CORRELATIONS BETWEEN ISCHAEMIC CEREBRAL WHITE MATTER CHANGES AND THE NEUROCOGNITIVE PROFILES IN APPARENTLY ASYMPTOMATIC INDIVIDUALS

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By

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LIST OF ABBREVIATIONS AND ACRONYMS

AD	Alzheimer's disease
AR	Arithmetic
ARIC	Atherosclerosis Risk in Communities
BD	Block Design
ARWMC	Age related white matter changes
CA	Cancellation
CD	Coding
CI	Confidence interval
CMS	Children's Memory Scales
CO	Comprehension
CSF	Cerebrospinal fluid
CRP	C-reactive protein
CSVD	Cerebral Small Vessel Disease
CT	Computed Tomography
df	Degree of freedom
DSS	Digit Symbol Subtest
DS	Digit Span
DTI	Diffusion tensor imaging
DWM	Deep white matter
DWMH	Deep white-matter hyperintensities
DWR	Delayed word recall
FLAIR	Fluid attenuated inversion recovery
fMRI	Functional MRI
FSIQ	Full Scale Intelligence Quotient
FW	Figure Weights
GAI	General Ability Index
GM	Grey matter
HDL	High Density Lipoprotein
HRB	Halstead-Reitan Battery
HUSM	Hospital Universiti Sains Malaysia
IHD	Ischemic Heart Disease
IN	Information
KRK	Klinik Rawatan Keluarga
LN	Letter-Number Sequencing
M	Mean
MMSE	Mini Mental State Examination
MR	Matrix Reasoning
MRI	Magnetic Resonance Imaging
PCm	Picture Completion
POI	Perceptual Organization Index
PRI	Perceptual Reasoning Index
PSI	Processing Speed Index
PVH	Periventricular hyperintensities
PVWM	Periventricular white matter
QRISK2	Cardiovascular risk prediction
RAVLT	Rey Auditory Verbal Learning Test

SD	Standard deviation
SI	Similarities
SPSS	Statistical Package for the Social Sciences
SS	Symbol Search
UK	United Kingdom
VaD	Vascular dementia
VC	Vocabulary
VCI	Verbal Comprehension Index
VP	Visual Puzzle
WAIS-III	Wechsler Adults Intelligence Scale –third Edition
WAIS-IV	Wechsler Adults Intelligence Scale –fourth Edition
WAIS-R	Wechsler Adult Intelligence Scale - Revised
WF	Word fluency
WM	White Matter
WMCs	White matter changes
WMHs	White Matter Hyperintensities
WMLs	White Matter Lesions
WMI	Working Memory Index

KORELASI DI ANTARA PERUBAHAN ISKEMIA SEREBRUM JISIM PUTIH DAN PROFIL NEUROKOGNITIF DALAM INDIVIDU ASIMPTOMATIK

ABSTRAK

Hiperintensiti jirim putih (WMHs), asimptomatik 'lacunar infarcts', pendarahan kecil otak (BMBs) dan ruang perivaskular yang diperbesarkan (EPVS) telah dikenal pasti sebagai lesi senyap yang boleh dikaitkan penyebab kepada penyakit pembuluh darah kecil otak (CSVD). Semua petanda ini telah dikaitkan secara individu untuk kecenderungan kemerosotan nilai kognitif. Kajian ini bertujuan untuk mengkaji hubungan antara CSVD dari penemuan MRI dan prestasi neuropsikologi di kalangan individu yang kelihatannya sihat. Kelulusan etika telah diperolehi daripada Jawatankuasa Etika Penyelidikan Manusia Universiti Sains Malaysia (JEPeM-USM) [Ruj: USM / JEPeM / 15030096]. Ini merupakan satu kajian perintis dengan anggaran saiz sampel, yang berasaskan penyelidikan berkaitan sebelumnya. Subjek dipilih daripada populasi rawak yang menghadiri Klinik Rawatan Keluarga (KRK), Hospital Universiti Sains Malaysia (HUSM), dengan umur dan jantina dipadankan. QRISK2, iaitu ramalan risiko kardiovaskular berasaskan dalam talian telah digunakan untuk menentukan tahap risiko kardiovaskular subjek yang mengambil bahagian dalam kajian. Enam puluh (n=60) subjek yang memenuhi kriteria inklusi dan ekslusi, telah diambil dan menjalani imbasan otak iaitu Pengimejan Resonans Magnet (MRI) menggunakan pengimbas Philips 3-Tesla Achieva MR, serta menyiapkan penilaian neuropsikologi menggunakan Weschsler Adult Intelligence

Scale –Edisi keempat (WAIS-IV) (2008). Imej-imej asas MRI digunakan untuk menentukan kewujudan WMHs dan dikira menggunakan skala Fazekas. Ujian neuropsikologi dilakukan ke atas tiga skala indeks seperti Indeks Penaakulan Persepsi (PRI), Indeks Memori Kerja (WMI) dan Indeks Kelajuan Pemprosesan (PSI). Analisis telah dilakukan menggunakan IBM SPSS Statistik versi 22.0. Daripada enam puluh subjek (18 lelaki dan 42 perempuan) yang berumur antara 25 hingga 62 tahun yang telah direkrut, kira-kira 30% daripada mereka mempunyai sejarah keluarga yang mempunyai penyakit jantung, 10% dalam rawatan tekanan darah tinggi dan 60% tanpa komorbiditi. Dikalangan subjek, 23 orang (38.3%) daripada mereka mempunyai WHMs yang dikesan oleh MRI, dan selebihnya adalah normal. Di kalangan subjek yang mempunyai WMHs, 39.1% adalah dalam usia muda (25-39) dan 60.9% berada di pertengahan umur (40-62). Data primer mencadangkan bahawa skor ujian neuropsikologi adalah berubah-ubah antara subjek yang mempunyai WMHs, dengan kecenderungan kawasan otak. Terdapat kaitan yang signifikan antara subjek yang mempunyai atau tidak mempunyai WHMs dalam PRI, $t(0.07,58)=0.07$, $p=0.02$. Oleh itu, umur ($r = 0.3$, $p <0.05$) dan skor QRISK ($r = 0.4$, $p <0.05$) didapati berhubung kait dengan kehadiran WMHs. Keputusan ini menunjukkan bahawa di kalangan warga tua, CSVD boleh menyumbang kepada penurunan kognitif dengan mempengaruhi kelajuan pemprosesan maklumat dan fungsi eksekutif. Memandangkan kehadiran WMHs mungkin juga menunjukkan peningkatan risiko kejadian gejala serebrovaskular, dengan itu pentafsiran yang teliti diperlukan untuk menentukan perkaitan klinikal untuk setiap individu.

CORRELATIONS BETWEEN ISCHAEMIC CEREBRAL WHITE MATTER CHANGES AND THE NEUROCOGNITIVE PROFILES IN APPARENTLY ASYMPTOMATIC INDIVIDUALS

ABSTRACT

White matter hyperintensities (WMHs), asymptomatic lacunar infarcts, brain microbleeds (BMBs), and enlarged perivascular spaces (EPVS) have been identified as silent lesions attributable to cerebral small vessel disease (CSVD). All these markers have been individually linked to predisposition of cognitive impairment. This study aimed to examine the relationship between CSVD from incidental MRI findings and neuropsychological performance among apparently healthy individuals. An ethical approval was obtained from the Jawatankuasa Etika Penyelidikan Manusia Universiti Sains Malaysia (JEPeM-USM) [Ref: USM/JEPeM/15030096]. This was a pilot study that involved random selection of subjects' population who attended Klinik Rawatan Keluarga, Hospital Universiti Sains Malaysia. The QRISK2, an online-based cardiovascular risk prediction was employed to stratify the cerebrovascular risk for the recruited subjects. Sixty (n=60) subjects, who met the inclusion and exclusion criteria, were recruited and underwent MRI brain scanning using Philips 3-Tesla Achieva MR scanner as well as completed neuropsychological assessment using Wechsler Adult Intelligence Scale (WAIS-IV) (2008). The baseline MRI images were used to determine the presence of WMHs and scored using Fazekas scale. The neuropsychological testing included three index scales such as Perceptual Reasoning Index (PRI), Working Memory Index (WMI) and Processing

Speed Index (PSI). The analyses were carrying out by IBM SPSS Statistics version 22.0. Sixty subjects (n=18 males and n=42 females), aged between 25 to 62 years old were recruited. Approximately 30% of them had family history of heart attack, 10% on hypertension treatment and 60% without comorbidity. Among the subjects, 23 (38.3%) of them have WHMs on MRI, and the rest appeared normal. Among WMHs subjects, 39.1% were in younger age group (25-39) and 60.9% were in the middle-age (40-62) group. The primary data suggested that the scores of neuropsychological test were variable among WMHs subjects, with brain region predilections. There was a significant association between subjects with and without WMHs in PRI, t (0.07,58)=0.07, p=0.02. Thus, age (r=0.3,p< 0.05) and QRISK scores (r=0.4, p<0.05) appeared to be correlated to the presence of WMHs. This result suggests that in older people, CSVD may contribute to cognitive decline by affecting information processing speed and executive function. Given that presence of WMHs may also indicate an increased risk of symptomatic cerebrovascular events, thus careful interpretation is required in order to determine its clinical relevance for the individual subjects.

CHAPTER 1

INTRODUCTION

1.1 Study background

Cerebral Small Vessel Disease (CSVD) is related to the changes in the structure and function of the brain, mainly in the connective white matter (WM) and frequently as ischaemic lesions. The term CSVD has been used to reflect clinical, radiological or pathological phenomena attributed to disease of small perforating arteries and arterioles supplying deep brain structures. The most frequent morphologic findings on brain MRI that related with CSVD include white matter hyperintensities (WMHs;leukoaraiosis), small subcortical infarcts, and microbleeds. WMHs are the most common manifestations of CSVD. Therefore, it is an important clinico-pathological condition that is recognised to results in 20% of strokes worldwide, and the most common precursor for vascular and mixed dementia (vascular dementia (VaD) and Alzheimer's disease (AD)); (Pantoni 2010; Philip B. Gorelick *et al.*, 2011).

The spectrum of features seen on neuroimaging by conventional MRI include recent small subcortical infarcts, lacunes, white matter changes (WMCs) or white matter hyperintensities (WMHs), perivascular spaces, microbleeds, and brain atrophy (Pantoni 2010). WMHs (leukoaraiosis) are seen as patchy areas of hypodensity on Computed Topography (CT) scans, or hyperintensity on T2-

weighted, fluid attenuated inversion recovery (FLAIR), and proton density-weighted images on MRI, including the periventricular and centrum semiovale white matter (Haller *et al.*, 2013; Schmahmanna *et al.*, 2008; Wardlaw *et al.*, 2015a).

On MRI images, the difference between normal and abnormal tissue is often clearer compared with CT. In addition, there is no ionizing radiation needed in an MRI scan, but it can be a noisy exam and takes longer than a CT. The absolute contraindications to MRI involve cardiac pacemakers, cochlear implants, implanted stimulators, ferromagnetic implants, aneurysm clips and metal in the eye (Sherllock *et al.*, 1993). Therefore, the subjects with contraindications of MRI will not be admitted to the scan room due to risk of injury.

WMHs are recognised to be ordinary MRI findings in patients with cardiovascular risk factors and symptomatic cerebrovascular disease (Li *et al.*, 2013; Simoni *et al.*, 2012), and have a relationship with increased risk of functional decline, dementia, and even death (De Groot *et al.*, 2000; Debette and Markus, 2010; Inzitari *et al.*, 2009; Jeerakathil *et al.*, 2004; Longstreth *et al.*, 1996; Pantoni *et al.*, 2005; Prins and Scheltens, 2015; van Dijk *et al.*, 2002). However, WMHs have been reported to be prevalent in healthy elderly on MRI scans done in selected populations (Sachdev *et al.*, 2005; Yoshita *et al.*, 2005).

WMHs characterization in terms of volume, location and number of lesions which are assessed either by visual rating scales or quantitative measurements, has also been recently included within the standards for reporting vascular changes on neuroimaging, both in the routine clinical settings and for research purposes (Wardlaw *et al.*, 2013b). There are several visual rating scales used to assess WMHs, the common ones include the Fazekas scale (Fazekas *et al.*, 1987), the Scheltens scale (Scheltens *et al.*, 1993) and the age-related white matter changes (ARWMC) scale (Wahlund *et al.*, 2001). Beyond the routine use in clinical settings, these scales are finding purpose in research setting as well (Kreisel *et al.*, 2013; Simoni *et al.*, 2012). In this study, Fazekas scale is selected as the most widely used method in visual rating and has been in use for over two decades to produce an overall impression of WMHs presence in the entire brain.

At present, WMHs are widely regarded to represent the radiological appearance of a vascular process linked mainly with cerebral small-vessel changes (Pantoni and Garcia, 1997; Pantoni *et al.*, 1999). Although the association between WMHs and aging has been consistently shown across different studies (Aine *et al.*, 2014; Pantoni and Garcia, 1995; Schmidt, 2005; Smith *et al.*, 2017) conflicting conclusions remained as far as other risk factors and clinical correlates are concerned.

In healthy individuals, executive dysfunction seems to correspond with WMHs (DeCarli *et al.*, 1995; O'Brien *et al.*, 2002). The overall severity of WMHs is known to link with the reduction in the speed processing and executive performance in patients with subcortical ischaemic vascular dementia (Mungas *et al.*, 2001). In contrast, such global cognition deficit is not seen in those with additional heterogenous vascular dementia (Cohen *et al.*, 2002). Nebes et al (2006) found a significant relationship between WMHs severity and processing speed in older healthy adults aged 65-80 years (Nebes *et al.*, 2006).

By using Wechsler Adults Intelligence Scale –fourth Edition (WAIS-IV), this study assessed Perceptual Reasoning Index (PRI), Working Memory Index (WMI) and Processing Speed Index (PSI) for cognitive ability.

1.2 Rationale of study

In general, the current study is designed to find the correlation between the magnetic resonance image (MRI) finding of CSVD in apparently asymptomatic (healthy) individuals and their neurocognitive profiles on specific neuropsychological tests. Although there were many previous studies which had correlated WMHs MRI finding of CSVD with neurocognitive profiles, these had largely been in older adults, dementia and post-stroke patients with other specific neurocognitive tests such as Mini Mental State Examination (MMSE), Clock Drawing Test and Stroop. The selection of WAIS-IV as a neuropsychological test in this study reflected the fact that there have been fewer studies on healthy individual for both young adults and older adults related to CSVD such as WMHs (Loring and Bauer, 2010a).

Cerebral Small Vessel Disease (CSVD) is not often mortal; however, it does influence the quality of life among those affected. CSVD tend to progress very slowly (and thus asymptomatic subjects/subclinical) and it tends to manifest clinically (i.e symptomatic) only after many years. At present, the treatment choice is very restricted and often recommended based on the therapeutic principles applied in the larger cerebral artery stroke. Therefore, such data may be useful in understanding of the natural history of subclinical CSVD and its relation as a predictor of cognitive impairment in apparently healthy individuals, and essentially can help guide for wider preventive actions in the society.

1.3 Objectives and hypotheses of the study

1.3.1 General objective

To assess the relationship between subclinical CSVD from MRI findings and the neuropsychological test performance.

1.3.2 Specific objectives

1. To compare MRI finding with neuropsychological performance.
2. To determine the association of QRISK2, imaging changes and psychological assessment.
3. To determine whether QRISK2 predicts the correlation with psychological findings.

1.3.3 Null Hypotheses

1. There are no significant different of MRI finding with neuropsychological performance.
2. There is no significant correlation between QRISK2, imaging changes and psychological assessment.
3. Psychological findings (PRI, WMI and PSI) do not predict QRISK2.

1.4 Summary

In summary, this introduction chapter has covered the important areas of the research such as the study background, rationale of study as well as objectives and hypotheses of the study.

CHAPTER 2

LITERATURE REVIEW

2.1 Cerebral Small Vessel Disease (CSVD)

Cerebral Small Vessel Disease (CSVD) refers to pathological processes that affect the structure or function of small vessels on the surface and within the brain, including arteries, arterioles, capillaries, venules, and veins (Pantoni 2010). Two pairs of blood vessels supplying the brain are the vertebral and internal carotid arteries which are interconnected in the cranial cavity to produce an arterial circle called Circle of Willis (see Figure 2.1). Approximately 80% of the total cerebral blood flow are contributed by carotid artery, while rest about 20% coming from the vertebral arteries.

CSVD remarkably affects perforating end-arteries branching customarily perpendicularly from a large parent artery. In other words, CSVD is correlated with structural and functional changes within the brain, mainly in the connective white matter (WM), during the development of ischaemic lesions. It is also an important clinico-pathological condition that cause of 20% of strokes worldwide, and the most common causes of vascular and mixed dementia [vascular dementia (VaD) and Alzheimer's disease (AD)] (Gorelick *et al.*, 2011; Pantoni 2010).

Neuroimaging is used as a method to detect the consequences of pathological changes of small vessels to the brain. These consequences comprise white matter hyperintensities, small infarctions or hemorrhages in white or deep grey matter, enlargement of perivascular spaces, and brain atrophy (Wardlaw *et al.*, 2013a).

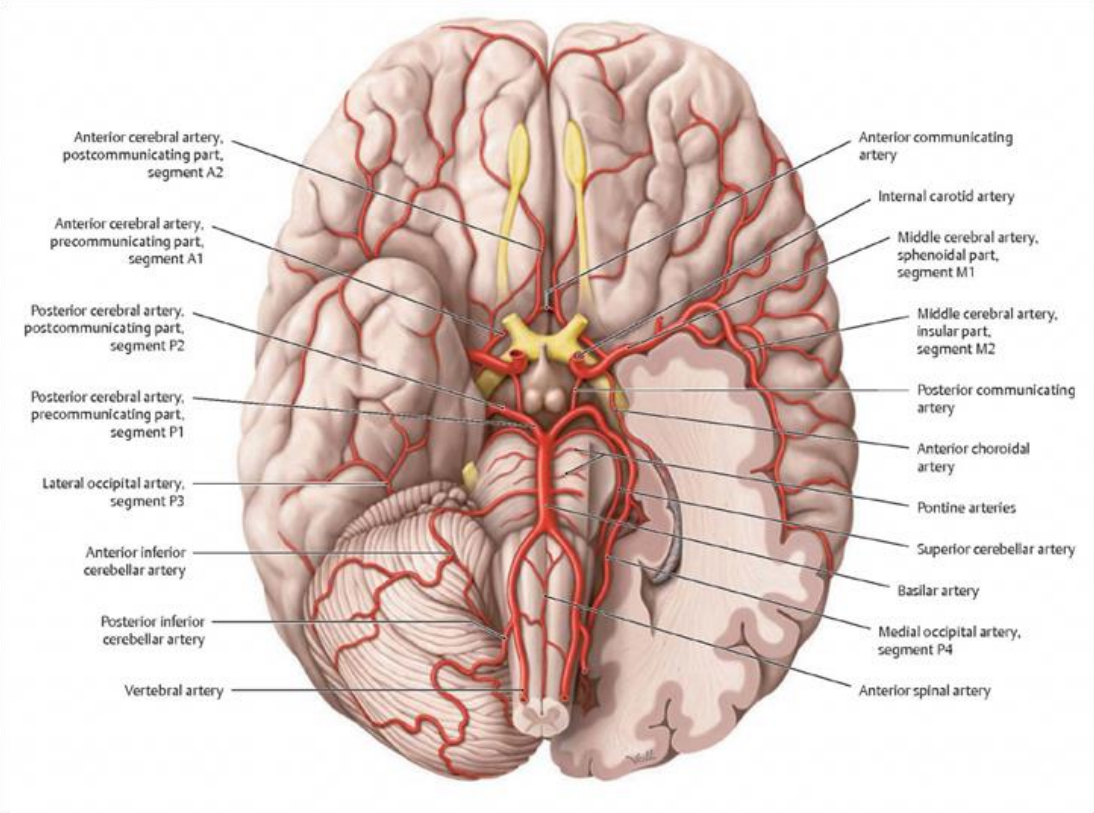

Figure 2. 1 : Arterial Circle on Base of Brain (adapted from (Hansen, 2014)).

2.2 White Matter Hyperintensities (WMHs)

White matter is composed of millions of bundles of axons (nerve fibres) that connect neurons in different brain regions into functional circuits which lie beneath the grey matter cortex. The white colour is derived from the electrical insulation (myelin) that coats the axons and formed by non-neuronal cells,

oligodendrocytes, which wrap up to 150 layers of tightly compressed cell membrane around axons (Field, 2010). The location of white matter in the brain includes the central and subcortical regions of the cerebral and cerebellar hemispheres. Thus it accounts for about 60% of the total brain volume. White matter changes known as leukoaraiosis are generally referred to as a periventricular white matter disease, or WMHs, due to their bright white appearance on T2-weighted MRI scans (Kim *et al.*, 2014)(see Figure 2.2). In addition, they are identified on Computed Tomography (CT) as diffuse areas of hypodensity, and high signal intensities on T2-weighted, proton density and fluid-attenuated inversion recovery (FLAIR) images. Hence on T1-weighted images, they can be presented as isointense or hypointense according to the severity of the underlying pathological changes (Seiler *et al.*, 2012).

WMHs are categorized into two groups based on their anatomical location; the ventricles and deep white matter (Fazekas *et al.*, 2002). They are typically related with age, hypertension and other cardiovascular risk factors (Longstreth *et al.*, 1996). Thus, the prevalence of WMHs ranges in adults aged 64 raises from 11-12% and increases about 94% in adults at age 84 (Thompson and Hakim, 2009). Incidental WMHs are common in brains of healthy people in their 60s and may be identifying as early as the 30s and 40s.

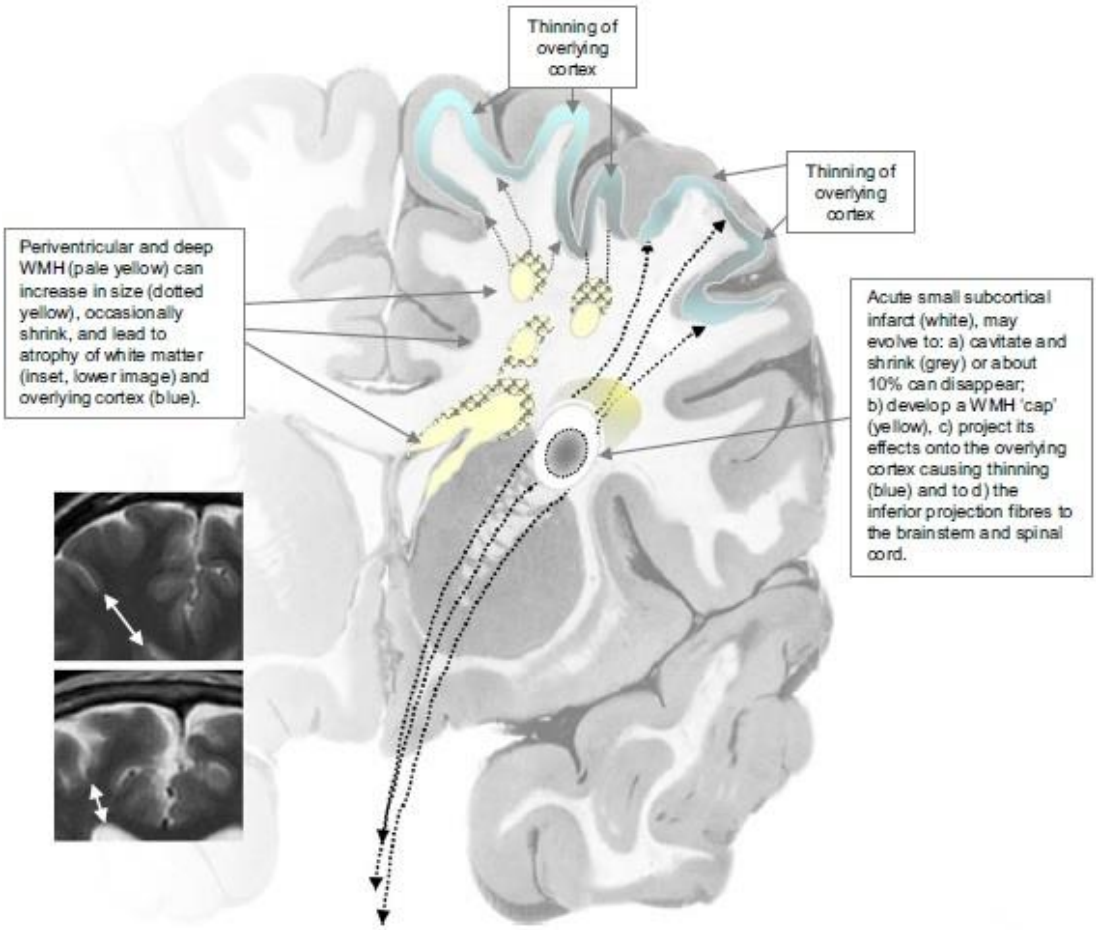

Figure 2.2 : Diagram of dynamic mechanisms by which WMHs and CSVD lead to brain damage (adapted from (Wardlaw *et al.*, 2015b)).

2.3 Aetiology and consequences of WMHs

WMHs were first described as radiological finding in 1986 (Pantoni, 2008) and was followed by attempts to contribute a pathological description (Wardlaw *et al.*, 2013b). The aetiology of WMHs is still unclear, despite there are progressively histopathological, epidemiological, and physiological studies that contribute important information about it.

Healthy white matter is more myelinated than white matter of Alzheimer patients (Bartzokis G *et al.*, 2003) and has a high content of long-chain fatty acids and less 12% of water compared with grey matter. Previous studies have reported that WMHs are consistently related with age, hypertension, and other cardiovascular risk factors (Prabhakaran *et al.*, 2012). Therefore, individual with extensive WMHs are at high risk for future stroke. Nevertheless, WMHs occurs around 30% of healthy subjects over 60 years of age, and their prevalence show a steady rise with increasing age (Meyer *et al.*, 1992).

Brain atrophy, reduced cerebral blood flow and focal neurologic signs have been found to be correlated with volume and number of WMHs (DeCarli *et al.*, 1995). Roman (1987) reported that WMHs associated with cognitive impairment, with a suggestion that a certain threshold must be achieved before this becomes clinically apparent (Roman, 1987). WMHs are also related with major depression, bipolar disorder and schizophrenia (Sachdev and Brodaty, 1999).

Since the progression of WMHs is related to aging (Prins and Scheltens, 2015) testing the brain of individuals in middle age offers the opportunity to determine the distribution of lesions in their early phase while provides a baseline for the examination of the impact of age, hypertension, diabetes and other risk factors as the severity and distribution of WMHs.

2.4 WMHs and cognitive function

Junque et al.(1990) reported that WMHs were correlated with cognitive impairment (Junqué *et al.*, 1990). On neuroimaging, with high prevalence of WMHs, even in healthy elderly population without cognitive impairment, Fazekas et al (2009) argued that WMHs were unlikely to be associated with cognitive performance and decline (Fazekas *et al.*, 2009).

O'Brien (2006) pointed out that patients with moderate to severe WMHs might present a high risk of lesion progression and as a result of clinical decline in vascular cognitive impairment (O'Brien, 2006). Furthermore, Reinhold Schmidt et al (2010) reported that people with moderate and severe WMHs did not show differences in performances on mini-mental state examination (MMSE) and executive function tasks (Reinhold Schmidt *et al.*, 2010).

Cognitive domains were highly correlated with brain volume, but the relationships between WMHs volume and cognition were considered low (Benjamin *et al.*, 2014). In other studies done by Oosterman et al. found a significant relationship between WMHs and fronto-executive functions in a subject with risk factors for cerebrovascular disease that inhibitory control, planning and working memory (Oosterman *et al.*, 2008). They also noted that hippocampal atrophy was also correlated with executive function, showing a

high input to performance in working memory and set-shifting tasks (Oosterman *et al.*, 2008).

2.5 Magnetic Resonance Imaging (MRI)

A magnetic resonance imaging (MRI) scan is a common procedure used by all hospitals around the world and is the most sensitive tool to assess CSVD. By providing detailed non-invasive images of the brain, MRI has transformed from routine clinical use to the tool for furthering research into the functional and structural of changes in healthy and diseased brain. Images of the human body that provided by MRI were sliced same as a loaf of bread can be in any direction, as well as thin as a couple of millimeters. It also provides better soft tissue contrast compared to Computed Tomography (CT) and make differentiated fat, water, muscle, and other soft tissue better than CT. Thus, it is the best way to view the soft tissues especially brain and without any exposure to radiation.

The basic protocol to neuroimaging set up of WMHs is the combination of T1-weighted, T2-weighted and FLAIR sequences. T1-weighted sequences are very useful and informative structural MRI methods. Later T1-weighted sequences create images which maximize the contrast among grey matter (GM), WM and cerebrospinal fluid (CSF). By viewing these images, CSF shows hypointense (dark) and GM has less intensity (appears darker) compared with WM.

In addition, T2-weighted and FLAIR images are also important structural views for MRI sequences. On T2-weighted image of normal MRI, grey matter is seen brighter than white matter together with hyperintensity of CSF. However, in small lesion of brain, the similar finding of hyperintensity of CSF could also be presented. This can lead to confusion when interpreting the result. FLAIR images are T2-weighted image where CSF signal is perfectly suppressed while lesions still appear hyperintense, which allows the optimal visualization and contrast of WM abnormalities such as WMHs (Fazekas *et al.*, 2002).

2.6 MRI grading of WMHs severity

Currently, there are diverse of techniques to quantify the presence of WMHs on MRI ranging from visual rating scales to semi-automated or fully automated volumetric. WMHs are composed of deep white-matter hyperintensities (DWMH) and periventricular hyperintensities (PVH). The WMHs severity can be rated visually on axial FLAIR images using various scale such as the Fazekas rating scale, Scheltens rating scale, Wahlund rating scale, Ylikoski and Manolio (see Table 2.1).

Visual rating is fast and can be used for images of different quality obtained on different scanner. In clinical practice and research involving large subjects, it is preferable to use visual rating scales than of more time-consuming quantitative measurements to assess WMHs. However, visual rating scales inevitably have

some limitations, including non-linearity of data, lack of sensitivity to small changes, and susceptibility to ceiling effects (Kim *et al.*, 2008). In addition, existing scales are heterogeneous, which may be contributed to the dissimilar results in previous research on WMHs (Kloppenborg *et al.*, 2014).

Table 2.1 : Summary of visual scales of MRI for WMHs (adapted from (Issac *et al.*, 2016)).

Scales for MRI (WMH)	**Assessment of severity**	**Scores**
Fazekas	Periventricular and deep WMCs are rated separately. A total score is obtainable by summing the 2 partial scores. Periventricular hyperintensities Scores are as follows: 0 = absence, 1 = "caps" or pencil-thin lining, 2 = smooth "halo," and 3 =irregular periventricular hyperintensities extending into the deep white matter. Deep white matter hyperintense signals Scores are as follows: 0 = absence, 1 = punctuate foci, 2 = beginning confluence of foci, and 3 =large confluent areas.	Total score minimum, 0; maximum, 6
Modified Scheltens	Periventricular hyperintensities (minimum, 0; maximum 6) Scoring is as follows: caps, occipital 0/1/2, and frontal 0/1/2; bands, lateral ventricles 0/1/2 (0 =absent, 1 = ≤5 mm, 2 = ≥6 mm, and ≤10 mm). White matter hyperintensities(minimum, 0; maximum, 24) Scoring is as follows: frontal 0/1/2/3/4/5/6, parietal 0/1/2/3/4/5/6, occipital 0/1/2/3/4/5/6, and temporal 0/1/2/3/4/5/6 (0 = no abnormalities; 1 = ≤3 mm, $n \leq 5$; 2 = ≤3 mm, $n \leq 6$; 3 = 4 to 10 mm, $n \leq 5$; 4 = 4 to 10mm, $n \geq 6$; 5 = ≥11 mm, $n \geq 1$; 6 = confluent).	Minimum, 0; maximum, 30
Ylikoski	WMCs located at 4 locations (frontal horns, body of the ventricles, trigones, and occipital horns) are rated separately on each hemisphere. Periventricular leukoaraiosis (minimum, 0; maximum, 24) Scoring is as follows: 0 = no hyperintensity; 1 = punctuate, small foci (mild); 2 = cap,pencil-thin lining (moderate); and 3 = nodular band, extending hyperintensity (severe). Centrum semiovale leukoaraiosis, including watershed areas (minimum, 0; maximum, 24) Scoring is as follows: 0 = no hyperintensity; 1 = punctuate, small foci (mild); 2 = beginning confluent (moderate); and 3 = large confluent areas (severe). Total leukoaraiosis score is periventricular leukoaraiosis score plus centrum semiovale leukoaraiosis score equal to 0 to 48.	Minimum, 0; maximum 48

Table 2.1 : Summary of visual scales of MRI for WMHs (adapted from(Issac *et al.*, 2016). (continued))

Scales for MRI (WMH)	**Assessment of severity**	**Scores**
Manolio	Periventricular and subcortical regions are not rated separately. Including 9 grades: 0 = no white matter signal abnormalities; 1 = discontinuous periventricular rim or minimal "dots" of subcortical white matter; 2 = thin, continuous periventricular rim or few patches of subcortical white matter lesions; 3 = thicker continuous periventricular rim with scattered patches of subcortical white matter lesions; 4 = thicker shaggier periventricular rim and mild subcortical white matter lesions and may have minimal confluent periventricular lesions; 5 = mild,periventricular confluence surrounding frontal and occipital horns; 6 = moderate periventricular confluence surrounding frontal and occipital horns; 7 = periventricular confluence with moderate involvement of centrum semiovale; 8 = periventricular confluence involving most of centrum semiovale; and 9 = all white matter involved.	Minimum, 0; maximum, 9
Wahlund	Deep white matter lesions (WMLs) and periventricular hyperintensity combined and called WMLs: 1 = No white matter changes; 1.5 = Small solitary white matter changes; 2 = Multiple discrete or large solitary white matter changes; 2.5 = Multiple, partly confluent white matter changes; 3 = Multiple, large confluent white matter changes.	Minumum, 1; maximum, 3.

2.6.1 Fazekas Scale

Fazekas rating scale rates periventricular and deep WML separately. Periventricular hyperintensities are scored as: 0 = absence, 1 = ‘caps’ or pencil-thin lining, 2 = smooth ‘halo’ and 3 = irregular periventricular hyperintensities extending into the deep white matter. Deep white matter hyperintensities are scored as: 0 = absence, 1 = punctuate foci, 2 = beginning confluence of foci and 3 = large confluent areas. A range of total score is from 0 to 6 was obtained by total both periventricular and deep WMHs Fazekas scores (see Figure 2.3).

Fazekas scale is one of the most widely used visual rating scales and has been in use for over two decade. It is the simplest WMHs scale. Hence, this scale is also closely associated with quantitative measures of WMHs volumes (Valdes Hernandez Mdel *et al.*, 2013).

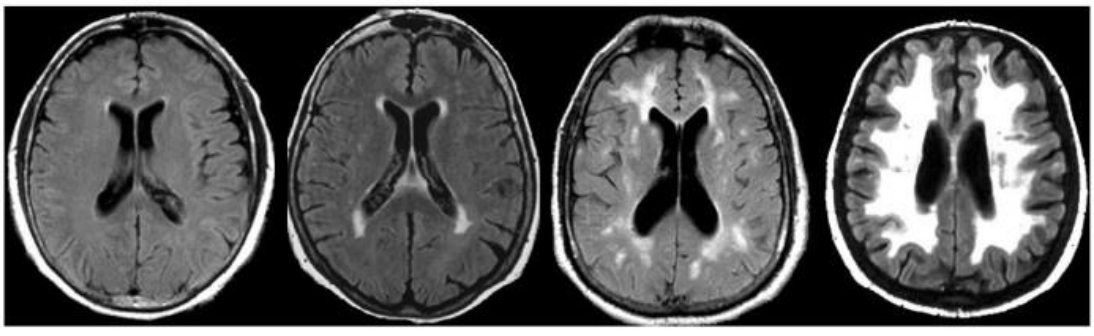

Figure 2.3 : Subcortical hyperintensities on MRI, ranging in severity from none (left), through mild and moderate, to severe (right). (Adapted from (Malloy *et al.*, 2006)).

2.7 Conventional risk factors for cerebrovascular diseases

Risk factors for cerebrovascular disease in the population setting were first recognised in the Framingham Heart Study in the early 1960s (Syed S Mahmood *et al.*, 2014). The prevention of cardiovascular morbidities and mortality is critical by understanding of such factors. Age, gender, race, ethnicity, and heredity have been recognized as risk for stroke. Although these factors cannot be modified, they help identify those at high risk, enabling vigorous treatment of those risk factors that can be adjusted.

The strongest determinant risk factor for stroke is age. For every successive 10 years after age 55 years old, the rate to get stroke is more than doubles in both men and women (Brown *et al.*, 1996; Wolf *et al.*, 1992). Furthermore, stroke incidence rates are 1.25 times higher in men compared to women because women tend to live longer than men (Wong, 1999).

Between racial groups, stroke incidence and mortality rates widely varied. According to several studies, stroke incidence is higher among black patients, approximately double compared with white patients. The study in Manhattan by Sacco *et al.* found that stroke incidence among black patients was 2.4 times more than white patients; while among Hispanic patients were 1.6 times compared with white patients (Sacco *et al.*, 1998). In Asians, Chinese and Japanese, higher incidence rates of stroke had been reported (Ueshima *et al.*, 2008).

Stroke incidence also increased with a family history of stroke. The reasons of this are a genetic tendency for stroke, a genetic determination of other stroke risk factors, and a common familial exposure to environmental or lifestyle risks. Earlier studies suggested an increased risk for men whose mothers died of stroke and women who had a family history of stroke (Seshadri *et al.*, 2010). In the Framingham Study an offspring analysis revealed that both paternal and maternal history of stroke was related with an increased risk of stroke (Kiely *et al.*, 1993).

Currently, an online calculator has been established to predict the risk for cerebrovascular disease within 10 years, including QRISK2 (Collins and Altman, 2010).

2.7.1 QRISK2

QRISK2 is an online based risk prediction of cardiovascular disease (Collins and Altman, 2010). (http//:www.QRISK.org/index.php) (University of Nottingham and EMIS). It was developed in the United Kingdom (UK) based on information compiled between 1993 and 2010 that contained the data for over 10 million patients registered with 550 general practices in the UK. Hence, it is used internationally and is updated annually.

QRISK2, the updated version of QRISK1, is a new multivariable risk score that comprises all the risk factors in QRISK1 including self-assigned ethnicity and conditions associated with cardiovascular risk (including diagnosed type 2 diabetes, treated hypertension, rheumatoid arthritis, renal disease, and atrial fibrillation) (Hippisley-Cox *et al.*, 2008). Interactions between age and Townsend score, body mass index, systolic blood pressure, family history, smoking status, treated hypertension, diagnosis of type 2 diabetes, and atrial fibrillation also are considered in QRISK2 (see Table 2.2).

Table 2.2 : Summary the risk factors in QRISK1 and QRISK2 adapted from (Collins and Altman, 2010)

QRISK1

Age (continuous)
Ratio of total serum cholesterol:high density lipoprotein (continuous)
Systolic blood pressure (continuous)
Smoking status (current smoker/non-smoker (including former smoker))
Body mass index (continuous)
Family history of coronary heart disease in first degree relative under 60 years (yes/no)
Townsend deprivation score (output area level 2001 census data evaluated as continuous variable)
Receiving treatment for blood pressure at baseline (at least one current prescription of at least one antihypertensive agent) (yes/no)
Systolic blood pressure × Receiving treatment for blood pressure at baseline

QRISK2

Age (continuous)
Ratio of total serum cholesterol:high density lipoprotein (continuous)
Systolic blood pressure (continuous)
Smoking status (current smoker/non-smoker (including former smoker))
Body mass index (continuous)
Family history of coronary heart disease in first degree relative under 60 years (yes/no)
Townsend deprivation score (output area level 2001 census data evaluated as continuous variable)
Treated hypertension (diagnosis of hypertension and at least one current prescription of at least one antihypertensive agent) (yes/no)
Self- assigned ethnicity (white (or not recorded)/Indian/Pakistani/Bangladeshi/ other Asian/black African/black Caribbean/other (including mixed))
Type 2 diabetes (yes/no)
Rheumatoid arthritis (yes/no)
Atrial fibrillation (yes/no)
Renal disease (yes/no)
Age × body mass index
Age × Townsend score
Age × systolic blood pressure
Age × family history of cardiovascular disease
Age × smoking current
Age × treated hypertension
Age × type 2 diabetes
Age × atrial fibrillation

2.8 Neuropsychological tests

Neuropsychological tests are specially designed tasks to examine brain function and cognitive abilities. There are many kinds of neuropsychological tests that evaluate functioning in a number of areas, such as: intelligence, executive functions (such as planning, abstraction and conceptualization), attention, memory, language, perception, sensorimotor functions, motivation, mood state and emotion, quality of life, and personality styles (Philip, 2012).

Now, most of the neuropsychological tests are based on traditional psychometric theory that includes the measurement of knowledge, abilities, attitudes and personality traits. There are wide varieties of neuropsychological tests with different functions and purposes (see Table 2.3). The Wechsler Scales such as the Wechsler Adult Intelligence Scales, Wechsler Intelligence Scale for Children, and Wechsler Memory Scales are among the commonly used tests. The Halstead-Reitan Battery and the California Verbal Learning Test which is under The Trail-Making Test are frequently used to test of auditory supraspan memory. The Halstead-Reitan Battery (HRB) is the commonly used neuropsychological test battery that being utilized by approximately 15% of the neuropsychologists surveyed (Rabin LA *et al.*, 2005). The top 10 tests administered are the Rey Ostereith Complex Figure Test that is a test for construction, planning and visual memory, the Wisconsin Card Sort Test for executive functioning test, and tests of supraspan auditory learning are the Rey Auditory Verbal Learning Test (RAVLT).