ASSOCIATION BETWEEN INCIDENCE OF WHITE MATTER HYPERINTENSITIES IN MAGNETIC RESONANCE IMAGING OF THE BRAIN AND SMOKING

DR MITCHELL MODI MIJOL

DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE

(RADIOLOGY)

UNIVERSITI SAINS MALAYSIA

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BY

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DISCLAIMER

I declare that this dissertation records the results of the study performed by me and that it is of my own composition.

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(MITCHELL MODI MIJOL)

Date:

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LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

CT	Computed Tomography
DICOM	Digital Imaging and Communications in Medicine
FLAIR	Fluid Attenuated Inversion Recovery
MRI	Magnetic Resonance Imaging
PACS	Picture Archiving and Communication System
RIS	Radiology Information System
T2WI	T2 Weighted Images
USG	Ultrasonography
USM	Universiti Sains Malaysia
VIARAD	Visual Interaction Assistant for Radiology
WMH	White Matter Hyperintensities
WHO	World Health Organization

ABSTRAK

HUBUNGKAIT DIANTARA HIPERINTENSITI PERKARA PUTIH DI DALAM PENGIMEJAN RESONANS MAGNETIK OTAK DAN MEROKOK

Latar belakang: Hiperintensiti perkara putih (WMH) merupakan satu penemuan yang biasa dilihat di dalam pengimejan resonans magnet (MRI) otak pesakit yang lebih tua. Terdapat kaitan diantara WMH dengan penyakit dementia dan penyakit Alzheimer. Perkembangan teknologi telah meningkatkan pemahaman tentang patogenesis WMH secara lebih mendalam. Beberapa mekanisme patogenesis telah dicadangkan termasuk mekanisme yang memfokuskan pada anatomi, gangguan penghalang darah otak, autoregulasi aliran darah serebral, kolagenasa vena dan faktor genetik. Beberapa kajian juga menunjukkan perkaitan diantara merokok dengan insiden WMH.

Kaedah: Satu kajian retrospektif telah dilakukan di Hospital USM, Kota Bharu, Malaysia. MRI otak pesakit berusia 18 tahun ke atas yang merangkumi urutan berwajaran T2 (T2WI) dan pemulihan penyonsangan dilemahkan cecair (FLAIR) telah dikaji. Pesakit dengan lesi otak atau kelainan struktur, atau sejarah penyakit yang menunjukkan adanya jangkitan intrakranial, penyakit radang atau proses demyelinating yang berterusan adalah dikecualikan. Data demografi mengenai tahun-pak, usia permulaan / penghentian, tempoh merokok, jenis rokok (dengan penapis, tanpa penapis, rokok elektronik) dikumpulkan dan dianalisis dengan menggunakan kaedah korelasi Pearson, ujian Fisher Exact dan Ujian-T sampel tak bersandar mengikut kesesuaian.

Keputusan: Terdapat hubungan yang signifikan antara usia ($p < 0,001$), status merokok ($p < 0,001$) dalam kumpulan bekas-perokok dan perokok pasif ($p = 0,022$),

dan komorbiditi (p <0,001) dengan insiden WMH. Umur rata-rata peserta dalam kumpulan WMH adalah lebih tinggi daripada kumpulan tanpa WMH (p <0.001). Untuk status merokok, lebih ramai pesakit yang tidak merokok terdapat dalam kumpulan tanpa WMH. Terdapat peratusan peserta yang tinggi tanpa komorbiditi yang dilaporkan dalam kumpulan tanpa WMH (n = 80, 77.7%).

Kesimpulan: Hubungan yang signifikan dijumpai antara usia, status merokok (bekas perokok dan perokok pasif), dan komorbiditi dengan insidens WMH.

Kata kunci: Hiperintensiti Perkara Putih, Merokok dan Penyakit Serebrovaskular, Patogenesis Hipertensiti Perkara Putih.

ABSTRACT

ASSOCIATION BETWEEN INCIDENCE OF WHITE MATTER HYPERINTENSITIES IN MAGNETIC RESONANCE IMAGING OF THE BRAIN AND SMOKING

Background: White matter hyperintensity (WMH) is a common finding on T2 weighted MRI brain or CT Brain among the older subjects. There has been a recognized linkage between the development of Dementia and Alzheimer's disease. Technological advancements in recent years have made the understanding of the pathogenesis of WMHs deeper, with several proposed mechanisms, focusing on anatomy, blood-brain barrier disruption, cerebral blood flow autoregulation, venous collagenases, and genetic factors. Smoking has been postulated to have an influence on WMH in several reports.

Methods: A retrospective study was conducted in Hospital USM, Kota Bharu, Malaysia with MRI brain of patient aged 18 years and above were reviewed. The MRI must include both T2WI and FLAIR sequences. Patients with gross brain lesions, structural abnormalities, and history suggestive ongoing intracranial infection, inflammatory or demyelinating diseases were excluded. Demographic data regarding pack-years, age of initiation/cessation, duration of smoking, type of cigarettes (non-filtered, filtered, e-cigarette) was collected and analysed using Pearson's correlation method, Fisher exact test, and Independent T-test as necessary.

Results: There was a significant association between age ($p<0.001$), smoking status ($p<0.001$) especially in the ex-smoker and passive smoker group ($p=0.022$), and comorbidities ($p<0.001$) with WMH. The mean age of participants in the WMH group was higher than No WMH ($p<0.001$). For smoking status, a higher prevalence of non-

smoker was found in the No WMH group. There was a high percentage of participants with no comorbidities reported to be in the No WMH group (n=80, 77.7%).

Conclusion: Significant association was found between age, smoking status (Ex-smoker and passive smoker), and co-morbidities with WMHs.

Keywords: White Matter Hyperintensities, Smoking and Cerebrovascular disease, Pathogenesis of White Matter Hyperintensities.

CHAPTER 1: BACKGROUND

1.1 Introduction and Problem statement

Based on the latest available National Health and Morbidity Survey (NHMS) in 2006, smoking prevalence among adult males was 46.5% with a mean age of smoking initiation of 18.3 years (Lim *et al.,* 2013). Subsequent study performed shows that by 2015, 1 in 10 Malaysians in 13 to 17 years old age were smokers (Hum, Hsien and Nantha, 2016). Smoking-related diseases such as cardiovascular diseases and cancers are the main global cause of premature death (Mathers and Loncar, 2006). In Malaysia, this is a major problem because smoking-related diseases have been the number one cause of mortality for the past three decades (Ministry of Health Malaysia, 2016). Among the effects of smoking is the effect on the pathogenesis of cerebrovascular diseases.

Effects of smoking on cerebrovascular disease have also been studied in the past, with some studies showing positive correlations. This will be discussed further in our literature review segment. Possible mechanisms for increased risk of cerebrovascular disease are plenty, which includes carboxyhemoglobinemia (Whincup *et al.*, 2006), increased fibrinogen levels (Swarowska *et al.*, 2014), increased platelet aggregability (Pamukcu *et al.*, 2011), and reduced HDL cholesterol (Forey *et al.*, 2013). Among the cerebrovascular changes are white matter hyperintensities.

White matter hyperintensities (WMHs) are areas of abnormal signal intensities on magnetic resonance imaging, predominates in the periventricular and deep white

matter, commonly referred to as white matter lesions. These areas appear hyperintense on T2-weighted image, proton density-weighted image, and fluid-attenuated inversion recovery (FLAIR) MRI sequences (Wardlaw, Valdés Hernández, and Muñoz-Maniega, 2015).

Hopkins et al. in 2005, performed a study with a hypothesis that there should not be WMHs in the normal healthy population. Their results showed that it was uncommon for WMHs to occur in a younger healthy population. Only 5.3% out of their 243 subjects have WMHs, with the median age of the without WMH group was 34.5 years compared to 57.0 years in WMHs (Hopkins *et al.*, 2006).

There are sparse data regarding the incidence of WMHs in relation to smoking especially in young adults, which leads to the question of does smoking affects the incidence of WMHs, especially among the young adults? Therefore, this study is conducted to find the association between WMHs and smoking habits (including e-cigarettes) in MRI brain with age and pack-years as the independent variables.

Objectives

1.1.1 General Objective

To determine the association between the incidence of WMHs and smoking habit in young adult population.

1.1.2 Specific Objectives

1. To compare the proportion of WMHs between smokers and non-smokers.
2. To determine the association between WMHs and pack years.

1.2 Hypothesis

Null hypothesis: WMH has no correlation with smoking status.

1.3 Research Question

Are WMHs more prevalent among smokers than non-smokers?

CHAPTER 2: LITERATURE REVIEW

2.1 White Matter Hyperintensities; The clinical significance

In several studies, white matter hyperintensities have shown clear evidence linking it with cognitive decline and a role in the development of dementia (Debette *et al.*, 2007; Smith *et al.*, 2008; Stewart *et al.*, 2008). Furthermore, vascular factors and cerebrovascular pathologies such as WMHs are increasingly recognized to be involved in the etiology of Alzheimer's disease (Van Dijk *et al.*, 2008). Advancements in technology in recent years have improved the understanding of the WMHs pathogenesis. Several mechanisms were proposed including theories focusing on anatomy, blood-brain barrier disruption, cerebral blood flow autoregulation, venous collagenases, and genetic factors (Lin *et al.*, 2017).

2.2 White Matter Hyperintensities; Pathogenesis and Pathophysiology

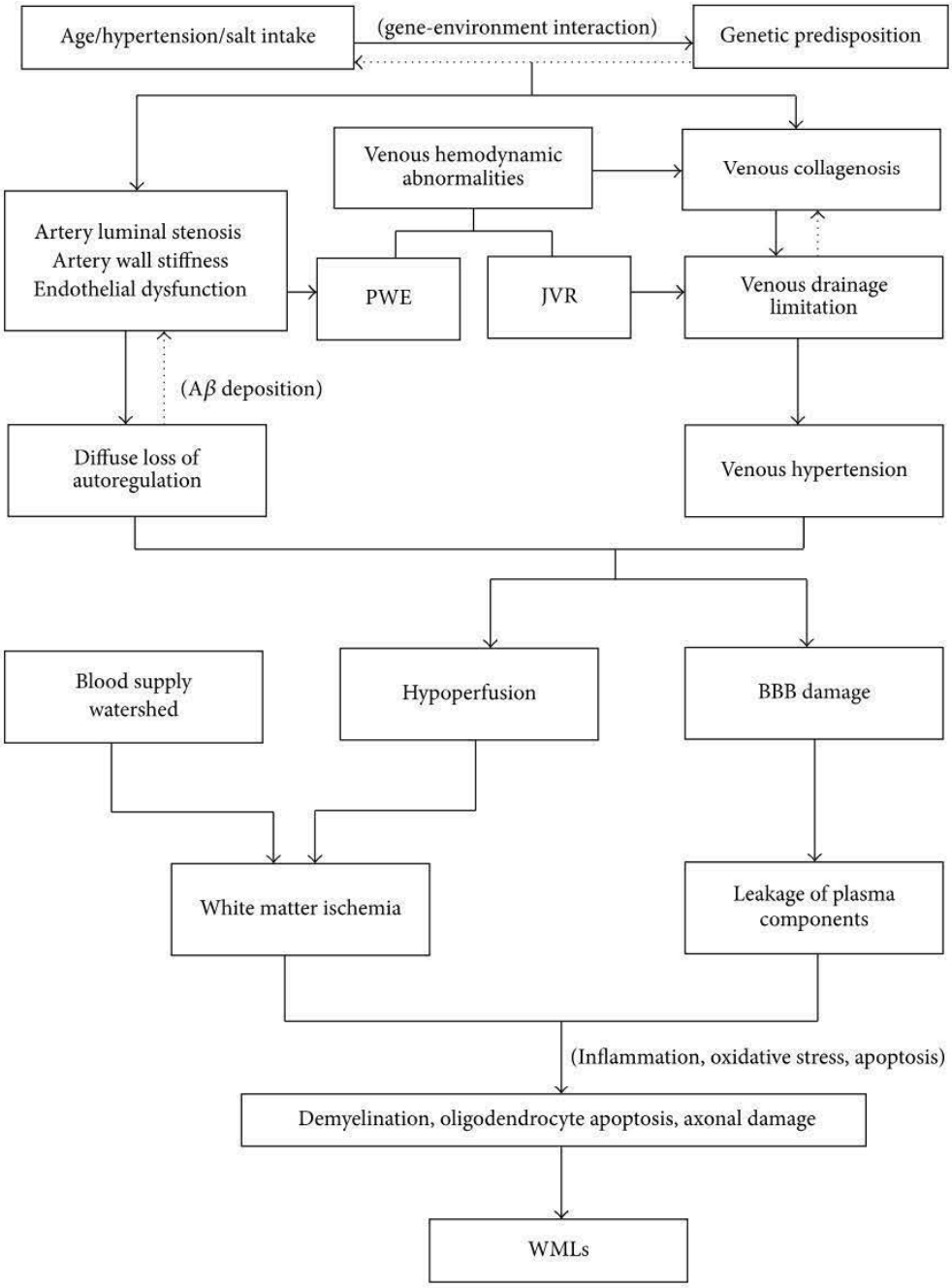
Periventricular white matter obtains its blood supply primarily through long perforating branches and ventriculofugal vessels. These two terminal vessels sparsely communicate with each other, forming a blood supply watershed region, which predisposes the periventricular white matter to ischemic damage (Rowbotham and Little, 1965). Subcortical white matter receives its blood supply mainly through the short branch arteries originating vertically from the long perforating branches, which have a long and tortuous course, near the subcortical white matter. These anatomical characteristics make it susceptible to hypoxic-ischemic damage (Rowbotham and Little, 1965).

The two most common subtypes of acute ischemic stroke, large atherosclerosis, and small artery occlusion, cause impairments of dynamic cerebral autoregulation (dCA) in differing ways. Several studies have shown that large artery atherosclerotic strokes cause worse ipsilateral dCA than contralateral dCA, and postulated that hypoperfusion resulting in angiectasis and limiting the vessels' ability to expand and accommodate the increased demand for blood supply (Reinhard *et al.*, 2004; Immink *et al.*, 2005). While large atherosclerotic causes preferential ipsilateral dCA, small artery occlusion causes extensive cerebral small vessel disease in both sides of the brain (Guo *et al.*, 2015).

Venous ischemia is also gaining some attention as one of the causes of WMHs. A study was done by Chung et al. in 2011 which interestingly demonstrated that groups with severe jugular venous reflux (JVR) had increased WMHs compared to groups without JVR (Chung *et al.*, 2011). This phenomenon was also observed in a case study of two patients done by Waragai et al. in 2006. The patients with dural venous fistula initially presented with symptoms of dementia underwent selective embolization of the dural arteriovenous fistula. Post embolization, both patients cognitive functioning improved drastically. MRI pre- and post-embolization showed a reduction of WMHs (Waragai *et al.*, 2006).

The blood-brain barrier (BBB) is a term used to describe the central nervous system's microvasculature, which consists of continuous non-fenestrated vessels with additional unique properties to allow for the exchange of ions and solutes across it (Daneman, 2012). A study done by (Young, Halliday, and Kril, 2008) examined 23 brains with in vivo MRI and histological as well as immunohistochemical stains. Results showed that brains with WMHs showed a significant reduction of p-

glycoprotein expression in areas of WMHs compared to areas of normal white matter region, indicating BBB involvement in areas of WMHs.



Jing Lin et al. Multiple factors involved in the pathogenesis of white mater lesions.

2.3 Smoking and WMH

Cigarette smoking is a risk factor for stroke. A cross sectional study with a representative sample of 21445 adults in Malaysia by Lim et al. shows that the overall prevalence of smoking was 22.8%, with the majority of smokers observed in males and more than half (59.3%) within age range of 25 to 44 years(Lim *et al.*, 2018). Active light smokers are those who smoke less than 20 cigarettes a day, while heavy smokers are those who smoke 20 or more cigarettes a day. Both this group had a significantly higher risk for stroke than non-smokers according to a study done by Hatta et al. (Hata *et al.*, 2011), individuals who were exposed to environmental tobacco smoke (ETS) also have an increased risk of developing stroke compared to non-smokers (Bonita *et al.*, 1999).

The mechanism of how stroke occurs by smoking has been a topic of interest over the past few years. Baldassarre et al. did a study that showed a significant dose-dependent relationship between smoking and carotid intima-media thickness, a marker for subclinical atherosclerosis (Baldassarre *et al.*, 2009). Endothelium dysfunction is an early feature of atherogenesis (Łuszczewski *et al.*, 2007). A study done by (Celermajer *et al.*, 1996) showed statistically significant impaired flow-mediated dilatation in groups exposed to ETS compared to control groups.

Several studies have shown a significant association between smoking and WMHs. A longitudinal study done by Power et al. showed that current smokers for at least six years and increasing pack years are associated with WMH progression, further demonstrating a dose-dependent association (Power *et al.*, 2015). A

retrospective study by Kim et al. similarly showed a higher burden of WMHs in cigarette smokers particularly in the elderly (Kim *et al.*, 2012).

Another study with a younger subset of the population (mean age, n=17.8 years), using diffusion tensor imaging to assess axonal integrity and intercellular space change, found a significant difference in fractional anisotropy and mean diffusion sensitivity between regular smokers compared to irregular and non-smokers (Van Ewijk *et al.*, 2015). However, it is not possible to interpret the data further using the currently available neurobiological data. The study's result is comparable to a study done by Gons et al. in many elderly patients (mean age, n= 65.6 years) (Gons *et al.*, 2011).

2.4 Other risk factors

Other risk factors for the development of WMHs have been studied, with several of these studies suggesting an association with vascular risk factors such as hypertension and diabetes. A study done by Brunnereau et al. showed that hypertension was associated with an increased risk of having severe WMHs, and higher blood pressure reading was associated with a higher risk of developing severe WMHs (Brunnereau, Alpérovitch, and Tzourio, 2001). The main assumption of the etiology of WMHs in this study agrees with one of the aforementioned theories in which WMHs are a consequence of cerebral hypoperfusion with resultant ischemia and cell damage.

A different study in 2003 showed that there is an increase in the frequency of the white matter lesions in the periventricular region in a subset of patients with long-standing type 1 diabetes complicated with diabetic retinopathy. Periventricular white

matter lesions were also encountered frequently, present in one-third of scans (Ferguson *et al.*, 2003). These changes have been attributed to cerebral diabetic microangiopathy as the proponent for WMHs formation which results in brain matter hypoperfusion.

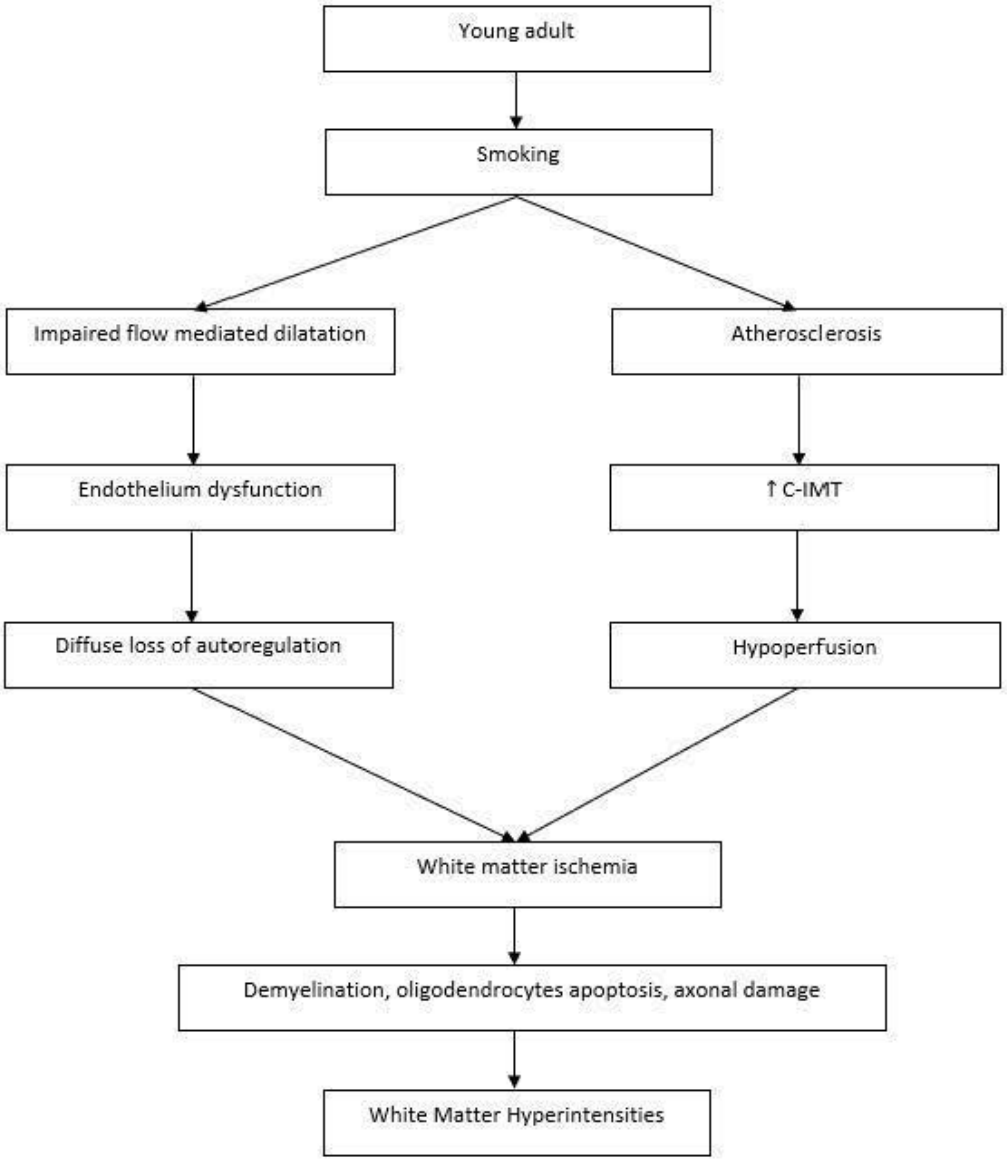
2.5 Imaging Modality of Choice

A study was done by Ferguson et al. which compared calculated volumes of the same lesions on both computed tomography (CT) and magnetic resonance imaging (MRI) of the brain. The study reveals that more lesion volumes were detected in T2 weighted image and Fluid Attenuated Inversion Recovery (FLAIR) sequences of the MRI (314.38 mm^3) compared to CT (239.6 mm^3) (Ferguson *et al.*, 2018). Based on the increased sensitivity of the pick-up rate for WMH, MRI is chosen as the imaging modality of choice in this study.

2.6 Young adults

There are multiple definitions for young population age group classification, World Health Organization (WHO) defines it as 'Youth' covering the age range of 15-24 years while the 'young' group covers the age range 10-24 years. United Nations defines those persons ages of 15 to 24 as youth. A study done by Hammond et. Al on the smoking behaviour among young adults defines 'young adults' covering the age range of 18-29 years (Hammond, 2005). For our study, the age group from 18 to 29 will be taken as young adults.

2.7 Conceptual framework



2.8 Rationale of the study

As mentioned above, WMHs and smoking are associated with the development of cerebrovascular diseases, with multiple studies showing positive correlation between smoking status and WMHs. Most of previous studies have only included older age groups in their studies. Such patients might also have other WMHs confounding factors such as underlying diabetes or hypertension. Meanwhile, the increasing popularity of e-cigarettes, which is claimed to promote early initiation of smoking, is also troubling (Barrington-Trimis *et al.*, 2016). A survey done by Ab Rahman et al. on the prevalence of e-cigarettes in Malaysia shows that the overall prevalence of current and dual users of e-cigarettes are 3.2% and 2.3% respectively. The survey have also shown that the current e-cigarettes users were more prevalent in younger adults (age range 24 to 44 years), males, and current cigarette smokers (Ab Rahman *et al.*, 2019). New data regarding the impacts of smoking (including e-cigarettes) on the cerebrovascular system are much needed, particularly in the young adult subset, to derive new data on potential hazards of smoking on the cerebrovascular system.

CHAPTER 3: METHODOLOGY

3.1 Study Design

This was a retrospective study conducted in Hospital Universiti Sains Malaysia, Kota Bharu, Malaysia for a period of 24 months from May 2018 to December 2020. Data from 1st June 2018 – 31st May 2020 were reviewed.

3.2 Sample Population

i. Reference population : Kelantan Population

ii. Source population : Subjects coming to Hospital Universiti Sains Malaysia (USM) for treatment or follow-up.

iii. Target population : Subject who were referred for MRI brain in Hospital USM.

3.3 Sample Size Calculation

1. For specific objective 1:

In a study within a healthy population aged between 16 and 65 years old, the prevalence of WMHs is 5.3% (13 out of 243) (Hopkins *et al.*, 2006). In another study done by Qing Lin et al. among 4683 patients hospitalized for various reasons; 32.7% of smokers were found to develop a worse degree of WMHs compared to non-smokers (Qing Lin et al., 2017). Based on these two studies, we calculated the sample size using these values.

Alpha = 0.05 (The Type I error probability for a two-sided test. This is the probability that we will falsely reject the null hypothesis.)

Power = 0.8 (The probability of correctly rejecting the null hypothesis that the relative risk (odds ratio) equals 1 given *n* case-patients, and a Type I error probability α).

P_0 = 0.053 (For case-control studies, p_0 is the probability of exposure in controls. In prospective studies, p_0 is the probability of the outcome for a control patient).

P_1 = 0.2 (For case-control studies, p_1 is the probability of exposure in cases. In prospective studies, p_1 is the probability of the outcome in an experimental subject).

m = 4 (control patients per case-patients). Based on the two aforementioned studies above, 5.3% vs 32.7%, m value of 6.2 is obtained. However, a conservative value of 4 is chosen in this study.

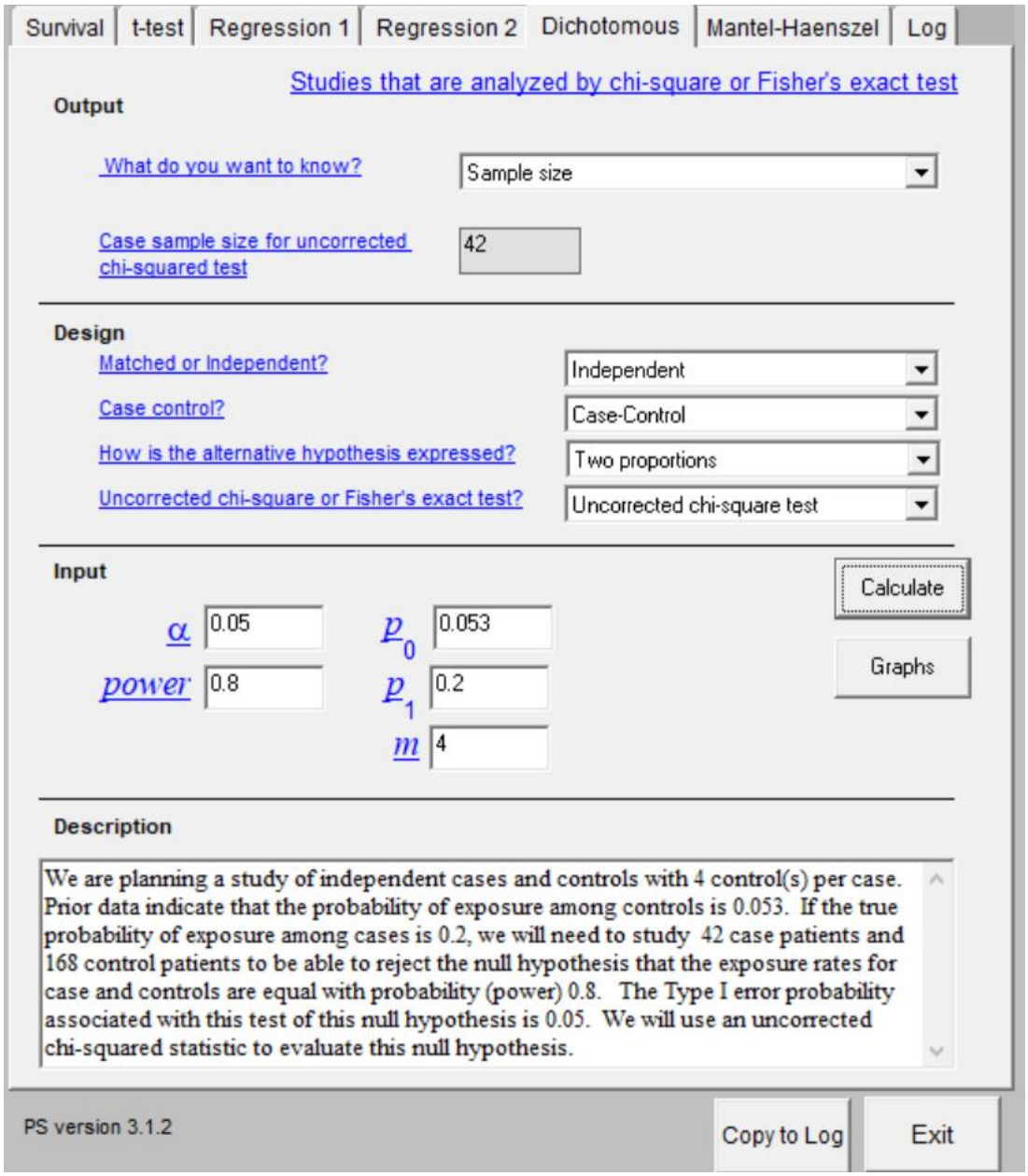
The case sample size for uncorrected chi-square test: 42

Sample needed for control = 42

Sample needed for non-control = 168 (42 x 4)

Total samples needed = 210

If dropouts are to be considered; with an estimated 10% drop-out, the total sample needed = 231



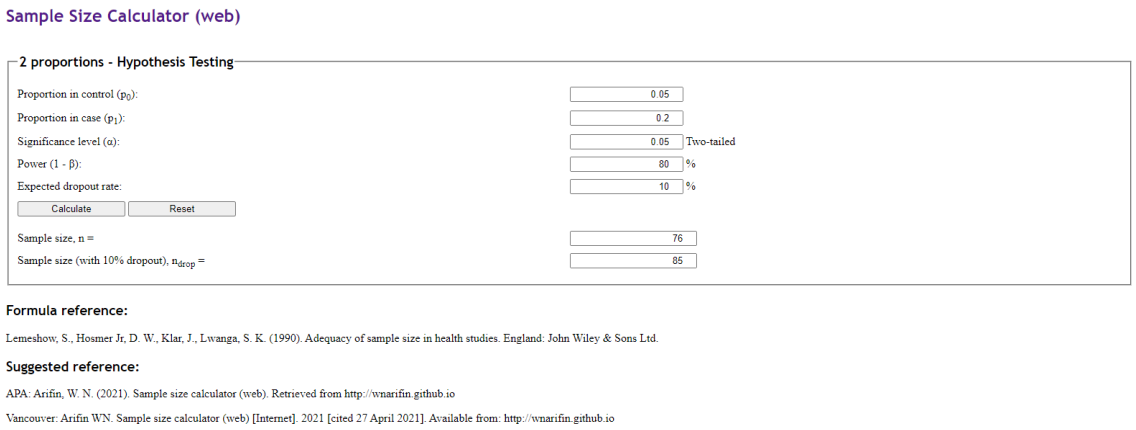
2. For specific objective 2:

Using the same p values in objective 1,

$P_0 = 0.053$

$P_1 = 0.2$

With an expected drop-out of 10%, the total sample size required is 85.



3.4 Sampling Method

Simple random sampling.

3.5 Inclusion Criteria

1. Adult age >18 years old.

2. Brain MRI with T2WI and FLAIR sequences.

3.6 Exclusion criteria

1. Gross brain lesions or structural abnormalities other than WMHs.

2. History suggestive of ongoing intracranial infection, inflammatory or demyelinating diseases.

3.7 Research tools

1. Hospital USM Picture and Archiving System (PACS) GE Medical systems (The United States) Version 6.0 for viewing Digital Imaging and Communications in Medicine (DICOM) images. DICOM images are the format in which MRI images (and other modalities imaging such as CT, USG, Mammogram etc.) are processed and stored within.

2. MRI Philips 3 Tesla Achieva Scanner (Netherlands).

3. Radiology Information System (RIS), which are stored in the Visual Interaction for Radiology 5 (VIARAD5) database (Viamed, Seremban).

3.8 Operational Definition

WMH	:	White matter lesions appearing as hyperintensities on T2WI and FLAIR imaging sequences[4].
Pack years	:	Packs of cigarettes per day multiplied by the number of years.
Active smoker	:	Person who smoked at least one cigarette a day, for the last 6 months[23].
Ex-smoker	:	Person who previously regularly smoked (more than 6 months), but who had not smoked in the previous month.
Exposure to ETS	:	Exposure to cigarette smoke due to household member regularly smoked in their presence, or co-worker smoked in the same indoor room in their presence for more than one year during the past ten years[23].
Young adult	:	Age group 18 to 29.

3.9 Data Collection

Patient Selection

Data are collected from the Radiology Information System (RIS), which is stored in Visual Interaction for Radiology 5 (VIARAD5). All requests, appointments, and reports are stored here. Images from patients who did MRI brain in Hospital USM and fulfilled the inclusion and exclusion criteria were selected and reviewed.

Secondary Data Acquisition

The history of patients whose images were selected will be reviewed. If secondary data are inadequate, the patient was contacted via telephone. Verbal consent was obtained before questioning, which includes the reason for calling, explanation of the study process, data storage, and confidentiality were explained to patients. If the individual verbally consents, more data were obtained via direct questioning. Data collected via phone calls were recorded in our data collecting form (Annex 1).

Information regarding demographic data, smoking status, pack-years, age of initiation/cessation, smoking duration, type of cigarettes (non-filtered, filtered, e-cigarette) was acquired; either from history written in VIARADS or acquired from the patient via phone call.

Information collected was documented in the datasheet, without the patient's identifying information. Patients' data were labelled with a unique serial research

number to maintain the privacy and confidentiality. This information was saved in a password-protected computer and accessible only to the research team members.

MRI

Our study was conducted on a 3 Tesla MRI scanner (Philips 3-Tesla Achieva MR Scanner). The patient was put on head coil in the supine position, headfirst. The patient was scanned in from vertex to base of skull. Standard imaging parameters for both sequences, T2WI and FLAIR sequences were used. The parameters for T2WI sequence are as follows; TE /TR 80/3000ms, matrix 512 x 512; FOV 230.0x 230.0, NEX 1.0; slice spacing 1.0mm, slice thickness 5.0mm, flip angle 90. The parameters for FLAIR sequence are as follows; TE /TR /TI 125/ 11000/2800ms, matrix 512 x 512; FOV 230.0x 230.0, NEX 1.0; slice spacing 1.0mm, slice thickness 5.0mm, flip angle 90. No extra contrast administration was given in our study.

Data validation

The presence or absence of WMHs was determined by the investigator, validated by a radiologist (Dr. Chandran Nadarajan) who has more than five-years of experience as a clinical radiologist. Data obtained will then be recorded and analyzed by the investigator.

3.10 Statistical analysis

All data were analyzed using Statistical Product and Service Solutions (SPSS) for Windows, SPSS Inc.© (Version 26, SPSS Inc., Chicago, IL, USA). The descriptive statistics for discrete variables (gender, smoking status) were presented as n=frequency (%), and the continuous variables (age, pack-years) were presented as mean, standard deviation, and 95% CI.

Statistical analysis was presented on figures and tables.

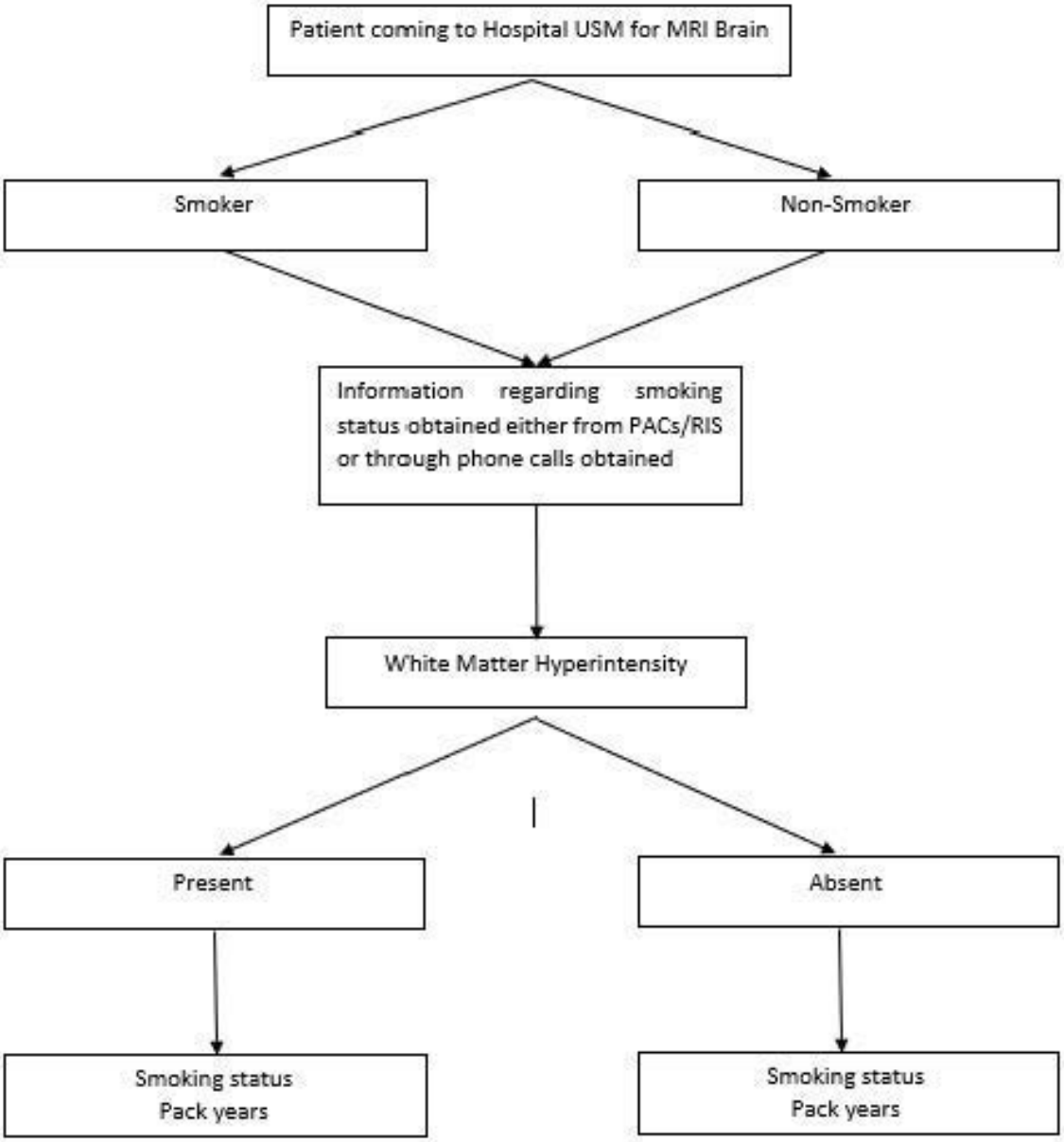
3.11 Confidentiality and Privacy

Unique serial research numbers identified the subjects. No individual patient identifiable data were shared publicly. Upon completion of the study, all data were stored in a password-protected computer. This computer is only able to be accessed by the research team members. The researchers retained the data for knowledge purposes only. The data will be presented as collective data. Neither the name nor any identifying information was used in any publication or presentation resulting from this study.

3.12 Ethical Consideration

The study was approved by the Human Research Ethics Committee of Universiti Sains Malaysia (JEPeM code: USM/JEPeM/20010074), which complies with the Declaration of Helsinki (see Appendix).

3.13 Study Flow Chart



CHAPTER 4: MANUSCRIPT