 11 were excluded from the study due to death (n=1); defaulting follow-up (n=4); chronic alcoholism (n=1) and language barrier (n=2). We further excluded three patients with co-existing major depression (n=3) as diagnosed by a broad-certified psychiatrist (WKT) according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition. (APA, 1994) Patients were not excluded based on the severity of cognitive impairment at study entry. Details of the recruitment process is published elsewhere. (Mok et al., 2004) The study was approved by the ethics board of the institution and subjects gave written informed consent for participation. In sum, 75 patients completed the study.

4.2.1 Cognitive assessment and clinical interview

At 3 months after the index stroke each patient attended an outpatient stroke research clinic along with a close caregiver (spouse, adult children, relatives, etc). A

broad-certified neurologist (VCTM) performed a semi-structured interview upon the patients and their accompanying caregivers. Trained research assistants and nurses administered cognitive and mood assessments upon the patients.

4.2.2 Determination of post-stroke cognitive complaint

Post-stroke cognitive complaint was defined as a complaint of stepwise deterioration in one or more cognitive functions occurring shortly after the index stroke. Three structured questions were directed to the patient and the caregiver: 'Do you (to the patient)/Does (name of the patient; to the caregiver) have worse memory after the stroke that occurred 3 months ago?', 'Do you (to the patient)/Does (name of the patient; to the caregiver) have worse problem solving ability after the stroke?', 'Do you (to the patient)/Does (name of the patient; to the caregiver) have slower thinking after the stroke?'. These questions are designed to survey common features of vascular cognitive impairment (VCI) including impairments in executive functions and mental speed (Desmond, 2004; Kramer et al., 2004; Prins et al., 2005; Snaphaan and de Leeuw, 2007) in addition to memory symptoms. Post-stroke cognitive complaint was ascertained if both the patient and caregiver gave a positive response to at least one of these questions.

4.2.3 Objective psychometric assessment

We used the validated Chinese version of the Mini Mental State Examination (MMSE) (Chiu et al., 1994) and Alzheimer's Disease Assessment Scale - cognitive subset (ADAS-cog) (Chu et al., 2000) for the assessment of general cognitive functions. These tests evaluate verbal learning and memory, verbal working memory, orientation, praxis and language. Executive functions were measured using the Chinese version of

Mattis Dementia Rating Scale Initiation/Perseveration subset (MDRS I/P) (Chan et al., 2003). This is a brief 15 minutes test with items assessing set shifting and clustering, psychomotor speed and cognitive/motor programming. It has been used as a donor scale in an extensive executive function battery used in dementia research (Mungas et al., 2003) and its Chinese version has been proven to be useful in lacunar stroke patients. (Wen et al., 2004; Wong et al., 2007) There were two missing values for the MDRS I/P and one for ADAS-Cog because two patients had significant motor disability that had prevented them from completing certain items on these tests.

4.2.4 Clinical profile

We recorded the presence of the following vascular risk factor: hypertension, diabetes mellitus, hyperlipidemia, heart disease (ischemic heart disease, congestive heart failure, atrial fibrillation), previous transient ischemic attack or stroke, and history of smoking and drinking (both current and past). Hyperlipidemia was defined as total cholesterol of .6.2 mmol/L or low-density lipoprotein of .4.1 mmol/L. (Mok et al., 2004) In addition, we measured plasma homocysteine in a subset of 57 patients and recorded the number of patients with hyperhomocysteinemia defined by total plasma homocysteine level of $\geq$14.88μmol/L. (Wong et al., 2006) Stroke severity was indexed by the National Institute of Health Stroke Scale (NIHSS) (Brott et al., 1989) performed within 24 hours of index admission.

4.2.5 Depressive symptoms

We used the Chinese version of the 15-item Geriatric Depression Scale. It has been validated locally (Chiu HFK, 1994) and shown to have acceptable psychometric properties. (Tang et al., 2004)

4.2.6 Neuroimaging features

We recorded the proportion of patients with silent infarcts (Kobayashi et al., 1997) and the volume of WMC to reflect the severity of SVD. Presence of thalamic infarct and basal ganglia infarct as well as their volume were recorded. WMC were defined as hyperintensities ≥5 mm on T2-weighted or proton density imaging, and hypointensities on T1-weighted MRI. The volumetric measures of WMC and lacunar infarcts were the same to the method in Chapter 3, in brief, they were calculated based on a semi-automated segmentation method described previously. (Wen et al., 2004) In addition, we recorded the number of patients with an acute left-sided infarct on admission due to previously reported relationship between infarcts laterality and depressive symptoms. (Spalletta et al., 2002) To determine the cerebral atrophy index, we first measured the intracranial and parenchymal volumes. Afterward, the cerebrospinal fluid volume was determined by subtracting the parenchymal volume from the intracranial volume. The following formula was used: Cerebral atrophy index=(cerebrospinal fluid volume/intracranial volume)x100%.

4.2.7 Statistical analysis

Comparisons were made between patients with (CC+) and without (CC-) post-stroke cognitive complaints. We used the χ^2 test or Fisher's exact for categorical variables. Each continuous variable were first submitted to the Kolmogorov-Smirnov test to examine its normality. Independent sample t test and Mann-Whitney U test were used for comparing normally and non-normally distributed variables, respectively. MMSE, MDRS I/P, ASAS-cog, and GDS were normally distributed. Psychometric tests performance was contrasted using analysis of covariance (ANCOVA) with age,

sex and education adjusted in the model. We additionally adjusted for GDS scores in a second ANCOVA model to examine whether differences on psychometric performance were independent of the influence of depressive symptoms.

We carried out binary logistic regression models to examine the predictors for post-stroke cognitive complaints in lacunar stroke patients. Candidate variables included demography, NIHSS, psychometric scores, geriatric depression scale (GDS) and neuroimaging measures. We used square-root transformation to normalize the distribution of WMC volume prior to its submission to the regression model. Each candidate variable was first tested in an exploratory univariate model. Afterwards, variables that were significant in the univariate models ($p \leq 0.05$) were entered simultaneously to a final multivariate model. In a post-hoc secondary analysis we performed a linear regression model to examine factors contributing to GDS. This model treated GDS as the dependent variable and the same set of candidate variables (except GDS itself) to examine factors predicting depressive symptoms in these patients. All statistical procedures were carried out using Statistical Package for Social Sciences (SPSS) version 15.0 and α was set to 0.05 for all tests.

4.3 Results

Thirty-two (42.7%) of the 75 lacunar stroke patients had post-stroke cognitive (CC+) complaints whereas 43 (57.3)% did not (CC-). Among these patients, 23 (71.9%) complained of new onset of cognitive symptoms and 9 (28.1%) complained of worsening of pre-existing symptoms after the index stroke. Most patients complained of memory symptoms (93.8%) and decreased mental speed (75%). The two groups were well matched in age, gender and educational level and had similar stroke

severity at admission. Discordance of complains between patient and caregiver was found in one case, where the complaint was raised only by the caregiver. This patient was a 77 year old male. His performance on the MMSE and MDRS I/P were 18 and 20, respectively. His score on GDS was 4, which was not suggestive of clinical depression (Woo et al., 1994). In view of the complaints raised by the caregiver and the poor cognitive performance, this patient was classified into the CC+ group. There were no differences in the frequency of vascular risk factors, WMC volume and infarct measures between the two groups. However, CC+ patients had higher GDS scores (indicating more depressive symptoms) than CC- patients ($t(73) = -2.5$, $p=0.015$). On psychometric testing, CC+ patients performed more poorly on the MMSE ($F(1, 70) = 8.9$, $p = 0.004$), ADAS-cog ($F(1, 69) = 5.3$, $p = 0.032$) and the MDRS I/P ($F(1, 68) = 5.3$, $p = 0.024$), indicating worse general and executive functions in the former group. Adjusting for GDS did not meaningfully change the pattern of the results. Table 4-1 shows the group comparison of demographic, clinical, and neuroimaging features. Table 4-2 shows the comparisons of psychometric scores.

Table 4-1 Comparison of clinical and radiological measures

	CC-	CC+	
	N=43	N=32	*p*
Demographic			
Age	70.0 (12.5)	71.7 (9.4)	0.525
Female (%)	23 (53.5%)	13 (40.6%)	0.27
Education in years	4.5 (3.9)	5.3 (4.4)	0.403
Stroke severity and depression			
NIHSS	4.1 (2.6)	4.7 (2.6)	0.312
GDS	4.0 (3.3)	5.9 (3.2)	0.015
Vascular risk factors			
HT	36 (83.7%)	28 (87.5%)	0.749
DM	20 (46.5%)	8 (25.0%)	0.057
Hyperlipidemia	15 (34.9%)	8 (25.0%)	0.359
Heart disease	6 (14.0%)	4 (12.5%)	1
Previous TIA/stroke	11 (25.6%)	6 (18.8%)	0.485
Hyperhomocysteinemia[a]	9 (30.3%)	5 (18.5%)	0.315
Smoking	15 (34.9%)	14 (43.8%)	0.435
Drinking	11 (25.6%)	10 (31.3%)	0.589
Neuroimaging features			
Presence of silent LI	26 (60.5%)	17 (53.1%)	0.525
Presence of left thalamic lacune	10 (23.3%)	7 (21.9%)	0.888
Left thalamic lacune volume, cm^3	0.0(0.0-0.0)	0.0(0.0-0.0)	0.941
Presence of right thalamic lacune	9 (20.9%)	7 (21.9%)	0.921
Right thalamic lacune volume, cm^3	0.0(0.0-0.0)	0.0(0.0-0.0)	0.611
Presence of left basal ganglia lacune	10 (23.3%)	7 (21.9%)	0.888
Left basal ganglia lacune volume, cm^3	0.0(0.0-0.0)	0.0(0.0-0.0)	0.866
Presence of right basal ganglia lacune	9 (20.9%)	5 (15.6%)	0.56
Right basal ganglia lacune volume, cm^3	0.0(0.0-0.0)	0.0(0.0-0.0)	0.82
Presence of left-sided acute infarct	26 (60.5%)	15 (46.9%)	0.242
WMC volume, cm^3	2.3 (5.7)	2.3 (6.6)	0.515
Cerebral atrophy index	8.0 (3.2)	8.2 (3.1)	0.732

Abbreviations: Hypertension (HT), Diabetes Mellitus (DM), Transient Ischemic Attack (TIA), Lacunar Infarct (LI), White Matter Changes (WMC)

[a]Plasma homocyteine measured in a subset of 57 patients

WMC volume is presented as median (interquartile range)

Table 4-2 Comparison of psychometric test performance

	CC-	CC+	p_a	p_b
MMSE	25.8 (3.2)	23.5 (5.6)	0.004	0.005
MDRS I/P	29.8 (5.3)	26.5 (7.2)	0.024	0.043
ADAS-cog	14.7 (6.6)	19.0 (11.8)	0.032	0.024

[a]adjusted for age, sex and education

[b]adjusted for age, sex, education and GDS

4.3.1 Determinants for post-stroke cognitive complaints

Univariate binomial logistic regression identified that the MMSE, MDRS I/P and GDS significantly predicted the presence of post-stroke cognitive complaints. In the multivariate model, only GDS remained significant (OR 1.169, 95% CI: 1.001-1.365). WMC volume was not associated with post-stroke cognitive complaints. Because the ADAS-cog is a more extensive test for general cognitive function and it had borderline significance in the univariate model (p=0.06), we performed a second multivariate model using ADAS-cog, MDRS I/P and GDS as independent variables. The results remained virtually identical. We also tested the interaction terms for GDS, MMSE and MDRS I/P, none of them were significant in the models. Table 4-3 shows the detailed results of the logistic regression analyses for post-stroke cognitive complaints.

Table 4-3 Predictors for post-stroke cognitive complaints

	Univariate			Multivariate (model 1)			Multivariate (model 2)		
	OR	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Age	1.01	0.97-1.06	0.520						
Female	0.60	0.24-1.50	0.270						
Education in years	1.05	0.94-1.18	0.400						
NIHSS at admission	1.10	0.92-1.31	0.310						
MMSE	0.88	0.78-0.99	0.040	0.92	0.80-1.06	0.251			
MDRS I/P	0.92	0.84-0.99	0.030	0.95	0.86-1.05	0.315	0.95	0.85-1.06	0.364
ADAS-cog	1.06	1.00-1.13	0.060				1.03	0.94-1.12	0.543
GDS	1.20	1.03-1.39	0.020	1.17	1.001-1.37	0.048	1.18	1.01-1.38	0.039
Presence of silent LI	0.74	0.29-1.87	0.530						
Presence of left-sided acute infarct	0.58	0.23-1.46	0.244						
WMC volume*	1.16	0.86-1.56	0.337						

Model 1: MMSE, MDRS I/P and GDS entered as independent variables

Model 2: ADAS-cog, MDRS I/P and GDS entered as independent variables

Abbreviations: Hypertension (HT), Diabetes Mellitus (DM), Transient Ischemic Attack (TIA), Lacunar Infarct (LI), White Matter Changes (WMC)

* Square-root transformed

4.3.2 Determinants for GDS

Post-hoc linear regression for GDS showed that only NIHSS significantly accounted for the variance in GDS (standardized $\beta=0.278$, $p=0.016$). Neither WMC volume nor the location of lacunar infarcts independently predicted scores on the GDS.

4.4 Discussion

In this study we showed that in a small cohort of 75 lacunar stroke patients without major depression, informant-corroborated post-stroke cognitive complaints are prominently related to subclinical depressive symptomatology. We were unable to show any relationship between post-stroke cognitive complaints and WMC volume. Depressive symptoms, in turns appeared to be associated with the severity of stroke.

It is important to note the few key differences between this and similar past studies. First, the present study investigated cognitive complaints in the post-stroke context rather than that in the non-stroke populations. (Flicker et al., 1993; Schmand et al., 1996; Schofield et al., 1997; Geerlings et al., 1999; Wang et al., 2000; de Groot et al., 2001; Jorm et al., 2001; Mol et al., 2006; Purser et al., 2006; Glodzik-Sobanska et al., 2007) Therefore, we did not restrict the definition of cognitive complaint to memory symptoms alone. Instead, we extrapolated these complaints to symptoms common in stroke patients. (Desmond, 2004; Kramer et al., 2004; Prins et al., 2005; Snaphaan and de Leeuw, 2007) Second, we excluded patients with major depression in this study, whereas many of the previous similar studies included subjects with significant depression. (Derouesne et al., 1989; Schofield et al., 1997; Derouesne et al., 1999; Riedel-Heller et al., 1999; Wang et al., 2000; Minett et al., 2005; Mol et al., 2006) Third, while cognitive complaints were self-rated in most studies (Derouesne et al.,

1989; Jonker et al., 1996; Schofield et al., 1997; Derouesne et al., 1999; Riedel-Heller et al., 1999; Wang et al., 2000; Minett et al., 2005), ascertainment of post-stroke cognitive complaints in our study required confirmation from a proxy.

The important clinical implication of this study is that in lacunar stroke patients without major depression, sub-clinical depression still remains the most prominent associative factor for post-stroke cognitive complaints. Our results serve as an extension of the general findings in non-stroke samples that cognitive complaints are more related to depression than to objective cognitive performance. (Derouesne et al., 1989; Minett et al., 2005)

The frequency of dementia after lacunar stroke varies from 11 to 27%. (Wolfe et al., 1990; Miyao et al., 1992; Samuelsson et al., 1996; Desmond et al., 2000; Mok et al., 2004) Cognitive impairment without dementia is even more common, ranging from 52-75%. (Mok et al., 2004; Grau-Olivares et al., 2007; Rasquin et al., 2007) Given the close relationship between cognitive impairment and lacunar stroke, our results do not in anyway imply that post-stroke cognitive complaints are purely related to depressive symptomatology but not to genuine cognitive decline. In fact, our patients with post-stroke cognitive complaints had worse psychometric performance than those without, even after adjusting for severity of depressive symptoms. This indicates that there were true objective neuropsychological differences between the two groups that were independent of the influence of mood. Certainly, post-stroke cognitive complaints are multi-factorial, and the relationship between cognitive impairment and depression is interactive and complex. (Robinson, 1998) Our findings call for a particular attention to examine the presence and role of subclinical depression in

lacunar stroke patients without major depression who complain of cognitive decline after stroke, even if the complaints are substantiated by a proxy.

The interplay between post-stroke cognitive complaints, cognitive impairment and depressive symptoms and cerebrovascular lesions is complex. Lesions in the deep brain structures have been recognized to contribute to depression among elderly persons and hence the 'vascular depression' hypothesis was proposed. (Alexopoulos et al., 1997) WMC are related to late life depression in large cross-sectional (Teodorczuk et al., 2007) and longitudinal studies (O'Brien et al., 2006). WMC-associated depression may also remotely contribute to the presence of post-stroke cognitive complaints independent of objective cognitive impairment (Minett et al., 2005). In this study we were unable to show that WMC or silent infarct was related to depressive symptoms or to post-stroke cognitive complaints. It is possible that the very mild and restricted range of SVD severity and depressive symptoms in our patients limited the statistical power to detect any relationships between post-stroke cognitive complaints and SVD markers. Moreover, in line with the results of two major review reports (Singh et al., 1998; Carson et al., 2000), we showed that the laterality of acute infarcts was not significant related to depressive symptoms.

In the post-hoc analysis we showed that the severity of stroke at admission determined the severity of depressive symptoms 3 months after the stroke. This finding is sensible given the emotional impact from the sudden loss of sensory or motor abilities after stroke, despite that lacunar stroke patients typically have milder physical disability compared to patients of other stroke subtypes (Petty et al., 2000), as reflected in the

low NIHSS score in our cohort (mean NIHSS = 4.3; *SD* = 2.6).

Our study is among the first in investigating the factors underlying post-stroke cognitive complaints. The strength of this study includes a consecutive cohort design and the exclusion of significantly depressed patients. This study also has ecological validity in the way that it addresses a clinical issue very commonly encountered by clinicians working with stroke patients. However, this study has several limitations as well. First, our patients represent a highly selected group and therefore our results apply only to lacunar stroke patients with mild SVD burden and no major depression. Second, the fact that post-stroke cognitive complaints were elicited by clinician rather than being presented spontaneously by the subjects might have inflated the rate of complaints. Third, ascertainment of post-stroke cognitive complaint was based only on responses to three questions. Other studies used more detailed questionnaires in evaluating subjective complaints (Derouesne et al., 1989; Schmand et al., 1996; Derouesne et al., 1999; Pearman and Storandt, 2004), but simple questions had been used as well (Schofield et al., 1997; Wang et al., 2000; Clarnette et al., 2001). In fact, we may actually see the use of simple questions as a strength of our study because it is unlikely that detailed instruments for cognitive complaints will be used in actual clinical settings, and our method of using simple questions maybe more representative of what is normally done in everyday clinical practice. Fourth, we only used brief cognitive tests, which might have been underpowered to detect the relationship between objective performance and post-stroke cognitive complaints. Fifth, the GDS may not be a valid indicator of depressive symptoms in the one patient who lacked insight into his cognitive problem. Finally, our small sample size of 75 patients might lack sufficient power to detect the association between certain putative factors and

post-stroke cognitive complaints.

4.5 Conclusions

Post-stroke cognitive complaints are common among lacunar stroke patients without major depression and are associated with a strong emotional component but not WMC. Clinicians should pay special attention to evaluate subclinical depressive symptoms in these patients, even if the cognitive complaints are corroborated by a proxy.

III. Evaluation of WMC severity

Chapter 5 The Age-Related White Matter Changes Scale Correlates with Cognitive Impairment

5.1 Introduction

Age-related WMC are considered a manifestation of arteriosclerotic SVD (Roman et al., 2002). Community studies have shown that varying severity of WMC is almost endemic among the elderly with prevalence reaching as high as 90% (Liao et al., 1997; de Leeuw et al., 2001). Studies have consistently shown that severity of WMC correlates with various cognitive functions, including executive function, memory, and global cognition, among community elderly (de Groot et al., 2000; van der Flier et al., 2005; Jokinen et al., 2009). Even in AD, WMC are common, with prevalence ranging from 28.9% to 100% (Aharon-Peretz et al., 1988; de Leeuw et al., 2004; Targosz-Gajniak et al., 2009) and presence of WMC probably enhances the cognitive decline in AD as well (Targosz-Gajniak et al., 2009).

Given the clinical relevance of WMC, methods that can reliably grade its severity will be useful in both clinical and research settings. Automated volumetric quantification based on MRI is the ideal method. However, the required expertise has restricted its use for research purpose only. On the other hand, although visual rating scale lacks the sensitivity, its relative simplicity makes it more applicable for daily practice. Over the decades, many visual WMC rating scales have been proposed, and each has its own merits and limitations (Scheltens et al., 1998). The VCI Harmonization Standards (Hachinski et al., 2006) has recently proposed to use the ARWMC scale (Wahlund et al., 2001) in grading WMC. Comparing ARWMC scale with 2 other commonly used visual scales (simplified Fazekas scale and Sheltens scale) (Gouw et al., 2006), its

complexity lies in between the simplified Fazekas scale and the more complex Sheltens scale. A unique advantage of this scale is its applicability in either MRI or CT (Wahlund et al., 2001). The recent LADIS (Leukoaraiosis and Disability) study also showed good correlation between ARWMC scale and WMC volume (van Straaten et al., 2006). To date, the association between ARWMC scale and cognitive performances has not been studied. In this study, we aimed to investigate the association between ARWMC scale and cognition among stroke patients.

5.2 Methods

5.2.1 Participants

Subjects were participants of the VITATOPS (**VITA**mins **TO** **P**revent **S**troke) MRI substudy (VITATOPS Trail Study Group,2002) (n=97) and SSVD (**S**troke associated with **S**mall **V**essel **D**isease) study (n=75) (Mok et al., 2004). The VITATOPS study recruited stroke patients who had confluent WMC as defined by a score of ≥ 2 in the ARWMC scale in at least one brain region. Recruitment began at October 2004 and completed in November 2006. The SSVD study consecutively recruited lacunar stroke patients from the acute stroke unit with no to confluent WMC from 2002 to 2003. We excluded patients with severe cognitive (e.g. severe aphasia) and/or physical impairment preventing cognitive assessment, and those with known concurrent diseases that may affect cognition (e.g. alcoholism). We used the baseline data of these 2 studies. Among these 172 participants, we collected following clinical data: age, gender, years of education, and vascular risk factors (current smoker, alcohol intake, hypertension, diabetes mellitus, hyperlipidemia, ischemic heart disease, and atrial fibrillation). Alcohol intake was defined as ≥ 1 drink per day. A psychologist (A.W.) performed Chinese MDRS I/P (Chan et al., 2003) and Chinese MMSE (Chiu

HFK, 1994) at around 3 months after acute stroke for all the participants. The MDRS I/P is a brief and validated measure for executive function (Mungas et al., 2003). It contains 11 items that assess verbal fluency and verbal and motor programming. The MMSE reflects general cognition. The VITATOPS and SSVD studies were approved by the joint Chinese University of Hong Kong and New Territories East Cluster clinical research ethics committee and all subjects gave written informed consent.

5.2.2Neuroimaging measures

Brain MRI was performed on a 1.5-tesla scanner (Sonata, Siemens Medical System, Erlangen, Germany) within 1 week of hospital admission. The MRI protocol consisted of axial T1-weighted imaging (TR/TE=425/14 ms), T2-weighted imaging (TR/TE=2500/120 ms), FLAIR (TR/TE=8000/100 ms), diffusion weighted imaging (DWI), gradient recall echo T2-weighted MRI (TR/TE=350/30 ms), with slice thickness 5 mm, gap 0.5 mm, FOV 230 mm and matrix of 256 x 256.

According to the original study of the ARWMC scale, we defined WMC as ill-defined hyperintensities ≥5 mm on both T2 and PD/FLAIR images on MRI (Wahlund et al., 2001). Volume of WMC and infarcts were measured on the coronal FLAIR sequence and axial T1-weighted MRI sequence respectively using the semi-automated segmentation method by the Easy Vision 4.3 software (Philips Medical Best, the Netherlands) (Mok et al., 2005). For the quantification of WMC, we first adjusted the threshold to delineate the border of WMC. We then dropped seeds in the WMC and the software automatically calculated the volume of WMC on each layer. We added up the volume of each layer to obtain the total volume of WMC. We used similar method to measure the infarct volume. We defined symptomatic infarct mainly by

DWI. Infarcts other than the symptomatic one were classified as silent. We defined microbleed as a circular area of marked and homogeneous signal loss on gradient recall echo T2-weighted MRI, of size ranges from 2-10 mm, that was not located in sulcal areas, to avoid confusion with flow void from cerebral vessels (Mok et al., 2004). The WMC volume, presence of silent infarct, total infarct volume, number and volume of thalamic infarct and basal ganglia infarct, and presence of microbleed for participants of the VITATOPS study were recorded by a single neurologist (X.Y.C.) (Mok et al., 2008), while that for participants of the SSVD study were recorded by another neurologist (Y.H.F.) (Mok et al., 2005).

5.2.3 ARWMC scale rating

Using the ARWMC scale (Wahlund et al., 2001), two experienced raters, V.M. and Y.Y.X., rated WMC severity for participants of the SSVD study and VITATOPS MRI substudy, respectively. The ARWMC scale grades WMC severity in 5 brain regions (frontal lobe, parietal-occipital lobe, temporal lobe, infratentorial region, basal ganglia) on a 4-point scale (score 0, 1, 2, and 3). The ARWMC scale can be presented as the total score and global score, and both have been shown to correlate with volume (Fan et al., 2003; van Straaten et al., 2006). The total score is the sum of score for each region in both hemispheres, which ranges from 0 to 30. The global score of ARWMC scale is the score of region with the most severe WMC. Hence, this global score provides only 4 grading of WMC severity, with score ranges from 0 to 3. All the raters were blinded to clinical data.

5.3 Statistical analysis

WMC volume and total score of ARWMC scale were transformed into normal

distribution using square root arithmetic transformation. MDRS I/P scores were normally distributed, while MMSE scores were skewed. Pearson and spearman rank correlations were used to assess the relationships between MDRS I/P and 3 WMC measures (WMC volume, total score and global score of ARWMC scale), demographic features (age, gender and years of education), vascular risk factors (current smoker, alcohol intake, hypertension, DM, hyperlipidemia, ischemic heart disease, and atrial fibrillation) and infarct measures (total infarct volume, number and volume of thalamic infarct and basal ganglia infarct, presence of silent infarct and microbleed). We then performed separate multivariate linear regression analyses to evaluate the ability of the 3 WMC measures to predict scores on the MDRS I/P after adjusting for other significant variables in the univariate tests. Overall, 3 multivariate linear regression analyses were performed for MDRS I/P. Since the statistical assumptions of multivariate linear regression analysis for MMSE were not fulfilled, MMSE was dichotomized with scores <24 being considered to indicate cognitive impairment. To investigate the association between ARWMC ratings and MMSE, we used independent-samples t test for normally distributed data, Mann-Whitney U test for skewed data, χ^2 tests for categorical data, and trend test for ordinal data to test the differences between groups with respect to MMSE. Then the 3 WMC measures were separately put into multiple logistic regression models using forward method with other significant factors in the univariate analyses as covariates in order to determine the association between WMC measures and MMSE. We further performed linear regression models and logistic regression models with age, gender and education as covariates to explore the interaction of WMC volume with infarct measures (presence of silent infarct and total infarcts volume) on MDRS I/P and MMSE, respectively.

5.4 Results

Characteristics of the subjects are summarized in table 5-1. Subjects in VITATOPS MRI substudy and SSVD study were comparable in age and gender composition, and there was no statistical difference between the two substudies with respect to smoker, hypertension, DM, ischemic heart disease and atrial fibrillation. The VITATOPS MRI substudy had higher proportion of educated subjects, drinker, hyperlipidemia, presence of silent infarct and presence of microbleed. WMC volume is larger in the VITATOPS study subjects (mean volume = 39.6 cm^3) than in the SSVD subjects (2.3 cm^3). Taken subjects from both studies as a whole, total score and global score of ARWMC scale closely correlated with WMC volume ($r=0.726$, $p<0.001$; $rho=0.781$, $p<0.001$, respectively).

Table 5-1 Characteristics of the subjects

	Current study (N=172)	VITATOPS MRI substudy (N=97)	SSVD (N=75)
Demographic features			
Age, mean±SD, years	73.1±9.6	72.7±9.6	73.6±9.6
Gender (% male)	90 (52.3%)	51 (52.6%)	39 (52.0%)
Years of education (>6 years)	114 (66.3%)	80 (82.5%)	34 (45.3%)*
Smoker (%)	78 (45.3%)	49 (50.5%)	29 (38.7%)
Drinker (%)	33 (19.2%)	12 (12.4%)	21 (28%)*
Hypertension (%)	154 (89.5%)	86 (88.7%)	68 (90.7%)
Diabetes mellitus (%)	62 (36.0%)	34 (35.1%)	28 (37.3%)
Hyperlipidemia (%)	85 (49.4%)	62 (63.9%)	23 (30.7%)*
Ischemic heart disease (%)	22 (12.8%)	14 (14.4%)	8 (10.7%)
Atrial fibrillation (%)	3 (1.7%)	3 (3.1%)	0 (0.0%)
Cognitive function			
MMSE score, median (IQR)	24.0 (20.0-27.0)	22.0 (17.5-26.0)	26.0 (21.0-29.0)*
MMSE score<24	74 (43.0%)	46 (47.4%)	28 (37.3%)*
MDRS I/P score, mean±SD	26.7±6.7	25.2±6.7	28.4±6.4*
MRI data			
Presence of silent infarct (%)	131 (74.9%)	88 (90.7%)	43 (57.3%)*
Total infarcts volume, cm^3	0.8 (0.4-1.3)	0.8 (0.4-1.5)	0.7 (0.4-1.1)
Presence of microbleed (%)	89(50.9%)	74(76.3%)	15(19.0%)*
WMC volume, median (IQR), cm^3	20.0 (2.7-40.8)	39.6 (25.6-49.5)	2.3 (0.3-5.9)*
Total score of ARWMC scale, median (IQR)	8 (4-10)	8 (7-10)	5 (2-8)*
Global score of ARWMC scale, n (%)			
0	15 (8.7%)	0(0.0%)	15 (20.0%)*
1	19 (11.0%)	0 (0.0%)	19 (25.3%)
2	79 (45.9%)	47 (48.5%)	32 (42.7%)
3	59 (34.3%)	50 (51.5%)	9 (12%)

SD, standard deviation; IQR, interquartile range; * $p<0.05$

Univariate analysis showed that WMC volume, total and global scores of ARWMC scale were significantly associated with MDRS I/P ($r=-0.362$, $p<0.001$; $r=-0.344$, $p<0.001$; $rho=-0.311$, $p<0.001$, respectively), other variables that had significant correlations with MDRS I/P included age ($r=-0.414$, $p<0.001$) and education ($rho=0.272$, $p<0.001$). Separate multivariate regression analyses showed that all 3 measures of WMC independently predicted the MDRS I/P score ($p<0.05$) after adjusting for age and education (table 5-2). Volumetric measure was the strongest predictor for MDRS I/P performance, followed by total ARWMC score and global score of ARWMC scale.

Table 5-2 Multivariate regression results of WMC measures and executive function

	MDRS I/P	
	Beta	P value
WMC volume	-0.271	<0.001
Total score of ARWMC scale	-0.248	0.001
Global score of ARWMC scale	-0.218	0.005

WMC volume and total score of ARWMC scale were transformed into normal distribution using square root arithmetic transformation. The three WMC measures were separately entered into multivariate linear regression models with age and education as covariates.

Univariate analysis showed that WMC volume, total and global scores of ARWMC scale predicted MMSE performance (Z=-3.428, p=0.001; Z=-3.826, p<0.001; trend=15.358, p<0.001, respectively). Other variables significant in the univariate analyses were age, gender, education, smoker, DM, presence of silent infarct and presence of microbleed. Separate multiple logistic regression analysis with forward method showed that after adjusting for confounders, each of the WMC measure remained independently predictive of MMSE performance. The adjusted odds ratio (95% confident interval) for WMC volume, total score and global score of ARWMC scale were 1.021(1.003-1.038), 1.181 (1.038-1.343) and 1.740 (1.063-2.847), respectively. Age, education and diabetes mellitus were also independent predictors in all multivariate models for MMSE performance.

WMC volume was associated with presence of silent infarct (rho=0.432, p<0.001) and total infarcts volume (r=0.184, p=0.019). Only WMC volume was an independent predictor for MDRS I/P and MMSE whereas presence of silent infarct, total infarcts volume, interaction terms were not significant predictors, with p>0.05 after adjusting for age, gender and education.

5.5 Discussion

The present study showed that the ARWMC scale correlated with cognitive performances. The correlation between ARWMC scale and cognition remained robust even adjusted for other clinical variables. The finding that volumetric method had the strongest correlation among the 3 WMC measures is consistent with other studies, which showed the superiority of volumetric measure over visual scales (Gunning-Dixon and Raz, 2000; van Straaten et al., 2006; Tiehuis et al., 2008).

We also found that the various WMC measures correlated with both executive function and global cognition. Although some studies suggested that WMC selectively impair executive function and psychomotor speed (Schmidt et al., 1993; Wen et al., 2004), other studies of larger sample size or that included subjects with more severe WMC showed that WMC severity correlated not only with executive function, but also with global cognition as well (de Groot et al., 2000; van der Flier et al., 2005; Jokinen et al., 2009). Our findings are thus consistent with that of other studies. Our study also suggests WMC volume was a better indicator of cognitive impairment than infarcts, which is again consistent with Mungas study(Mungas et al., 2001).

Noteworthy is the recent findings of the LADIS study, which showed that the ARWMC scale failed to distinguish subjects with and without subjective memory complaints (Gouw et al., 2006). Since subjective memory complaints may indicate mild cognitive impairment (Jonker et al., 2000), findings of LADIS study may suggest that the ARWMC scale is not sensitive in differentiating subjects with and without mild cognitive impairment. However, other studies have shown that subjective memory complaints are probably only crude reflection of objective cognitive impairment (Mitchell, 2008) and may even be more closely correlated with depression (Minett et al., 2005) or personality traits (Hanninen et al., 1994) than objective cognitive impairment. Hence, firm conclusion on the association between ARWMC scale and objective cognitive impairment cannot be derived from findings of LADIS study. Our present study differs mainly from the LADIS study in that we investigated the association between the ARWMC scale and objective cognitive

performances, rather than subjective cognitive complaints.

In this study, apart from using the total score of the ARWMC scale, we also explored the clinical utility of a global score of ARWMC. Our previous study showed that the global score was able to detect statistical significant difference in WMC volume between all grades (Fan et al., 2003). The present study showed that it correlated significantly with cognitive performances. The global score is similar to the simplified Fazekas scale, which also provides one global score (range 0 to 3) in grading WMC (Fazekas et al., 1987; Inzitari et al., 2007). However, the global score of ARWMC scale differs from the Fazekas scale in that it considers WMC in both deep white matter and periventricular regions as a whole brain region, and it only scores the most severe region, whereas the simplified Fazekas scale scores mainly the deep white matter region. Further study is needed to explore the relationship between these 2 scales and whether these 2 scales detect different clinical groups. Overall, the global score of ARWMC scale and the simplified Fazekas scale are considered to be simple visual scale and preference for its use may depend on experience of individual center.

Some potential limitations of this study need to be addressed. First, we used only brief measures for executive function and global cognition. Although both MDRS I/P and MMSE are valid instruments for evaluation of executive function and global cognition respectively (Mungas et al., 2003), the correlation between ARWMC scale and objective cognitive impairment may require confirmation by other study using more extensive neuropsychological batteries. Second, despite we investigated a wide range of imaging variables, we did not include data on brain atrophy or hippocampal volume, which may be important predictors for cognition as well (Mungas et al.,

2001). Mungas study found that after adjusting for cortical gray matter volume and hippocampal volume, WMC volume were not independent predictors for executive function and global cognition (Mungas et al., 2001). The association between ARWMC scale and cognitive impairment may thus be weakened if atrophy measures are added into the regression models. Last, all our subjects were participants of two different studies and they all had clinical stroke, so our study may have selection bias and findings of our study may not be generalized to stroke-free persons.

In conclusion, the present study shows that the ARWMC scale correlates with cognitive impairment. Findings of our study lend support to the recommendation of the VCI harmonization standards in using ARWMC scale for rating WMC severity.

Chapter 6 Operational Definitions Improve Reliability of the Age-Related White Matter Changes Scale

6.1 Introduction

Age-related WMC are endemic in the elderly population (de Leeuw et al., 2001). Recent community studies have consistently shown that increasing WMC correlates with cognitive impairment and decline (Longstreth et al., 1996; de Groot et al., 2000; Debette and Markus, 2010). Given this association between severity of WMC and cognitive impairment, methods that can reliably grade the severity of WMC will be important for clinical practice and researches. Although volumetric measurement provides continuous data without ceiling or floor effect, it is time consuming and can only be applied on MRI. Various visual rating scales have been proposed (Scheltens et al., 1998; de Groot et al., 2000; Wahlund et al., 2001), each has its own merits and limitations. They are easy to apply on CT and/or MRI, and are still commonly used in both clinical practice and researches. However, application of different scales by different centers makes comparison between studies difficult.

To establish a minimum dataset so that different studies (e.g. large scale epidemiological studies) could pool data for comparison and cross-validation, the VCI Harmonization Standards recommended ARWMC scale (Wahlund et al., 2001) as the preferred visual rating scale for measuring severity of WMC (Hachinski et al., 2006). The scale has been validated against volumetric measurement (van Straaten et al., 2006) , cognitive impairment(Xiong et al., 2010), and widely used in recent studies (Jickling et al., 2009; Pu et al., 2009). Apart from its simplicity and ability in providing grading at different brain regions, a unique property is its applicability in

both MRI and CT. Although the ARWMC scale provided similar scores on CT and MRI for most cases at various regions, its inter-rater reliability for CT was only fair (kappa=0.48) (Wahlund et al., 2001), which we hypothesize may be related to the obscurity of certain aspects of its scoring definitions.

Currently, in developing countries (e.g. China) where dementia burden is the greatest (Ferri et al., 2005; Llibre Rodriguez et al., 2008), only CT may be readily accessible. Hence, having a reliable visual rating scale based on CT will be particularly useful. Furthermore, if the same scale can also be applied to MRI, data from studies based on CT can then be compared with that based on MRI. In this study, we aimed to operationalize the ARWMC scale and investigate the effect of this operationalization on reliability and validity on MRI and CT. We hypothesize that the operationalized ARWMC scale can improve the reliability.

6.2 Methods

6.2.1 Subjects

Patients were participants of the MRI substudy of the **VITA**mins **TO** Prevent Stroke (VITATOPS) study in Hong Kong (n=100). The VITATOPS study is a multi-center, randomized, double-blind, placebo-controlled trial evaluating whether homocysteine lowering (folate 2mg, B_6 25mg, B_{12} 500mcg) is effective for secondary stroke prevention (NCT00097669) (VITATOPS Trail Study Group, 2002). The recruitment in our centre was described in detail previously.(Mok et al., 2010) In current study, three patients' MRI quality did not fulfill assessment, so 97 patients' data was used. The study was approved by the the joint Chinese University of Hong Kong and New Territories East Cluster clinical research ethics committee, and all subjects gave

written informed consent.

For each patient a plain cerebral CT scan (10 mm slice thickness at 10 mm intervals supratentorially and 5 mm slice thickness and 5 mm intervals through the posterior fossa) was performed within 24 hours after admission. The interval between CT and MRI examination was less than 1 week. Brain MRI was performed on a 1.5-tesla scanner (Sonata, Siemens Medical System, Erlangen, Germany). The MRI protocol consisted of axial T1-weighted imaging (TR/TE=425/14 ms), axial T2-weighted imaging (TR/TE=2500/120 ms), coronal FLAIR (TR/TE=8000/100 ms), proton density (TR/TE=2124/7.1ms), gradient recall echo T2-weighted MRI (TR/TE =350/30 ms), with slice thickness 5 mm, gap 0.5 mm, FOV 230 mm and matrix of 256 x 256.

WMC were defined as ill-defined hyperintensities ≥5 mm on both T2 and PD/FLAIR images and isointensity on T1-weighted imaging on MRI, and as ill-defined and moderately hypodense areas of ≥5 mm on CT (Fazekas et al., 2002). WMC volume was measured on the coronal FLAIR sequence using the semi-automated segmentation method by the Easy Vision 4.3 software (PhilipsMedical Best, the Netherlands). We first adjusted the threshold to delineate the border of WMC. We then dropped seeds in the WMC and the software automatically calculated the volume of WMC on each layer. WMC volume was recorded by a neurologist (X. C.).

6.2.2 Visual rating scales

In the ARWMC scale (Wahlund et al., 2001), WMC were rated separately in frontal lobe, parietal-occipital lobe, temporal lobe, infratentorial region and basal ganglia on

a 4-point scale. The total score is the sum of scores for each area (score range 0–3) in both hemispheres ranging from 0 to 30.

Operational definitions of the ARWMC scale were derived mainly from Erkinjuntti research criteria for subcortical vascular dementia (Erkinjuntti et al., 2000) and Scheltens scale (Scheltens et al., 1993). Axial FLAIR images were used to rate the severity of WMC. For each lobe, the slice with the most severe lesion in that lobe was chosen for scoring. Lesions were defined as PVWMC when their largest diameter was adjacent to the ventricle otherwise they were defined as DWMC (de Groot et al., 2000). The PVWMC divides into caps and bands. Caps are rounded hyperintensities around the frontal and occipital horns, bands are smooth hyperintensities along the ventricle (Zimmerman et al., 1986). In operationalized ARWMC scale (Table 7-1), PVWMC were classified into three categories (< 5 mm, 5-10 mm, > 10 mm), according to the diameter of the caps and bands which were measured parallel for caps and perpendicular to the ventricle for bands. DWMC were categorized as 5-9 mm, 10-25 mm and > 25 mm according to the largest diameter of irregular lesions in deep white matter region. If there was connecting bridge between two focal lesions, they were considered to be beginning confluence of lesions. The basal ganglia include striatum, globus pallidus, thalamus, internal/external capsule, and insula. For each brain hemisphere, the WMC were rated separately in 5 regions (frontal lobe, parietal-occipital lobe, temporal lobe, infratentorial region and basal ganglia) on a 4-point scale, ranging from score 0 to 3. The total score of the operationalized ARWMC scale is the sum of scores for both hemispheres (i.e. 10 regions), ranging from 0 to 30. Figure 6-1 shows the diameter measurements of WMC on MRI and CT.

Table 6-1 Operational definitions of ARWMC scale

Score	Frontal lobe, parietal-occipital lobe, temporal lobe, infratentorial region	Basal ganglia
0	No lesions (PVWMC: symmetrical, well-defined ventricle, or DWMC< 5 mm)	No lesions
1	Focal lesions (PVWMC: non-symmetrical caps or bands < 5 mm, or DWMC between 5 and 9 mm)	One focal lesion
2	Beginning confluence of lesions (PVWMC between 5 and 10 mm, or DWMC between 10 and 25 mm or connecting bridge between two focal lesions)	More than one focal lesion
3	Diffuse involvement of most region (PVWMC > 10 mm, or DWMC > 25 mm)	Confluence of lesions

ARWMC, age-related white matter changes; PVWMC, periventricular white matter changes; DWMC, deep white matter changes.

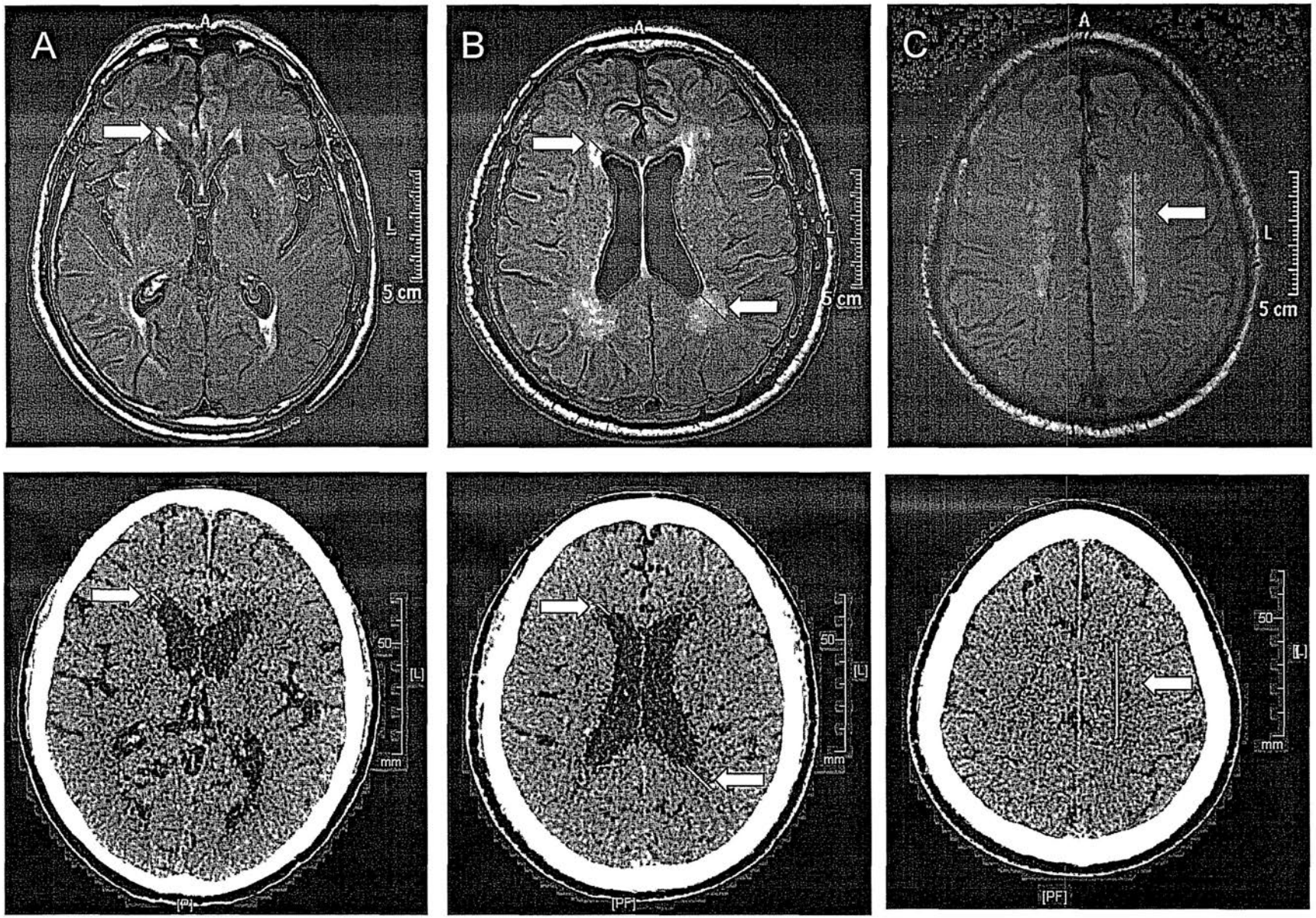
A
B
C
A
L
5 cm
50
mm
[L]
[PF]

Figure 6-1 The diameter measurements of WMC on FLAIR MRI and CT. The arrows show the lesions.

A: Right frontal lobe periventricular WMC, score 1, diameter 4 mm on both FLAIR MRI and CT.

B: Right frontal lobe periventricular WMC, score 2, diameter 8 mm on FLAIR MRI and 7 mm on CT; Left parieto-occipital lobe periventricular WMC score 3, diameter 16 mm on FLAIR MRI and 14 mm on CT.

C: Left frontal lobe deep WMC, score 3, diameter 46 mm on FLAIR MRI and 40 mm on CT.

6.2.3 Reliability and time recording

Two experienced observers (Y.X. and J.Y.) and 6 inexperienced observers (C.H.K.W., S.S.W.C., H.H.S.L., L.H.P.T., J.W.K.B. and G.C.Y.W.) were divided into 2 pairs and each pair had 4 raters (pair 1: Y.X., C.H.K.W., J.W.K.B., and S.S.W.C., and pair 2: J.Y., H.H.S.L., L.H.P.T., and G.C.Y.W.). Both pairs received a 2-hour teaching session at separate time in which pair 1 learnt the ARWMC scale and pair 2 learnt the operationalized ARWMC scale. We randomly selected 30 MRI and 30 CT hardcopies out of the 97 study subjects. In order to assess the interrater reliability of the scales for MRI and CT, 2 raters of pair 1 rated MRI and the remaining 2 raters rated CT films using the ARWMC scale. Similarly, 2 raters of pair 2 rated MRI and the remaining 2 raters rated CT films using the operationalized ARWMC scale. Both experienced raters were allocated to rate CT films using either the original or operationalized ARWMC scale. We recorded the time of each rater for rating the 30 images. Average time for rating per scans was calculated in each pair. The time for MRI included the time to find the T1 and T2 sequences films from 4 sets of MRI sequences (T1, T2, coronal Flair and gradient recall echo) of one patient. One week later, one observer of each sub-pair re-rated the same MRI or CT to assess the intrarater reliability. With this arrangement, interrater and intrarater reliability of both scales for MRI and CT were obtained (table 2).

6.2.4 Validity against volumetric measure

The experienced observer Y.X. rated the whole 97 MRI and CT films using the ARWMC scale and the operationalized ARWMC scale. We then tested the correlation between WMC volume and the scorings on MRI and the correlation between CT and MRI scorings for both scales.

6.2.5 Statistical Analyses

Intraclass correlation was used to determine consistency between raters and within rater on the ARWMC scale and the operationalized ARWMC scale. Intraclass correlation coefficient (ICC) is considered as excellent if ICC $\geq$ 0.75 (Landis and Koch, 1977). Spearman correlation was used to assess correlations between scorings on MRI of each scale and volumetric measure, and between the CT and MRI scorings of both scales. SPSS 13.0 was used to analyze the data.

6.3 Results

The mean age of these patients were 72.7±9.6years, 52.6% (51/97) of them were male. The median (interquartile range) of WMC volume was 39.6 (25.6-49.5) cm^3. The characteristics of the participants were described in detail previously (Xiong et al., 2010). Interrater reliability of the operationalized scale on CT (0.874, 95% confidence interval [0.780-0.934]) was significantly better than the original scale (0.569, 95% confidence interval [0.247-0.775]). Its intrarater reliability on CT and reliability on MRI was comparable with the original scale (Table 7-2). The time required to administer the operationalized scale was similar to that of the original scale (Table 6-2).

Table 6-2 Reliability of and time required to rate ARWMC scale and operationalized ARWMC scale

Items	ARWMC scale		Operationalized ARWMC scale	
	MRI	CT	MRI	CT
Average time/film	3'56"	1'16"	4'2"	1'18"
Interrater reliability (ICC [95%CI])	0.845 (0.730-0.919)	0.569 (0.247-0.775)	0.860 (0.756-0.967)	0.874 (0.780-0.934)
Intrarater reliability (ICC [95%CI])	0.853 (0.694-0.930)	0.750 (0.475-0.881)	0.838 (0.663-0.923)	0.869 (0.725-0.938)

ICC, intraclass correlation coefficient; CI, confidence interval.

Both the MRI scorings of the ARWMC scale and the operationalized ARWMC scale correlated significantly with WMC volume (rho=0.638, $p<0.001$; rho=0.613, $p<0.001$, respectively). The CT scorings of the operationalized ARWMC scale and the ARWMC scale significantly correlated with the MRI scorings (rho=0.648, $p<0.001$; rho=0.618, $p<0.001$, respectively).

6.4 Discussion

Our study found that the operationalized ARWMC scale had better interrater reliability than the original ARWMC scale on CT. Its reliability on MRI, time it took in rating the films and its correlation with quantitative WMC volume were comparable with the original scale.

Consistent with the Wahlund study (Wahlund et al., 2001), our study confirmed that the original ARWMC scale had good interrater reliability on MRI and only fair interrater reliability on CT. We also found that the MRI scoring of ARWMC scale correlated with WMC volume on MRI, which is in accordance with the LADIS study (van Straaten et al., 2006). Moreover, we found that scorings of CT correlated significantly with that of MRI for both scales.

The operationalized ARWMC scale was derived partly from the Scheltens scale (Scheltens et al., 1993) which also took into account both the size and location of the WMC on MRI. The Scheltens scale rated both DWMC and PVWMC, whereas, the operationalized ARWMC scale recorded the score of DWMC or PVWMC in brain regions, and it was less complex and applicable to CT as well. The operationalized ARWMC scale provides detailed definitions of lesion size and location. This probably

explains the reason for the improvement in reliability. Another possible explanation could be that the differences in rating reliability may reflect the fact that raters of Pair 2 were 'more accurate' and 'more committed' raters than those of Pair 1. However, these raters were mostly inexperienced observers being randomly divided into these two pairs, and both experienced observers rated CT films using different scales. Hence this later possibility is less likely.

It is noteworthy that the improvement is particularly significant on CT. Although CT may be more difficult to delineate the border or to ascertain the size of WMC when compared with MRI, our study showed that the use of a more detailed definition based on the actual size of the lesion is still feasible based on CT. Another visual rating scales, the Rezek scale (Rezek et al., 1987) also measured the lesion size and it had excellent intrarater and interrater reliability with kappa values ranging from 0.88 to 0.95 (Leys et al., 1990). However, it evaluates WMC in 15 areas in each hemisphere that may be too complex and time-consuming for clinical practice or for large epidemiological study. The Mendes Ribeiro scale (Mendes Ribeiro et al., 2001) categorizes WMC by regions (anterior and posterior frontal, parietal, occipital), severity (mild, moderate, severe) and extent (periventricular, extending to deep white, full thickness), but the interrater and intrarater for this scale were moderate to substantial with kappa value ranging from 0.55 to 0.7. Some scales (Jorgensen et al., 1995; DeCarli et al., 1996) distinguish subjects with and without WMC in a dichotomized method, which yields only limited information. Some published scales (Erkinjuntti et al., 1987; Aharon-Peretz et al., 1988; Charletta et al., 1995) on CT have not included any data on inter- and intra-rater reliability findings. Comparing with the above scales, the operationalized ARWMC on CT assessed the WMC through

anatomical distinction and lesion size with substantial reliability. Most important, the uniqueness of the operationalized ARWMC scale is that it is applicable to MRI as well.

Our study is probably one of the first to provide the time for rating WMC on both MRI and CT. Time taken for rating WMC is also an important consideration for choosing a scale, especially for large-scale studies. Although the operationalized ARWMC scale seems to be more complex than the original scale, it took comparable time to apply when compared with the original ARWMC scale. Rating WMC on MRI took more time than on CT in our study, probably because the time of rating MRI also included the time to find the correct films from the package and the observers needed to define WMC on both T1 and T2 sequences.

6.5 Conclusions

The operational definitions improve the reliability of the ARWMC scale on CT. The operationalized ARWMC scale may be particularly useful in developing countries where dementia burden is expected to escalate and where only CT is accessible.

IV. Mechanisms for cognitive impairment in WMC

Chapter 7 Cortical and Frontal Atrophy are Associated with Cognitive Impairment in Age-Related Confluent White Matter Changes

7.1 Introduction

Age-related WMC were endemic in the elderly population. (de Leeuw et al., 2001) They were currently thought to result from a complex interplay between occlusive arteriole and venous diseases, leading to hypoperfusion of the white matter. (Black et al., 2009) Recent community studies have consistently shown that increasing WMC correlates with decreasing cognitive function, in particular that of the executive function. (Longstreth et al., 1996; de Groot et al., 2000; Dufouil et al., 2003; Au et al., 2006) Most suggested that WMC impairs executive function by disconnecting the fronto-subcortical circuits. (de Groot et al., 2000; Roman et al., 2002) Despite accumulating evidence supporting the association between cognitive impairment and WMC, some observed that severe WMC were not necessarily associated with cognitive impairment. (Fein et al., 1990; Sabri O, 1999) Mechanisms explaining the association between WMC and cognitive impairment are probably complex.

Past studies investigating cognitive relevance of subcortical ischemic vascular disease have suggested that apart from WMC severity, other concurrent brain measures may also affect cognition. These may include infarct load and location, (Corbett et al., 1994; Mok et al., 2005; van der Flier et al., 2005) microbleed, (Werring et al., 2004) global atrophy (e.g. whole brain, (Sabri O, 1999; Schmidt et al., 2005) total cortical gray matter [cGM] (Constans et al., 1995; Mungas et al., 2001)), central atrophy (i.e. ventricular enlargement), (Corbett et al., 1994; Constans et al., 1995) regional brain atrophy (e.g. hippocampal atrophy (Constans et al., 1995; Mungas et al., 2001)), and

Alzheimer's pathology. (Constans et al., 1995) Most of these studies included subjects with a wide spectrum of WMC. Studies that focused among those with severe WMC are scarce.

In this study, we investigated the cognitive predictors in patients with confluent WMC with no to varying levels of cognitive impairment. Given the abundant structural and functional interconnection between white matter fibers and frontal cortex (Tullberg et al., 2004; Geroldi et al., 2006; Chen et al., 2009) and the association between frontal atrophy and executive dysfunction, (Gunning-Dixon and Raz, 2000; Zimmerman et al., 2006) we hypothesized that confluent WMC are associated with frontal atrophy, which accounts for the executive dysfunctions in these patients.

7.2 Methods

Subjects were participants of the MRI substudy of the VITATOPS study, which is a multi-center, randomized, double-blind, placebo-controlled trial evaluating the effects of homocysteine lowering treatment using vitamins on secondary stroke prevention (NCT00097669). (VITATOPS Trail Study Group, 2002) The MRI substudy evaluates whether homocysteine lowering can also slow the progression of SVD and cognitive decline. Inclusion criteria in our center were ischemic stroke within 7 months of the event and patients with confluent WMC on MRI. We defined confluent WMC by a score of $\geq$2 based on the ARWMC scale in at least 1 brain region. (Wahlund et al., 2001) We excluded hemorrhagic stroke patients, those with severe cognitive and/or physical impairment preventing cognitive assessment, and those with known concurrent diseases that may affect cognition (e.g. alcoholism). All subjects were recruited from the acute stroke unit of a teaching hospital. Brain MRI was performed

within 1 week of hospitalization. We classified stroke subtypes into large-artery atherosclerosis (LAA), cardioembolism (CE), small-artery occlusion (SAO), stroke of other determined cause, and stroke of undetermined cause (U). (Adams et al., 1993) A single experienced neurologist (V.M.) performed MRI screening and subject recruitment. We also collected blood for APOE genotyping, which was done by polymerase chain reaction-restriction fragment length polymorphism. Recruitment began at October 2004 and completed in November 2006. A total of 100 patients were recruited.

7.2.1 Cognitive assessment

An experienced psychologist (A.W.) administered Chinese version of MDRS I/P (Chan et al., 2001) and MMSE (Chiu HFK, 1994) upon all patients. The MMSE and MDRS I/P (score ranges between 0-37) are validated measures of global cognition and executive function(Mungas et al., 2003), respectively. The Clinical Dementia Rating scale (CDR) (Morris, 1993) was used to provide an index of the global cognitive status in our patients.

7.2.2 MRI imaging variables

All MRI examinations were performed on a 1.5-tesla scanner (Sonata, Siemens Medical System, Erlangen, Germany) with a standard protocol including T1-weighted imaging (TR/TE=425/14 ms), T2-weighted imaging (TR/TE=2500/120 ms), FLAIR (TR/TE=8000/100 ms), gradient recall echo T2-weighted MRI (TR/TE =350/30 ms), with slice thickness 5 mm, gap 0.5 mm, FOV 230 mm and matrix of 256 x 256, and time-of-flight MR angiography.

Volume of WMC was quantified using the semi-automated "seeding method" with Easy Vision 4.3 software on FLAIR sequence. (Wen et al., 2004) In brief, WMC region was first identified and a "seed" was dropped on that region. The "seed" would grow automatically to include all connected pixels until that region was outlined; and volume of outlined region would be generated automatically. The total WMC volume was recorded. Infarct volume was also quantified using the same method on T1 weighted images. Volume and number of all infarcts and infarcts in the basal ganglia (striatum, globus pallidus, thalamus, internal/external capsule, insula) and thalamus were recorded. In addition, we recorded the total number of microbleeds, which was defined as dot-like hypointensity on gradient recall-echo T2* weighted MRI. Two trained neurologists (Y.X. and Y.C.) who were blinded to patients' cognitive data rated all MRI measures. The intraclass correlations of 10 randomly selected MRIs among the 2 raters for total WMC volume, infarct volume, and microbleed number were 0.97, 0.90, and 0.93, respectively.

Brain volumes were quantified using a validated automated hybrid warping method. (Shen and Davatzikos, 2003) Firstly, a feature-based volumetric registration algorithm HAMMER was used to warp a model cortical surface to the individual space. (Shen and Davatzikos, 2003) Following, a surface registration algorithm based on the matching of geometric attribute vectors was used to further warp the model surface to the subject. After the high-dimensional hybrid registration and atlas-based warping, the subject brain image was segmented into various neuroanatomic regions by mapping the anatomic labels in the atlas to the subject. Since hypointensity of WMC in T1 structural image could be misclassified as gray matter or cerebrospinal fluid in the segmentation procedure, which may affect accuracy of brain parcellation, we

identified WMC to ensure a correct tissue classification map before the parcellation. The WMC was segmented from skull stripped FLAIR images using a fully automatic method, (Wu et al., 2006) followed by a manual removal of false positive inclusions. Then the segmented WMC regions were transformed into high resolution T1 image space using the rigid transformation matrix, which was preserved from registration of FLAIR to T1 image using Oxford FSL tools FLIRT (http://www.fmrib.ox.ac.uk/fsl/). Before parcellating the brain into various regions, the corresponding regions in tissue segmented maps occupied by the WMC were assigned as white matter. Using these methods, we obtained volumes of 6 frontal subregions, hippocampus, lateral ventricles and total cGM. Due to our a priori interest in the relation between frontal atrophy and cognitive impairment, 6 frontal subregions (superior frontal, middle frontal, inferior frontal, medial frontal, medial fronto-orbital, and lateral fronto-orbital gyrus) were examined. To correct for individual difference in intracranial volume (ICV), all volumetric data were normalized to ICV as corrected-ratios in subsequent statistical analyses.

7.2.3 Amyloid imaging

We performed amyloid imaging with PIB among 7 cognitive impaired participants (median age 74 years, 2 female, median MMSE 16 [range 11-25]). Five of them had a CDR of 0.5 and 2 had CDR $\geq$ 1. We also performed amyloid imaging upon 4 patients with clinical AD (median age 66 years, 3 female, median MMSE 20 [range 14-24]) and 3 healthy controls (median age 65, 1 female, MMSE 30). All 13 participants received a dose of 15 mCi ^{11}C-PIB intravenously after fasting (6 hours) and the brain was imaged at 5, 35, and 60 min after injection with 10 min emission acquisition at each time point using an integrated in-line PET/CT scanner (Biograph^{TM} 16 LSO

HI-REZ; CTI/Siemens Inc.). The ^{11}C-PIB PET images of 5 min were automatically coregistered to a brain atlas of MRI by MIMNeuro 2.0 for the localization of following regions of interest (ROIs): brain stem, caudate, cerebellar vermis, gyrus rectus, lateral temporal lobe, medial temporal lobe, frontal gyrus, occipital lobe, posterior cingulate gyrus, precuneus, putamen, thalamus, superior parietal lobule, and cerebellum. The ROIs were transferred to the corresponding 35 and 60 min PET images respectively. Stroke patients with increased PIB binding observed visually in frontal gyrus, posterior cingulate gyrus, precuneus, superior parietal lobule, and lateral temporal lobe were considered as having concurrent AD.(Ng et al., 2007) The sum of the total lesion glycolysis (TLG_global) of the above-mentioned ROIs (except cerebellum) was calculated for the series of PET images. The global standardized uptake value (SUV) was calculated by TLG_global/volume_global, where volume_global was defined as the sum of the volume of the above-mentioned ROIs (except cerebellum). The ratio of the global SUV and the mean cerebellum SUV was calculated for 5 min (ratio_5), 35 min (ratio_35) and 60 min (ratio_60) PET images respectively. The global PIB retention at 35 min and 60 min was eventually calculated by ratio_35/ ratio_5 and by ratio_60/ ratio_5 respectively. We used the global PIB retention value from 35-45min for comparison. The same experienced nuclear medicine specialist (E.Y.L.L.) assessed all images without knowledge of patients' clinical data. The institutional ethics committee approved the main study and the amyloid imaging substudy. All subjects provided written informed consent.

7.3 Statistical Analyses

7.3.1 Predictors for cognitive performances

We used Pearson or Spearman rank bivariate correlation to first explore the

association between cognitive scores (MMSE, MDRS I/P) and the following variables: demographic data (age, gender, education >6 years), clinical data (hypertension, DM, current smoker, current alcohol drinker, hyperlipidemia, ischemic heart disease, atrial fibrillation, homocysteine level, APOE ε4 carrier), total WMC volume, infarct measures (volumes and number of total infarct, basal ganglia and thalamic infarct), number of microbleed, volumes of cGM, lateral ventricles and regional measures including the frontal subregions and the hippocampus. These exploratory correlation analyses showed that age, education, infarct number, and volumes of total WMC, cGM, hippocampus, lateral ventricles and almost all the frontal subregions were significantly associated with MDRS I/P. All of the above variables, except for infarct number, also had significant associations with MMSE. Based on findings of the above exploratory analyses, we constructed multivariate linear regression models to predict performances on the MDRS I/P and MMSE using the following independent variables: age, education >6 years, infarct number, and volumes of total WMC, lateral ventricles, hippocampus, and cGM. Due to the non-normal distribution of infarct number, this variable was categorized into <5 and ≥ 5 according to the median number of infarcts in our sample. To find the contribution of frontal atrophy to cognitive performance, we constructed similar regression models for each cognitive measure with cGM substituted by one of the frontal subregions in each separate models. All continuous variables used in the regression models were shown to be normally distributed using the Kolmogorov-Smirnov test. Linearity of residuals between independent and dependent variables were further visually checked in residual plots.

7.3.2 Relation between WMC and brain atrophy

To explore the relationship between WMC and cognitively-relevant brain regions derived from the above analyses, we performed separate linear regression models for each relevant brain regions using total WMC volume as the independent variable with age and sex adjusted in the models.

7.4 Results

One hundred patients were recruited into the study. The mean duration between MRI and cognitive assessment was 73.6±42.8 days. Table 7-1 shows the demographic, clinical, and neuroimaging features of the study subjects.

Table 7-1 Baseline characteristics of the subjects (N=100)

Basic demographic and clinical features	
Age (years)	75.17 ± 7.60
Male	52
Years of education*	3.0 ± 6.0
Education >6 years	25
Stroke subtypes	
SAO / LAA / CE / U	60 / 34 / 1 / 5
MDRS I/P (range)	25.17 ± 6.65 (3-37)
MMSE (range)	21.61 ± 5.40 (10-30)
CDR 0/0.5/≥1	22 / 70 / 8
Hypertension	89
DM	34
Hyperlipidemia	62
Current smoker	51
Current alcohol drinker	12
Atrial fibrillation	3
Ischemic heart disease	14
Neuroimaging measures	
Infarct number ≥5	36
Microbleed number*	1.0 ± 10.0
Microbleed presence	62
Volumetric measures in cm^3	
Total WMC	39.2 ± 17.9
cGM	431.2 ± 55.5
Bilateral lateral ventricles	55.4 ± 19.1
Bilateral hippocampus	5.5 ± 0.9
Superior frontal gyrus	
Left	6.6 ± 1.8
Right	6.8 ± 1.9
Middle frontal gyrus	
Left	13.7 ± 3.0
Right	12.7 ± 2.5
Inferior frontal gyrus	
Left	9.9 ± 1.8
Right	7.4 ± 1.5
Medial frontal gyrus	
Left	9.3 ± 1.8
Right	10.5 ± 1.7
Medial frontal orbital gyrus	
Left	1.4 ± 0.4
Right	1.8 ±0.4
Lateral frontal orbital gyrus	
Left	8.3 ± 1.5
Right	8.6 ± 1.4

Continuous data are shown in mean ± SD or median ± interquartile range*

7.4.1 Predictors for cognitive performances

Exploratory bivariate correlation analyses identified that age, education, ≥5 infarcts, and volumes of total WMC, cGM, hippocampus, lateral ventricles, superior frontal gyrus (left and right), middle frontal gyrus (left and right), right inferior frontal gyrus, right medial frontal gyrus, medial frontal orbital gyrus (left and right) and lateral fronto-orbital gyrus (left and right) significantly correlated with performance on the MDRS I/P. Performance on the MMSE was significantly correlated with age, education, volumes of total WMC, cGM, hippocampus, lateral ventricles, superior frontal gyrus (left and right), middle frontal gyrus (left and right), medial frontal gyrus (left and right), medial fronto-orbital gyrus (left and right), and left lateral fronto-orbital gyrus.

Multivariate models with age, education, ≥5 infarcts, and volumes of total WMC, hippocampus, lateral ventricles and cGM entered as independent variables showed that only cGM volume independently accounted for performance on both the MDRS I/P (β=0.241, p=0.045) and MMSE (β=0.243, p=0.032). Separate models substituting cGM with the frontal subregions revealed that volumes of both left (β=0.424, p<0.001) and right (β=0.219, p=0.045) lateral frontal orbital gyri had independent influence on the performance on MDRS I/P whereas education (β=0.385, p<0.001) and left lateral frontal orbital gyrus (β=0.222, p=0.037) predicted MMSE performance. Details of multivariate regression models are presented in tables 7-2 and 7-3, respectively.

Table 7-2 Multivariate linear regression models for MDRS I/P performance

	Model 1						*Model 2*						*Model 3*					
	Std β	*Unstd β*	95% CI			*p*	*Std β*	*Unstd β*	95% CI			*p*	*Std β*	*Unstd β*	95% CI			*p*
Age	-0.128	-0.113	-0.288	to	0.062	0.201	-0.114	-0.101	-0.262	to	0.060	0.217	-0.144	-0.127	-0.300	to	0.045	0.145
Education >6 years	0.139	2.164	-0.825	to	5.152	0.154	0.132	2.062	-0.727	to	4.851	0.145	0.175	2.727	-0.248	to	5.702	0.072
≥5 infarcts	-0.107	-1.508	-4.209	to	1.193	0.270	-0.150	-2.105	-4.559	to	0.350	0.092	-0.162	-2.286	-4.907	to	0.336	0.087
WMC volume ratio	-0.119	-63.748	-175.323	to	47.827	0.259	-0.032	-17.094	-123.701	to	89.514	0.751	-0.107	-57.482	-171.341	to	56.377	0.318
Bilateral ventricular volume ratio	-0.172	-94.809	-211.090	to	21.472	0.109	-0.064	-34.976	-147.783	to	77.831	0.539	-0.175	-96.372	-212.647	to	19.902	0.103
Bilateral hippocampus ratio	0.076	803.581	-1593.116	to	3200.278	0.507	0.127	1340.447	-771.120	to	3452.013	0.210	0.107	1132.233	-1172.107	to	3436.574	0.331
cGM volume ratio	0.241	51.214	1.060	to	101.369	0.045												
Left lateral frontal orbital gyrus ratio							0.424	2827.861	1434.862	to	4220.861	<0.001						
Right lateral frontal orbital gyrus ratio													0.219	1537.584	37.074	to	3038.094	0.045

Std ß = Standardized ß; Unstd ß = Unstandardized ß

CI = confidence interval for unstandardized ß

All volumetric measures are presented as ICV-corrected ratios

Model 1 includes cGM while excluding frontal subregions

Model 2 includes left lateral frontal orbital gyrus while excluding cGM and right lateral frontal orbital gyrus

Model 3 includes right lateral frontal orbital gyrus while excluding cGM and left lateral frontal orbital gyrus

Table 7-3 Multivariate linear regression models for MMSE performance

	Model 1						*Model 2*					
	Std β	*Unstd β*	*95% CI*			*p*	*Std β*	*Unstd β*	*95% CI*			*p*
Age	-0.128	-0.091	-0.225	to	0.043	0.181	-0.144	-0.103	-0.235	to	0.029	0.125
Education >6 years	0.374	4.708	2.466	to	6.950	<0.001	0.385	4.847	2.609	to	7.086	<0.001
≥5 infarcts	0.054	0.604	-1.432	to	2.640	0.557	0.009	0.103	-1.878	to	2.085	0.918
WMC volume ratio	-0.129	-55.701	-140.126	to	28.724	0.193	-0.125	-54.026	-139.458	to	31.405	0.212
Bilateral ventricular volume ratio	-0.117	-51.531	-138.923	to	35.861	0.244	-0.059	-26.042	-116.891	to	64.806	0.570
Bilateral hippocampus ratio	0.019	161.346	-1654.610	to	1977.302	0.860	0.088	748.606	-955.257	to	2452.468	0.385
cGM volume ratio	0.243	41.943	3.594	to	80.291	0.032						
Left lateral frontal orbital gyrus ratio							0.222	1196.534	71.161	to	2321.907	0.037

Std ß = Standardized ß; Unstd ß = Unstandardized ß

CI = confidence interval for unstandardized ß

All volumetric measures are presented as ICV-corrected ratios

Model 1 includes cGM while excluding frontal subregions

Model 2 includes left lateral frontal orbital gyrus while excluding cGM and right lateral frontal orbital gyrus

7.4.2 Relation between WMC and brain atrophy

Total WMC volume was significantly associated with volumes of cGM (β=-0.433, p<0.001) and left (β=-0.405, p<0.001) and right (β=-0.439, p<0.001) lateral orbital frontal gyri after adjusting for age and sex.

7.4.3 Amyloid imaging

Among the 7 cognitive impaired stroke patients with PIB imaging, none had AD-like PIB binding. Only 1 patient (male aged 82 years, MMSE=25, CDR 0.5, global PIB retention 1.42) had slight PIB retention observed predominantly at the left occipital lobe, which might reflect cerebral amyloid angiopathy (figure 7-1). This patient had no history of hemorrhagic stroke. In contrast, AD-like PIB binding was found in all clinical AD patients and also in 1 healthy control (57 male, MMSE 30, global PIB retention 1.50). Mean global PIB retention for the 7 stroke patients (1.29, range 1.21-1.42) was lower in the 4 AD patients (1.65, range 1.46-1.88) and was similar to controls (1.35, range 1.25-1. 50). None of these 7 stroke patients were APOE ε4 carriers.

Figure 7-1 PIB binding of (a) an AD patient and (b) the stroke patient with mild PIB retention predominant at left occipital region (red arrow). Red color indicates the greatest PIB binding and the same color scale was used for both images.

7.5 Discussion

The present study investigated the cognitive predictors in stroke patients with confluent WMC. The mean WMC volume of our subjects (39.15 cm^3) is 7 times greater than that of our previous cohort (5.5 cm^3) with lacunar stroke. (Mok et al., 2005) Based on a larger cohort, we substantiated our previous observation that in patients with confluent WMC, executive function and general cognition are directly related to the lateral fronto-orbital gyrus and total cGM atrophy. (Mok et al., 2008) The finding that cGM atrophy and low education were associated with cognitive impairment is consistent with results of other studies in subcortical ischemic vascular disease. (Constans et al., 1995; Mungas et al., 2001; Dufouil et al., 2003; Mok et al., 2005) Moreover, we showed that there are significant associations between volumes of WMC and frontal subregions relevant to cognitive performance. Our results support the hypothesis that WMC are related to frontal atrophy, which accounts for poor performance in executive functions, and to a lesser extent, general cognitive functions.

The association between frontal lobe lesion and executive function has long been recognized.(Roman et al., 1993) Recent studies among healthy adults also showed that dorsolateral cortical atrophy was associated with executive dysfunction. (Gunning-Dixon and Raz, 2000; Zimmerman et al., 2006) In our study, volume of lateral fronto-orbital gyrus significantly predicted executive performance, and the effect is stronger in left than right, as shown in the respective ß coefficients. Lateral fronto-orbital gyrus lies inferior to the inferior frontal gyrus and at the inferior posterior region of the dorsolateral cortex. Such robust association between this specific region and executive performance may possibly be explained by the

executive measure that we used. In MDRS I/P, semantic verbal fluency test accounts slightly more than half (54%) of the total score, and the remaining battery evaluates programming and perseveration. Functional imaging study showed that left inferior frontal gyrus is particularly activated during verbal fluency task (Alzheimer, 1902) and lesion at dorsolateral cortex is responsible for errors in programming and perseveration. Hence, performance in MDRS I/P may be more related to left lateral fronto-orbital gyrus. Because different frontal subregions subserve specific executive subdomains, other ways of analyzing the prefrontal subregions (e.g. right superior medial region) and usage of other executive measures (e.g. reaction time based on Stroop test) may yield different findings. (Alexander et al., 2007) In comparison, the contribution of lateral frontal orbital gyrus to MMSE is less strong relative to MDRS I/P. This observation is consistent with previous arguments that performance on MMSE relies less heavily on frontal functions. (Royall et al., 2002)

We found that both global cGM and lateral frontal volumes were associated with WMC severity. Findings of the PIB imaging suggest a predominantly vascular basis for atrophy in these areas, as Alzheimer's pathology was uncommon. However, caution must be exercised when interpreting the implication of this finding as PIB data was available on a subset of only 7 patients, which is by no means representative of the whole study sample. Previous studies have shown that WMC were related to brain atrophy. (Constans et al., 1995; Geroldi et al., 2006; Wen et al., 2006; Chen et al., 2009) There are several mechanisms by which WMC causes cortical atrophy. Deinnervation associated with loss of white matter connections may result in secondary changes in the cortex. (Constans et al., 1995; Schmidt et al., 2005) Alternatively, cortical hypoperfusion or microinfarcts, that are not detected by current

neuroimaging, (Constans et al., 1995; Schmidt et al., 2005) but are associated with WMC, can also induce cortical atrophy. On the other hand, cortical neuronal loss may lead to downstream axonal loss and demylination, resulting in WMC. (Wen et al., 2006) Because of the cross-sectional nature of the study, the direction as well as the causal relationship between these two morphological brain changes could not be determined.

More importantly, we showed that the associations between WMC and cognition were lost when cGM and frontal volumes were added into the models. These findings suggested that cognitive impairment associated with confluent WMC was mediated by cGM and frontal atrophy. The mediating role of brain atrophy between WMC and cognitive performances was also found in the Austrian Stroke Prevention Study (ASPS). (Schmidt et al., 2005) In the ASPS, cognitive decline among stroke-free community elderly was related directly to brain atrophy, which in turn was secondary to WMC progression. Note that majority of subjects with WMC progression in the ASPS were those who already had confluent WMC at baseline. (Kapeller et al., 2003)

This study has a number of limitations. First, this is a cross-sectional study. The causal relationships between WMC severity, cortical and frontal atrophy, and cognitive impairment need to be verified in longitudinal studies. Second, all our subjects had stroke, and therefore our results may not be generalized to stroke-free community subjects with confluent WMC. Third, we used only brief cognitive measures. Yet, both are validated measures of cognition that have been used extensively in studies of cognitive impairment in cerebrovascular disease. (Mungas et al., 2003) In future studies, a more extensive battery should be employed for a more comprehensive

survey of cognition, in particular executive functions. Forth, we were only able to perform amyloid imaging in only a small subset of patients. Last, we did not examine microstructural integrity of the white matter fibers using diffusion tensor imaging, which may be potent cognitive predictors in subcortical ischemic vascular disease as well. (Hassan et al., 2004)

In conclusion, our study suggests that cognitive impairment in confluent WMC is directly related to frontal and global cGM atrophy and such atrophy is in turn related to WMC severity. Cognitive impairment in confluent WMC is probably mediated by frontal and global cortical atrophy.

Chapter 8 Predictors for Cognitive Decline in Stroke patients with Confluent White Matter Changes

8.1 Introduction

Age-related WMC are considered manifestation of cerebral SVD. Severity of WMC may vary from small punctate to more diffuse confluent lesions. In stroke patients, prevalence of confluent WMC varies from 9% to 30%. (Fu et al., 2005; Jimenez-Conde et al., 2010)) The PROGRESS (Perindopril Protection Against Recurrent Stroke Study) MRI-substudy showed that dementia-free stroke subjects harboring confluent WMC at baseline have 8 times higher risk for significant cognitive decline relative to those without WMC over 4 years. (Dufouil et al., 2009) It has been proposed that preventive trials in VCI should focus on those who already have confluent WMC at baseline. (Schmidt et al., 2004)

Although patients with confluent WMC are at high risk for cognitive decline, the risk varies among individuals. Some may have relatively stable cognition over long period of time despite having severe WMC. (Fein et al., 1990) In the present study, we investigated the association between baseline factors, imaging measures, incident stroke, and B vitamins with cognitive decline among stroke patients with confluent WMC. Since concurrent Alzheimer's pathology may hasten cognitive decline poststroke, (Mok et al.) We also investigated *in-vivo* whether significant cognitive decline in confluent WMC is related to concurrent amyloid plaques using PiB imaging. To date, stroke management mainly focuses in reducing recurrent stroke events and mortality. Data guiding strategies in preventing cognitive decline poststroke are limited. Understanding predictors for cognitive decline will be

important for devising preventive strategies in this group of stroke patients who are at high risk for cognitive decline.

8.2 Methods

Subjects were participants of the VITATOPS study, which is a multi-center, randomized, double-blind, placebo-controlled trial evaluating the effects of homocysteine lowering treatment using B vitamins (2mg folic acid, 25mg vitamin B6, and 0.5mg vitamin B12) on secondary stroke prevention (NCT00097669). (VITATOPS Trail Study Group, 2002) In our center, we particularly recruited ischemic stroke patients with confluent WMC on MRI. We defined confluent WMC by a score of $\geq$2 based on the ARWMC scale in at least 1 brain region. (Wahlund et al., 2001) We excluded hemorrhagic stroke patients, those with severe cognitive and/or physical impairment preventing cognitive assessment, and those with other known concurrent diseases that may affect cognition (e.g. alcoholism). All subjects were recruited from the acute stroke unit of a teaching hospital. Brain MRI was performed within 1 week of hospitalization. We classified stroke subtypes into large-artery atherosclerosis (LAA), cardioembolism (CE), small-artery occlusion (SAO), stroke of other determined cause and stroke of undetermined cause (U). (Adams et al., 1993) An experienced neurologist (V.M.) performed MRI screening and subject recruitment. We also collected blood for APOE genotyping, which was done by polymerase chain reaction-restriction fragment length polymorphism. Recruitment began at October 2004 and completed in November 2006. A total of 100 patients were recruited and 52 subjects were randomized to the active group. There was no significant difference between the active and placebo group in all the baseline basic demographic, clinical, imaging, and cognitive features. Sixteen patients discontinued from the study because

of reaching study endpoints of deaths (n=5) or incident non-fatal stroke (n=11). Eighty-four patients completed the 2 years follow-up. Among the 5 deaths, 1 was due to another fatal stroke. No patient was lost to follow-up. Completers were more likely to be female (52.3% for completers versus 21.4% for non-completers) and non-smokers (54.7% versus 14.3%) compared with the non-completers ($p<0.05$). The 2 groups did not differ significantly in age, education, profile of other vascular risk factors, and imaging measures. For patients who discontinued, we used their last recorded cognitive data. For the 11 subjects who discontinued due to non-fatal incident stroke, we performed cognitive assessment within 3 months of the recurrent stroke events.

8.2.1 Cognitive assessment

An experienced psychologist (A.W.) administered the CDR (Morris, 1993) at around 3 months (baseline), 6 months, 12 months, 18 months, and 24 months post-stroke. We also assessed changes in general cognition and executive function using the Chinese MMSE (Chiu HFK, 1994) and the MDRS I/P (Chan et al., 2001) respectively at baseline, 12 months, 18 months, and 24 months. We arbitrary defined dementia as a CDR grade of ≥ 1.

8.2.2 MRI imaging variables

All MRI examinations were performed on a 1.5-tesla scanner (Sonata, Siemens Medical System, Erlangen, Germany) with a standard protocol including T1-weighted imaging (TR/TE=425/14 ms), T2-weighted imaging (TR/TE=2500/120 ms), FLAIR (TR/TE=8000/100 ms), gradient recall echo T2*-weighted MRI (TR/TE =350/30 ms), all with 5 mm slice thickness, 0.5 mm slice gap, FOV=230 mm, matrix size=256 x

256, and time-of-flight MR angiography.

Volume of WMC was quantified using a semi-automated "seeding method" with Easy Vision 4.3 software on FLAIR sequence. Infarct volume was also quantified using the same method on T1 weighted images. Volume and number of all infarcts and infarcts in the basal ganglia and thalamus were recorded. In addition, we recorded the total number of microbleeds, which was defined as dot-like hypointensity on gradient recall-echo T2*-weighted MRI. Two trained neurologists (Y.X. and Y.C.) who were blinded to patients' cognitive data rated all MRI measures.

Brain volumes were quantified using a validated automated hybrid warping method. (Shen and Davatzikos, 2003) In brief, a feature-based volumetric registration algorithm HAMMER was first used to warp a model cortical surface to the individual space. (Shen and Davatzikos, 2003) Following, a surface registration algorithm based on the matching of geometric attribute vectors was used to further warp the model surface to the subject. After the high-dimensional hybrid registration and atlas-based warping, the subject brain image was segmented into various neuroanatomic regions by mapping the anatomic labels in the atlas to the subject. We obtained volumes of bilateral hippocampi, lateral ventricles, and total cGM. All volumetric data were normalized to intracranial volume as corrected-ratios for statistical analyses.

8.2.3 Amyloid imaging

We performed PiB imaging among 10 (53%) of the 19 participants who developed dementia during the study period. The reasons for not having PiB imaging for the other 9 dementia converters were infeasibility because of severe dementia (n=6) and

personal refusal (n=3). These 9 subjects were older and had more severe cognitive impairment (mean 79 years, mean MMSE 14) than those who had the PiB imaging (mean age 73 years, mean MMSE 18, $p<0.001$ for both variables). All the 10 participants with PiB imaging received a dose of 15 mCi ^{11}C-PIB intravenously after fasting (6 hours) and the brain was imaged at 5, 35, and 60 min after injection with 10 min emission acquisition at each time point using an integrated in-line PET/CT scanner (Biograph^{TM} 16 LSO HI-REZ; CTI/Siemens Inc.). Methods of the PIB imaging were described previously. (Mok et al.) Patients with increased PIB binding observed visually in frontal gyrus, posterior cingulate gyrus, precuneus, superior parietal lobule, and lateral temporal lobe were considered as having concurrent AD. (Mok et al.) We used the global standardized uptake value (SUV) PIB retention value from 35-45min for the evaluation. The same experienced nuclear medicine specialist (E.Y.L.L.) assessed all images without knowledge of patients' clinical data. The institutional ethics committee approved the main study and the amyloid imaging substudy. All subjects provided written informed consent.

8.2.4 Statistical Analyses

We used Pearson or Spearman rank bivariate correlation to first explore the association between cognitive changes (i.e. decliners versus non-decliners based on CDR and changes in MMSE and MDRS I/P scores) and the following variables: demographic data (age, gender, and years of education), baseline clinical data (hypertension, hyperlipidemia, diabetes mellitus, current smoker, current alcohol drinker, ischemic heart disease, atrial fibrillation, use of anti-hypertensive agents, anti-platelet agents, and statins, VITATOPS active treatment, APOE ε4 carrier, and baseline levels of systolic / diastolic BP, homocysteine, total cholesterol [TC], LDL,

HDL, and triglyceride (TG)), total WMC volume, infarct measures (volumes and number of total infarct, basal ganglia, and thalamic infarct), number of microbleeds, volumes of cGM, bilateral hippocampi, and lateral ventricles. Incident stroke during the study period was also recorded. Hyperlipidemia was defined as use of medications (e.g. statins) to control cholesterol pre-stroke, a fasting LDL level of > 2.6 mmol/L post-stroke, or both.

Binomial logistic regression was used to examine predictors for CDR changes whereas linear regression was used for changes in MMSE and MDRS I/P scores. Putative independent variables were first examined in a series of exploratory univariate models, and those with $p<0.10$ in the univariate models were further entered into stepwise multivariate regression models. We also entered baseline cognitive functions (i.e. CDR grade, MMSE, and MDRS I/P score) into the multivariate regression models as baseline cognitive impairment was consistent predictors for poststroke cognitive decline base on other studies.(Srikanth et al., 2006; Narasimhalu et al., 2009) For data that were not normally distributed, we performed square root transformation before entering into the regression models. We categorized cGM volume into quartiles.

8.3 Results

Table 8-1 shows the baseline characteristics of the subjects. More than half of the subjects (60%) had stroke due to SAO. Majority of subjects (92%) were not demented at baseline. All subjects had completed at least 1 cognitive assessment after randomization.

Thirty-three subjects (33%) had an increase in CDR grade. Among these 33 subjects, only 4 (12%) had acute stepwise cognitive decline after the incident stroke. The majority (n=29, 88%) of subjects with increase in CDR grade had progressive decline. Among the 92 subjects who were not demented at baseline, 19 (21%) developed dementia. The dementia incidence was 10.3 per 100 person-years (95%CI 6.5 to 15.18).

Table 8-1 Baseline characteristics of the 100 subjects

Basic demographic and clinical features		
Age (years)		75.17 ± 7.60
Male		52
Years of education*		3.0 ± 6.0
Education >6 years		25
Stroke subtypes		
SAO / LAA / CE / U		60 / 34 / 1 / 5
MMSE (range)		21.61 ± 5.40 (10-30)
CDR 0/0.5/≥1		22 / 70 / 8
Hypertension		89
DM		34
Hyperlipidemia		62
Current smoker		51
Current alcohol drinker		12
Atrial fibrillation		3
Ischemic heart disease		14
VITATOPS active treatment		52
Neuroimaging measures		
Microbleed number*		1.0 ± 10.0
Microbleed presence		62
Volumetric measures in cm^3		
Total infarct*		188.265 (73.7-349.79)
Basal ganglia infarct *		
	Left	36.31 (0-85.17)
	Right	0 (0-80.80)
Total WMC		39.2 ± 17.9
cGM		431.2 ± 55.5
Bilateral lateral ventricles		55.4 ± 19.1
Bilateral hippocampi		5.5 ± 0.9
Intracranial size		1369.81±104.93

Continuous data are shown in mean ± SD or median ± interquartile range*

8.3.1 Predictors of Cognitive Decline

Variables associated with increase in CDR grade in the univariate analyses were high age, low diastolic BP, absence of hyperlipidemia, no statins use post-stroke, small cGM volume, and small bilateral hippocampal volume. Because hyperlipidemia at baseline was highly related to statins use post-stroke, these 2 variables were separately entered into multivariate regression models (table 8-2). Taking as a whole, the regression models showed that cGM volume, diastolic BP, and absence of hyperlipidemia or no statins use were significant predictors for increase in CDR grade (table 8-2).

Table 8-2 Predictors for increase in CDR grade

*a. Univariate Analysis**	Decliners (n=33)	Non-decliners (n=67)	*p*
Diastolic BP, mmHg	80.5	85.7	0.026
Hyperlipidemia	15 (45%)	47 (70%)	0.017
Statins use post-stroke	16 (48%)	49 (73%)	0.015
cGM volume ratio quartiles**			0.004
1st	13 (40.6%)	11 (16.9%)	
2nd	9 (28.1%)	16 (24.6%)	
3rd	6 (18.8%)	18 (27.7%)	
4th	4 (12.5%)	20 (30.8%)	
Hippocampal volume ratio	0.0038	0.0042	0.061

b. Multivariate analysis			
Model A	OR	CI	*p*
cGM volume ratio quartiles	0.605	0.382-0.957	0.032
Diastolic BP	0.937	0.89-0.985	0.011
Hyperlipidemia	0.281	0.099-0.801	0.018
Model B			
cGM volume ratio quartiles	0.583	0.371-0.915	0.021
Statins use post-stroke	0.325	0.117-0.900	0.031
Diastolic BP	0.944	0.898-0.991	0.021

Model A: hyperlipidemia was entered into the regression analysis; model B: statins use post-stroke was entered into the regression analysis; *only variables associated with cognitive decline at $p<0.1$ level in the univariate analyses were shown in the table; ** 3 missing data due to poor MRI quality

Multivariate regression analyses showed that small cGM volume, absence of hyperlipidemia, small bilateral hippocampal volume, and low baseline MMSE score were independent predictors for greater decline in MMSE score; whereas small cGM volume, absence of hyperlipidemia, low TC level, old age, and low baseline MDRS I/P score were independent predictors for greater decline in MDRS I/P score (table 8-3). Statins use was not associated with changes in MMSE and MDRSI I/P scores.

Table 8-3 Multivariate analysis for predictors for change in MMSE and MDRS I/P scores

a. MMSE	ß	*p*
Hyperlipidemia	0.239	0.018
cGM volume ratio quartiles	0.253	0.026
Hippocampal volume ratio	0.227	0.037
MMSE baseline	-0.319	0.003
b. MDRS I/P		
Age	-0.189	0.045
Hyperlipidemia	0.308	0.001
TC	0.237	0.010
cGM volume ratio quartiles	0.363	0.001
MDRS I/P baseline	-0.395	<0.001

There was no significant difference in the proportion of subjects having incident stroke among the CDR decliners (n=5, 15%) and the non-decliners (n=6, 9%; p=0.5). VITATOPS active treatment was not associated with changes in any of the cognitive measures based on univariate analysis. Proportion of subjects taking active treatment was similar between those who had increase in CDR grade (57.6%) and those without (49.3%, p=0.43). Total WMC volume was negatively associated with cGM volume (β=-0.433, p<0.001) after adjusting for age and sex.

8.3.2 PiB imaging among dementia converters

Among the 10 dementia converters who had PIB imaging, only 1 had PIB binding suggestive of AD. The mean global SUV PIB retention for the 9 converters without PiB binding was 1.3 (range 1.23-1.48) while that for the patient with PiB binding was 1.60.

8.4 Discussion

The observed incidence of dementia (10.3 per 100 person-years) in our cohort is similar to the incidence of significant cognitive decline (9.1 per 100 person-years) among those with severe WMC in the PROGRESS MRI substudy.(Dufouil et al., 2009) In the PROGRESS MRI substudy, risk of significant cognitive decline in subjects with severe WMC was 8 times higher in those without WMC. (Dufouil et al., 2009) Our observed rate of cognitive decline is at most conservative as we had probably recruited more stable subjects into this study as all subjects were participants of a clinical trial. Noteworthy is that all our subjects were already receiving standard treatments for secondary stroke prevention. Hence, our findings highlight the need to explore additional strategies for preventing cognitive decline in this particular group

of stroke patients.

We found that the most consistent baseline factors predicting deterioration in all cognitive outcomes were small cGM volume and absence of hyperlipidemia. The association between baseline cGM atrophy and subsequent cognitive decline concurs with another study among subjects with subcortical ischemic disease. (Mungas et al., 2002) As in other studies, (Mungas et al., 2002; Wen et al., 2006) we found that cGM volume significantly correlated with WMC volume (β=-0.433, p<0.001). The Austrian Stroke Prevention Study shows that WMC probably mediates cognitive decline through increasing brain atrophy. (Schmidt et al., 2005) We thus hypothesize that those who already have greater cGM atrophy at baseline are more likely to have progressive cGM atrophy and cognitive decline because of having more severe SVD. Overall, our findings support that strategies for preventing development or progression of WMC are probably important in retarding cognitive decline. (Schmidt et al., 2004; van Dijk et al., 2008) Since other factors, e.g. APOE polymorphism, (Wishart et al., 2006) BP level, (Gianaros et al., 2006) may also affect cGM volume, further study is needed to investigate other predictors for cGM atrophy in stroke patients with confluent WMC.

We had no *a priori* hypothesis as to the baseline predictors for cognitive decline. Our finding that hyperlipidemia was associated with better cognitive outcomes is unexpected given that hyperlipidemia increases risk for stroke and cholesterol lowering prevents stroke recurrence. (Amarenco et al., 2006) Explanations for our finding are probably complex. Studies have shown that high cholesterol is associated with less severe WMC, (Schmidt et al., 1996; Jimenez-Conde et al., 2010) less

SVD-related intracerebral hemorrhage, (Woo et al., 2004) and even higher survival after ischemic or hemorrhagic stroke. (Dyker et al., 1997) Laboratory studies have also supported a neuroprotective role of cholesterols. (Joseph et al., 1997) Therefore, high cholesterol in our subjects may be associated with less severe SVD and/or more protection against the ischemic injury secondary to SVD. Another possible explanation is that patients with hyperlipidemia are more likely to receive statins treatment, which actually confers this protective effect. Consistent with this postulation is that statins use also independently predicted less CDR increase in the present study. However, the association between statins use and cognitive outcomes was less robust relative to hyperlipidemia because statins use did not predict changes in MMSE or MDRS I/P performance. We also noted that high baseline TC level was associated with less deterioration in MDRS I/P score. However, because we were unable to differentiate the separate effects of hyperlipidemia and statins use upon cognitive decline in this study, another study specifically designed for this purpose is needed to clarify this issue.

We found that lower baseline diastolic BP had mild but significant association with increase in CDR grade. The Rotterdam Scan Study shows that BP is associated with WMC progression only in those with no or mild WMC; whereas, in older elderly with severe WMC at baseline, high BP is not a risk factor for WMC progression anymore. (van Dijk et al., 2008) Furthermore, rigorous BP lowering may even worsen cognition as it may reduce cerebral perfusion in the presence of impaired cerebral autoregulation, which may be prevalent in the elderly and in those with diffuse SVD. (De Reuck et al., 1999; Verghese et al., 2003; van Dijk et al., 2008) The relevance of diastolic BP to cognitive decline is also consistent with that of the Bronx Aging Study.

(Verghese et al., 2003) Yet, the direction of the association between low BP and cognitive decline may also be reversed, in that the pathology for cognitive decline in our cohort may somehow cause low BP. Further study is needed to investigate the influence of BP levels and rate of cognitive decline in stroke subjects with confluent WMC.

Although rapid cognitive decline in stroke patient had commonly been attributed to concurrent AD, (Mok et al., 2010) we observed only 1 (10%) out of the 10 dementia converters who underwent PiB imaging had AD-like PiB retention. However, we were unable to perform PiB imaging among the other 9 dementia converters. Since these other subjects were older and were more demented than those who had PiB imaging, it is possible that these subjects might still have harbored concurrent Alzheimer's pathology. Overall, our study has demonstrated *in-vivo* that rapid and progressive cognitive decline in patients with confluent WMC can be explained by pure "vascular" mechanisms.

We did not find an association between WMC and cognitive decline, it may be due to lack of statistical power and baseline WMC volume may be less sensitive to cognitive decline compared with WMC progression. Further studies are in need to explore the relationship between WMC progression and cognitive decline.

Previous studies showed that hyperhomocysteinemia is associated with WMC severity (Vermeer et al., 2002; Wong et al., 2006) and subgroup analysis of the VITATOPS study suggests that B vitamins may have preferential benefits upon SVD. (Fazekas et al., 2002) In the present study, we could not observe any favorable trends of B

vitamins in retarding cognitive decline. Although our study was not designed nor powered to study the cognitive effects of B vitamins in stroke patients with confluent WMC, our findings suggest that cognitive benefits of B vitamins, if any, may not be apparent with 2 years of treatment.

The strengths of this study are that we had investigated multiple putative variables (e.g. various atrophy and ischemic measures, microbleeds). We had used quantitative methods for volumetric measures and PiB imaging for detecting concurrent amyloid plaques. Our sample size of stroke subjects with severe WMC is also relatively large. A limitation of the study is that our subjects were participants of a clinical trial. As mentioned earlier, this selection bias of more stable subjects for clinical trials might underestimate the rate of cognitive decline. Another limitation is that we did not examine microstructural integrity of the white matter fibers using diffusion tensor imaging, which may be a potent cognitive predictor in stroke patients with confluent WMC. (Nitkunan et al., 2008) Last, as mentioned earlier, we might underestimate the influence of Alzheimer's pathology among the dementia converters as we could not perform PiB imaging among almost half of the dementia converters.

In conclusion, baseline cortical atrophy, absence of hyperlipidemia, and low diastolic BP are associated with cognitive decline. Our findings raise concerns that aggressive cholesterol or BP lowering may have negative cognitive impact upon stroke patients harboring confluent WMC. Further studies are warranted to confirm our findings among other stroke cohort and to investigate the influence of cholesterol and BP levels upon cognitive decline in this high risk group.

PART III CONCLUSIONS

Chapter 9 Summary of the present studies

The studies in the present thesis addressed four major issues in WMC and VCI: WMC detection, cognitive impact of WMC, evaluation of WMC severity and mechanisms for cognitive impairment in WMC.

I Detection of WMC

Study 1: Evaluation of Age-Related White Matter Changes using Transcranial Doppler Ultrasonography

In this study, we explored whether TCD PI can reflect the severity of WMC. We identified that PI values had significant independent correlation with volume of WMC. We observed that that not only mean MCA PI, but also mean VB PI was higher in patients with WMC than those without WMC. The AUC of MCA PI for detection of WMC was good (0.85) and at an optimal cut-off of 1.15, a good sensitivity (73.70%) and specificity (82.00%) could be obtained. This study confirmed that PI was associated with WMC volume. Further study evaluating the clinical utility of TCD in screening for subclinical WMC among community elderly is warranted. Availability of a simple screening tool that can guide selective MRI scanning will promote early detection and management of WMC and also cost effective recruitment into clinical trials for subclinical WMC.

II Cognitive impact of WMC

Study 2 Frequency and Predictors of Proxy-Confirmed Post-Stroke Cognitive Complaints in Lacunar Stroke Patients without Major Depression

The study showed that the post-stroke cognitive complaints were frequent (42.7%) in lacunar stroke patients without major depression. The complaints were prominently related to subclinical depressive symptomatology. However, we failed to detect any relationship between post-stroke cognitive complaints and WMC volume. Depressive symptoms, in turns appeared to be associated with the severity of stroke. Clinicians should pay special attention to evaluate subclinical depressive symptoms in these patients, even if the cognitive complaints are corroborated by a proxy.

III Evaluation of WMC severity

Study 3 The Age-Related White Matter Changes Scale Correlates with Cognitive Impairment

The present study investigated the validation of ARWMC scale against cognition. We showed that WMC volume was strongest correlated with cognitive impairment which was assessed by MDRS I/P and MMSE, then followed by the total score and global score of ARWMC scale. The total and global ARWMC score were also significantly associated with WMC volume. Findings of our study lend support to the recommendation of the VCI harmonization standards in using ARWMC scale for rating WMC severity.

Study 4 Operational Definitions Improve Reliability of the Age-Related White

Matter Changes Scale

In this study, we developed operational definitions for the ARWMC scale including defining caps and bands, and the diameter of the lesions. We found that the operationalized ARWMC scale had significantly higher interrater reliability on CT than the original ARWMC scale. The rating time, interrater and intrarater reliabilities, and correlation with quantitative WMC volume on MRI were comparable between the operationalized and original scales. The operationalized ARWMC scale may be particularly useful in developing countries where dementia burden is expected to escalate and where only CT is accessible.

IV. Mechanisms for cognitive impairment in WMC

Study 5 Cortical and Frontal Atrophy are Associated with Cognitive Impairment in Age-Related Confluent White Matter Lesion

This study investigated the cognitive predictors in patients with confluent WMC with no to varying levels of cognitive impairment. The volume of cGM, frontal regions, WMC and ICV of 100 post-stoke patients were obtained. The study suggests that cognitive impairment in confluent WMC is directly related to frontal and global cGM atrophy and such atrophy is in turn related to WMC severity. Cognitive impairment in confluent WMC is probably mediated by frontal and global cortical atrophy.

Study 6 Predictors for Cognitive Decline in Stroke patients with Confluent White Matter Changes

This last study explored the predictors for cognitive decline in confluent WMC patients. We followed-up 100 patients with confluent WMC for two years, and 33 (33%) had cognitive decline which defined by increase CDR>1 or incident dementia. Among the 92 subjects who were not demented at baseline, 19 (21%) developed dementia. The dementia incidence was 10.3 per 100 person-years (95%CI 6.5 to 15.18). Baseline cortical atrophy, absence of hyperlipidemia, and low diastolic BP were associated with cognitive decline. Our findings raise concerns that aggressive cholesterol or BP lowering may have negative cognitive impact upon stroke patients harboring confluent WMC. Further studies are warranted to confirm our findings among other stroke cohort and to investigate the influence of cholesterol and BP levels upon cognitive decline in this high risk group.

Chapter 10 Future Research Directions

The present studies laid the foundation of future research on WMC and VCI in stroke patients. We found that TCD PI was associated with WMC in stroke patients. Whether it can be used as a screening test in community needs further investigation among stroke-free community residents.

To investigate the relationship between cognitive impairment and WMC or other brain measures, we had used only brief neuropsychological tests. We proposed that the 60 or 30 minutes battery of the VCI harmonization standard should be used in future research. As to the association between cognitive decline and longitudinal changes of brain measures and WMC, brain atrophy seems to affect cognition more directly than WMC. Hence, since risk factors for brain atrophy (cortical gray matter atrophy, and frontal atrophy) in WMC are not well examined, further investigation is needed in this area.

Regarding the pathophysiology of WMC, the inflammatory factors such as ICAM-1, Hs CRP and IL-6 are associated with WMC volume in cross-sectional studies. To our best knowledge, no study has prospectively investigated this causal relationship. Besides the inflammatory biomarkers, genetic burden in WMC is still controversial. Moreover, among Chinese, studies are very limited in this area. Much larger community study is thus needed to explore genetic risk for WMC, such as APOE, angiotensin converting enzyme, methylenetetrahydrofolate reductase, angiotensinogen genes or other putative genes, in particular, among our Chinese ethnic group.

The treatment of WMC is a challenge. Both hypertension and low blood pressure are risk factors for WMC, studies on the optimal blood pressure are in need to address the blood pressure control in community residents and stroke patients. Our VITATOPS MRI substudy indicated that hyperlipidemia, no statin and higher TC may be protective for cognition in 100 stroke patients with confluent WMC. Yet, considering the small sample size of this study and it is not a randomized design study, hence, whether statins will help or hasten WMC progression needs randomized clinical trails to investigate. Furthermore, since subgroup analysis suggested that memantine may benefit subcortical VaD and this is a well tolerated drug, future clinical trails targeting on memantine for treatment of confluent WMC and/or VCI are warranted.

Previous studies suggested that cerebral blood flow might be increased by enhanced external counterpulsation (EECP) and that outcome of stroke patients with large artery disease can be improved with EECP (Han et al., 2008). Hence EECP may be a potential treatment for WMC and further investigation is warranted.

Since DTI has been shown to be a more sensitive imaging marker than WMC volume in correlating with cognitive outcomes, future longitudinal studies and preventive trials should utilize this technique as a surrogate marker.

To conclude, WMC and cognitive impairment is an important and promising field for research. I do hope that the findings of our present studies will contribute to the ultimate goal of alleviating the burden of WMC and cognitive impairment in the elderly.

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APPENDIX

Common visual rating scales

Scheltens scale

periventricular regions (frontal and occipital caps and bands) :

score 1—a smooth halo, which extends not more than 5 mm

score 2—confluent lesions larger than 5 mm.

subcortical regions (frontal, parietal, occipital and temporal lobes) and 5 basal ganglia regions (caudate nucleus, putamen, globus pallidus, thalamus and internal capsule) and 4 infratentorial regions (cerebellum, mesencephalon, pons and medulla).

score 1—focal lesion< 4 mm,when there are not more than 5 lesions

score 2—focal lesion< 4 mm ,when there are more than 5 lesions

score 3— focal lesion between 4 and 10 mm, when there are not more than 5 lesions

score 4—focal lesion between 4 and 10 mm ,when there are more than 5 lesions

score 5—focal lesion> or =10 mm

score 6—confluent lesions

Modified Fazekas scale

Priventricular white matter changes

0=absence

1=caps or pencil-thin lining

2=smooth halo

3=irregular PVC extending into the deep white matter

Deep white matter changes

0=absence

mild=punctate lesions: a maximum diameter of a single lesion of 9 mm and of grouped lesions of 20 mm

moderate=early confluent lesions: single lesions between 10–20 mm, grouped lesions more than 20 mm in any diameter and no more than connecting bridges between individual lesions

severe= single lesions or confluent areas of hyperintensity of 20 mm or more in any diameter

Rotterdam Scan Study Scale

DWMC: small (<3 mm), medium (3–10 mm), or large lesions (>10 mm).

PVWMC were rated semiquantitatively per region: adjacent to frontal horn (frontal capping), adjacent to lateral wall of lateral ventricles (bands), and adjacent to occipital horn (occipital capping) on a scale of 0 (no white matter lesions), 1 (pencil thin periventricular lining), 2 (smooth halo or thick lining), or 3 (large confluent white matter lesions). This was done for both hemispheres simultaneously. The overall degree of PWMC was calculated by adding up the scores for the three separate categories (range 0–9).

The ARWMC scale

Frontal, temporal, parietal-occipital, infratentorial regions

0 No lesions (including symmetrical, well-defined caps or bands)

1 Focal lesions

2 Beginning confluence of lesions

3 Diffuse involvement of the entire region, with or without involvement of U fibers

Basal ganglia lesions

0 No lesions

1 1 focal lesion (> or =5 mm)

2 .1 focal lesion

3 Confluent lesions

Chinese Mattis Dementia Rating Scale Initiation / Perseveration Subset

1. 請你講俾我聽係超級市場可以買到o既野，儘量講，講得越多越好，直至我叫你停爲止・・・開始・・・(時限 60 秒，每個正確答案可得一分)

1. _____ 11. _____
2. _____ 12. _____
3. _____ 13. _____
4. _____ 14. _____
5. _____ 15. _____
6. _____ 16. _____
7. _____ 17. _____
8. _____ 18. _____
9. _____ 19. _____
10. _____ 20. _____

分數 (0-20) _____
(如果>13, 前往問題 5, 問題 1-4 則給滿分)

2. 請你講俾我聽所有關於衣服o既名稱，你可以用我同你身上o既衣服作爲參考 (時限 60 秒，每個正確答案可得一分)

1. _____ 2. _____
3. _____ 4. _____
5. _____ 6. _____
7. _____ 8. _____

分數 (0-8) _____

3. 請跟我講" bee" … 跟我講" key" … 跟我講" gee" …
依家請講 4 次" bee - key - gee"
" bee - key - gee" 4 次 (1 分) 分數 (0-1) _____

4. 請跟我講" bee" … 跟我講" bah" … 跟我講" boh" …
依家請講 4 次" bee - bah - boh" 分數 (0-1) _____

5. 依家我想你用手做一D 動作，睇住我做，然後照樣跟住我做
一隻手心向上，一隻手心向下，然後調轉・・・你繼續做，直至我叫你停爲止
一隻手心向上，一隻手心向下 -5 次 (1 分) 分數 (0-1) _____
(如果＝1，前往問題 8，問題 6-7 則給滿分)

6. 依家咁樣做：一隻手渣實拳頭，一隻手放開手指，然後調轉・・・你繼續做，直至我叫你停爲止
   一隻手渣實拳頭，一隻手放開手指 – 5 次 (1 分) 分數 (0-1) _____

7. 依家咁樣做：敲左・・・敲右，然後敲左，在敲右，然後在敲左・・・你繼續做，直至我叫你停爲止
   敲右，然後敲左 – 10 次 (1 分)　　分數 (0-1) _____

8. 畫出“璧壘”

分數 (0-1) _____
(如果＝1，問題 9-11 給滿分，全卷完)

9. 畫出 O

分數 (0-1) _____

畫出 X

分數 (0-1) _____

10. 畫出“ XOXOXOXOXOXO ”

分數 (0-1) _____

MDRS I/P 總分數：_____

Clinical Dementia Rating Scale

	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss, or slight inconstant forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loses; more marked for recent events; defect interferes with every day activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Some difficulty with time relationships, oriented for place and person at examination, but may have geographic disorientation	Usually disoriented to time, often to place	Oriented to person only
Judgment and problem solving	Solves everyday problems and handles business and financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities and differences	Moderate difficult in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community affairs	Independent function at usual level in job, shopping and volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home. Appears well enough to be taken to functions outside a family home	No pretense of independent function outside home. Appears too ill to be taken to functions outside a family home
Home and hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home, more difficult chores abandoned; more complicated hobbies and interests abandoned	Only single chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal care	Fully capable of self-care	Fully capable of self-care	Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

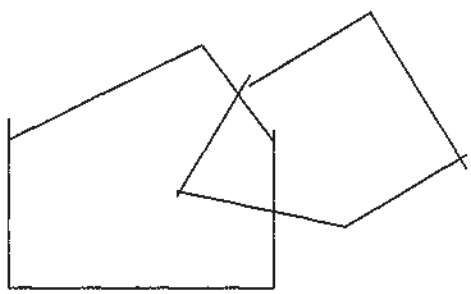
Subject Name/ID _____ Date _____

簡 短 智 能 測 驗 (MMSE)

最高分數	分數	
5	(　)	依家係乜野日子（年份）（季節）（月份）（幾號）（星期幾）？
5	(　)	我地依家係邊啡？ （九龍 / 新界 / 香港）（九龍 / 新界 / 香港既邊啡）（醫院）（邊層樓）（病房） 或:（九龍 / 新界 / 香港）（九龍 / 新界 / 香港既邊啡）（邊一科診所）（診所名字）（邊層樓） 或:（九龍 / 新界 / 香港）（九龍 / 新界 / 香港既邊啡）（邊條街）（邊一座）（邊層樓） 或:（九龍 / 新界 / 香港）（九龍 / 新界 / 香港既邊啡）（邊個屋村）（中心名字）（邊層樓）
3	(　)	依家我會講三樣既名，講完之後，請你重複一次。 請記住佢地，因為幾分鐘後，我會叫你再講番俾我聽。 （蘋果）、（報紙）、（火車）。依家請你講番哩三樣野俾我聽。 （以第一次講的計分，一個一分；然後重複物件，直至全部三樣都記住。）
5	(　)	請你用一百減七，然後再減七，一路減落去，直至我叫你停為止。（減五次後便停）（　　） 或：依家我讀幾個數目俾你聽，請你倒轉頭講番出黎。 （42731）　　（　　）
3	(　)	我頭先叫你記住既三樣野係乜野呀？
9	(　)	哩樣係乜野？（鉛筆）　　（手錶）。(2) 請你跟我講句說話（姨丈買魚腸）(1) 依家檯上面有一張紙。用你既右手拿起張紙，用兩隻手一齊將紙摺成一半，然後放番張紙係檯面。(3) 請讀出哩張紙上面既字，然後照住去做。(1) 請你講任何一句完整既句子俾我聽。例如:【我係一個人】、【今日天氣好好】。(1) 哩處有幅圖，請你照住黎畫啦。(1)

總分：_____

拍手



老 人 抑 鬱 狀 況 表 (GDS)

			評分
1. 你大致上滿唔滿意你自己嘅生活？	1＝ 唔滿意	0＝ 滿意	（ ）
2. 你係唔係放低咗好多你嘅活動同埋興趣呢？	0＝ 唔係	1＝ 係	（ ）
3. 你會唔會覺得你嘅生活好無聊？	0＝ 唔會	1＝ 會	（ ）
4. 你會唔會經常都覺得好悶？	0＝ 唔會	1＝ 會	（ ）
5. 你係唔係經常都覺得精神好好？	1＝ 唔係	0＝ 係	（ ）
6. 你會唔會擔心有 D 唔好嘅事會係你身上發生？	0＝ 唔會	1＝ 會	（ ）
7. 你係唔係時時都覺得好開心？	1＝ 唔係	0＝ 係	（ ）
8. 你係唔係成日都覺得冇乜人幫到你？	0＝ 唔係	1＝ 係	（ ）
9. 你係唔係鍾意留係屋企多過出街？	0＝ 唔係	1＝ 係	（ ）
10. 你覺唔覺得冇記性帶俾你多麻煩？	0＝ 唔覺得	1＝ 覺得	（ ）
11. 哪！你而家仲在生喎，你覺得開唔開心呀？	1＝ 唔覺得	0＝ 覺得	（ ）
12. 你覺唔覺得自己好冇用？	0＝ 唔覺得	1＝ 覺得	（ ）
13. 你覺唔覺得自己充滿活力？	1＝ 唔覺得	0＝ 覺得	（ ）
14. 你覺唔覺得而家嘅處境冇乜希望？	0＝ 唔覺得	1＝ 覺得	（ ）
15. 你係唔係覺得大部份人嘅生活都好過你？	0＝ 唔係	1＝ 係	（ ）

總分：（ ）

Alzheimer's Disease Assessment Scale-cognitive subscale
ADAS-COG

Subject Name: _____ Subject ID: _____

Gender/Age: _____ Education: _____

Assessor: _____ Date of Assessment: _____

Chinese ADAS – cog (13items) Revised 20090616

Cognitive domains	**Score**
1. Word recall task	/10
2. Naming objects and fingers	/5
3. Delayed word recall	/10
4. Commands	/5
5. Constructional praxis: figures	/5
6. Ideational praxis	/5
7. Orientation	/8
8. Word recognition test	/12
9. Remembering test instructions	/5
10. Spoken language ability	/5
11. Word finding difficulty	/5
12. Comprehension	/5
13. Concentration/ distractibility	/5
Total (11 items):	/70
Total (13 items):	/85

1. Word Recall 單詞回憶

「我而家俾一啲字詞你睇，你大聲讀出來，同埋記住佢，遲啲我會再問你。」

或「我而家讀一啲字詞你聽，你聽完後大聲讀出來，同埋記住佢，遲啲我會再問你。」[如不識字]

大聲讀出每個詞一次，然後即時出聲再諗一次，然後將十個詞盡量諗出來。總共三次測試。

第一次			第二次			第三次		
	能回憶	不能回憶		能回憶	不能回憶		能回憶	不能回憶
屋企	☐	☐	皮膚	☐	☐	火車軌	☐	☐
五毫子	☐	☐	細路仔	☐	☐	海	☐	☐
火車軌	☐	☐	小麥	☐	☐	國旗	☐	☐
細路仔	☐	☐	圖書館	☐	☐	軍隊	☐	☐
軍隊	☐	☐	屋企	☐	☐	小麥	☐	☐
國旗	☐	☐	海	☐	☐	細路仔	☐	☐
皮膚	☐	☐	火車軌	☐	☐	五毫子	☐	☐
圖書館	☐	☐	國旗	☐	☐	皮膚	☐	☐
小麥	☐	☐	五毫子	☐	☐	屋企	☐	☐
海	☐	☐	軍隊	☐	☐	圖書館	☐	☐
不能回憶的詞總數			不能回憶的詞總數			不能回憶的詞總數		

平均分數：(0-10)

2. Naming Objects and Fingers 物件名稱和手指名稱

每位測試者會逐一看 12 件物品， 每件看一次，然後說出它的名稱，問題如下：

“這件物品叫做甚麼名稱？”或 “這是甚麼？” 可以加少許提示：

物品	標準提示	總共 正確	不正確
花	生長於花園的生物	☐	☐
床	睡眠時用	☐	☐
銀雞（哨子）	你吹它會有聲出	☐	☐
鉛筆	寫字用	☐	☐
啷啷	BB 的玩具	☐	☐
面具	用來遮面	☐	☐
鉸剪	可以剪紙	☐	☐
梳	頭髮用	☐	☐
荷包	放錢用	☐	☐
口琴	樂器一種	☐	☐
聽筒	醫生用的儀器	☐	☐
夾	用來拿東西的工具	☐	☐

被訪者說出他（她）右手每一隻手指的名稱	正確	不正確（或說不出）
手指公	☐	☐
食指 （第二隻手指）	☐	☐
中指	☐	☐
無名指 （第四隻手指）	☐	☐
手指尾	☐	☐

分數　0=0-2 樣東西錯了　　3=9-11 樣東西錯了

1=3-5 樣東西錯了　　4=12-14 樣東西錯了

2=6-8 樣東西錯了　　5=15-17 樣東西錯了

分數

3. Delay Recall 延遲回憶測試

病人的分數是在此測試中忘記詞語的次數 （最高=10）

	能回憶	不能回憶
屋企	☐	☐
五毫子	☐	☐
火車軌	☐	☐
細路仔	☐	☐
軍隊	☐	☐
國旗	☐	☐
皮膚	☐	☐
圖書館	☐	☐
小麥	☐	☐
海	☐	☐

分數:

不能回憶的詞總數目 _____

4. Commands 口頭指令

在每一句指令讀出後，便要求被訪者做到以下行動。若做不到或做錯，便重新再讀一次指令。

指令	正確	不正確或做不到
握緊拳頭 （右手或左手）	☐	☐
先指一下屋頂，跟住指一下地下	☐	☐
在枱上面放一支鉛筆，手錶和啤牌，然後說出一下指令：		
將支鉛筆放係啤牌上面，跟住再將佢放番原位	☐	☐
將隻手錶放係鉛筆嘅旁邊，跟住反轉張啤牌	☐	☐
合埋雙眼， 用兩隻手指敲自己每邊膊頭兩下	☐	☐

要完成每一個在劃線上的動作，才代表完成指令

分數：
0=全對　　3=3 錯，2 對
1=1 錯，4 對　　4=4 錯， 1 對
2=2 錯，3 對　　5=全錯

分數：

5. Construction Praxis (Pencil and eraser) 繪圖行為

“呢度有一個圖形，你試下係呢張白紙上面繪一個同樣嘅圖”
每次容許兩次試畫，若果兩次皆不能畫出圖形，便作“錯”

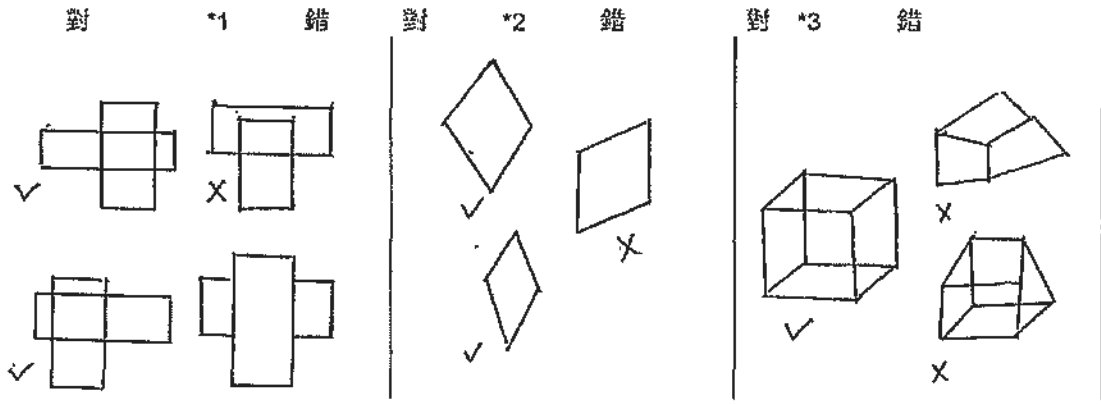
	對	錯（或畫不到）
圓形	☐	☐
兩個重疊的長方形	☐	☐
菱形	☐	☐
立方形	☐	☐

分數：
0=全對
1=1 形狀錯
2=2 形狀錯
3=3 形狀錯
4=4 全錯
5=完全畫不到； 畫了一部份；字而非圖形

分數：

附註：劃正確的圖形才可取分數。圖形的大小；隔離的寬窄；形狀的長短都不會計算在內。評分準則如下：

1. 圓形：要連續畫，沒有斷口
2. 兩個重疊的長方形，圖形是四邊，重疊， 如*2
3. 菱形， 圖形是四邊；四邊邊界線是差不多相同長度；上下對稱；如下*3
4. 立方形， 圖形是有三邊體 （正面及內線）對角線要平衡；如下*4



6. Ideational Praxis 意向指令行為

“呢度有一封寫好嘅信。我想你將封信摺好，放入信封里面；跟住將信封封口，在信封上寫上你自己的名和地址，再貼上郵票。”

指出每一步驟是對或錯、如他（她）做不到或不明白，可以重覆說出指示。

	對	錯或做不到	分數:	0= 全對
摺信	☐	☐		1= 1 個步驟做不到
將信放入信封里	☐	☐		2= 2 個步驟做不到
封口	☐	☐		3= 3 個步驟做不到
寫上姓名, 地址	☐	☐		4= 4 個步驟做不到
表示郵票貼上位置	☐	☐		5= 5 個步驟做不到
				分數:

7. Orientation 認知行為

作此測試之前，先拿走 （或遮蓋）時鐘，手錶或日歷。可以指出答案是對或錯。

	對	錯（沒有答）
全名（必須正確）	☐	☐
星期幾 （必須正確）	☐	☐
日期 （±1 天）	☐	☐
月份 （必須正確）	☐	☐
年 （必須正確）	☐	☐
季節 （±2 星期）	☐	☐
時間（± 1 小時）	☐	☐
地點 （例如醫院）	☐	☐

總分

評分=每錯一題計 1 分

註: 可以接受的答案包括日期（±1 天），季節（下一季的一周指內或上一季的兩周之內），時間(1 小時至內)，地點（可以說出地點部分的名稱）

8. Word Recognition 認字

"我依家俾一啲字你睇，你大聲讀出來同埋記住佢" 或 "而家讀一啲字你聽，你聽完跟我講一次，然後記住佢" [如病人不識字，由職員讀出]

甲) 第一次

12 個字: 河流 事件 皇后 位置 鴿子 信心 雨傘 提示 飛彈 代理權 龍蝦 標準

完成測試上述 12 個字後，便說 " 我而家再俾另一啲字你睇，有一啲字你頭先已經睇過，有啲就無睇過，你話俾我聽有無睇過啦？ " 或 "我而家再讀另一啲字俾你聽，有一啲頭先你已經聽過，有啲就無聽過，你話俾我聽有無聽過?" [如病人不識字，由職員讀出]

"呢個字頭先有無睇過 (聽過)? 然後 呢個呢?" 如病人不記得問題，可以重覆問題. 請記下每次的提示.

乙) 第二次 (同樣的十二個字)

河流 事件 皇后 位置 鴿子 信心 雨傘 提示 飛彈 代理權 龍蝦 標準

丙) 第三次 (同樣的十二個字)

河流　事件　皇后　位置　鴿子　信心　雨傘　提示　飛彈　代理權
龍蝦　標準

深色是先前看過(聽過)的名. 在病人的答案中　√ 圓形代表錯的答案,. 若要重複提示問題, 便在提示一方格以√ 表示.

	有	沒有	提示		有	沒有	提示		有	沒有	提示
粟米	O	□	□	河流	□	O	□	植物	O	□	□
努力	O	□	□	官員	O	□	□	河流	□	O	□
開會	O	□	□	思想	O	□	□	數量	O	□	□
可流	□	O	□	事件	□	O	□	事件	□	O	□
蟲蠢	O	□	□	皇后	□	O	□	皇后	□	O	□
諸物椪	O	□	□	位置	□	O	□	工業	O	□	□
事件	□	O	□	營地	O	□	□	位置	□	O	□
皂后	□	O	□	命運	O	□	□	時機	O	□	□
立置	□	O	□	高爾夫球	O	□	□	鴿子	□	O	□
品質	O	□	□	鴿子	□	O	□	搖籃	O	□	□
日落	O	□	□	信心	□	O	□	平凡	O	□	□
鴻子	□	O	□	准許	O	□	□	歌手	O	□	□
言心	□	O	□	雨傘	□	O	□	信心	□	O	□
雨傘	□	O	□	提示	□	O	□	雨傘	□	O	□
寓言	O	□	□	飛彈	□	O	□	假設	O	□	□
儆犬	O	□	□	水泡	O	□	□	提示	□	O	□
戎語	O	□	□	概念	O	□	□	飛彈	□	O	□
是示	□	O	□	代理權	□	O	□	代理權	□	O	□
飞彈	□	O	□	鋼琴家	O	□	□	繩結	O	□	□
朱寶	O	□	□	龍蝦	□	O	□	分別	O	□	□
弋理權	□	O	□	性別	O	□	□	龍蝦	□	O	□
龍蝦	□	O	□	標準	□	O	□	桶	O	□	□
票準	□	O	□	子彈	O	□	□	標準	□	O	□
欺騙	O	□	□	智力	O	□	□	法令	O	□	□
圓圈總數 (錯)				圓圈總數 (錯)				圓圈總數 (錯)			

分數 = 錯的總數或 "12" (以最少為答案)

第一次 (A): 分數 _____　提示 (次數) _____

第二次 (A): 分數 _____　提示 _____

第三次 (A): 分數 _____　提示 _____

總共提示 (用評估問題 8)_____ 分數 (0-12) (註: 三次平均數):

9. **Remembering Test Instructions** 在問題 7 的測試過程中, 評估病人記憶問題的能力.

分數:

0 = 不用提醒

1 = 非常輕微; 忘記一次

2 = 輕微; 提示兩次

3 = 中等; 提示三至四次

4 = 嚴重; 提示五至六次

5 = 非常嚴重; 提示七次以上

分數:

10. **Spoken Language Ability** 口語表達的能力

對被訪者給予一個整體總評分 (如清晰程度, 容易明白的程度等質素)

0 = 無困難

1 = 非常輕微困難

2 = 輕微困難 (少於四分之一)

3 = 中等困難 (四分之一至一半)

4 = 中等嚴重 (一半以上)

5 = 非常嚴重 (只能說單字或沒有內容的說話)

分數:

11. Word Finding Difficulty in Spontaneous Speech 說話時的用字缺陷

評估被訪者說話時是否有選詞方面的困難

分數 0=用字無困難

1=非常輕微困難

2=輕微困難（用其他子替代）

3=中等困難 （少了一些字又不會用其他子代替）

4=中等嚴重 （少了許多字）

5=非常嚴重 （差不多完全沒有內容；空調的發音；說 1 或 2 字）

分數:

12. Comprehension of Speech 理解語言的能力

評估病人理解語言的能力，口頭指令的行動不用計算在內

分數 0=無困難

1=非常輕微， 1-2 次不明白

2=輕微 3-5 次不明白

3=中等要重覆說多次

4=嚴重， 只能答是否等

5=非常嚴重， 很少適當地回答問題，而又不是因言語貧乏原因

分數:

Alzheimer's Disease 認知部分 （ADAS-cog）

總分 Item 1-12（0-70）:

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13. Concentration 注意力不集中

評估病人有沒有注意力接受測試， 或注意力受到分散的情況

分數 0=無困難

1=非常輕微， 1 次

2=輕微 2-3 次

3=中等 4-5 次

4=嚴重， 大部分時間不能集中精神

5=非常嚴重， 完全不能完成測試的工作

分數: