EFFECT OF PHYSICAL ACTIVITY ON PROGRESSION OF CEREBROVASCULAR DISEASE IN OLDER ADULTS AT RISK OF ALZHEIMER'S DISEASE

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Abstract:

Objective: Alzheimer's disease (AD) is a form of dementia without cure. Dementias are the only condition out of the top 10 causes of mortality worldwide without cure and represent a significant health burden. White matter hyperintensities (WMH) are a biomarker of brain white matter disease, and are associated with a number of neuropsychiatric disorders including dementia. WMH progression has been shown to be reduced by vascular risk factor (VRF) control. Physical activity (PA) has also been shown to slow the progression of WMH, control VRF related disease and has also been shown to reduce cognitive decline. It is therefore postulated that PA can slow WMH progression and could perhaps be a lifestyle related treatment that slows cognitive decline, which would have great public health implications. Conventional manual segmentation (CMS) is the current gold standard in WMH volumetry. Side-by-side (SBS) segmentation has shown promise in WMH visual rating scales and other areas in radiology but has not yet been applied to manual segmentation of WMH lesions.

We hypothesise that PA slows WMH progression, and this progression is slower in ApoE ε4 and PET Amyloid beta status negative patients. We also hypothesise that there is a concomitant positive association between baseline cognition measures and WMH progression. Finally, we hypothesise that side by side segmentation will give WMH volumes with more significant clinical associations than the traditional segmentation methods.

Method: Data was obtained as part of the AIBL Active trial. Participants are older adults at risk of AD with at least one VRF. Imaging data was obtained on a Siemens 3T Tim Trio scanner. Images were processed according to accepted standards, with FLAIR images used for WMH volumetry, and MPRAGE images used to obtain estimated total intracranial volume (ETIV). WMH were manually segmented under expert neuroradiologist guidance (A/Prof P. Phal), firstly obtaining CMS volumes and then SBS volumes. These volumes were corrected for ETIV and log transformed, then compared against age, gender, VRF, baseline functional fitness, Years of education, cognitive group (SMC/MCI) and baseline neurocognitive assessments using correlations, and subsequently general linear models.

Results: In older adults at risk of AD with at least one VRF, exercise over a 24 month period was not associated with a slowing of WMH progression. There was also no association between baseline functional fitness assessment and WMH progression. ApoE ε4 and PET Amyloid beta status were also not associated with a slowing of WMH progression. We did find correlations between WMH volume and age with both methods, with baseline WMH significantly predicting progression. Systolic blood pressure was also associated with WMH progression in correlations in the CMS general linear model. Anxiety was inversely associated with WMH progression while other cognitive measures were not. Side-by-side manual segmentation did not result in significant clinical differences compared to conventional manual segmentation.

Conclusion: Based on our results we were unable to show effectiveness of physical activity in older adults at risk of AD in slowing WMH progression. We also cannot conclude that SBS WMH segmentation is more effective than accepted methods.

Declaration:

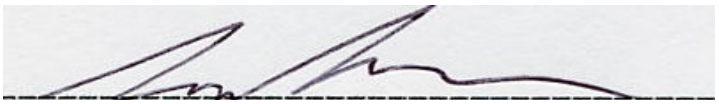
I hereby declare the following:

(1) This thesis comprises only my original work towards the degree of Doctor of Medical Science

(2) Due acknowledgement has been made in the text to all other materials used

(3) This thesis is fewer than 100,000 words in length, excluding tables, figures and references.

Signed:



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ABBREVIATIONS:

Aβ – Beta – Amyloid

ACH – Amyloid Cascade Hypothesis

AD – Alzheimer's disease

ADAS-Cog – Alzheimer's disease assessment scale - cognitive section

AD/LH – Arteriosclerotic disease and Lipohyalinosis

ApoE – Apolipoprotein E

B_o – Convention in MRI physics used for representation of a magnetic field

BMR – Basal Metabolic Rate

BRIEF-A – Behaviour Rating Inventory of Executive Function - Adult version

CAA – Cerebral Amyloid Angiopathy

CH_2 – Carbon – Hydrogen (2) – representation of hydrocarbons

CmsWMH – Conventional Manually Segmented White Matter Hyperintensities

CBF – Cerebral Blood Flow

CSF – Cerebrospinal Fluid

CT – Computed Tomography

DTI – Diffusion Tensor Imaging

DWMH – Deep White Matter Hyperintensities

FA – Fractional Anisotropy

FLAIR – Fluid Attenuated Inversion Recovery

fMRI – Functional Magnetic Resonance Imaging

FT – Fourier Transform

GWAS – Genome Wide Association Studies

HADS-A – Hospital Anxiety and Depression Score - Anxiety results

MAC – Microtubule Assembly Complex

MCI – Mild Cognitive Impairment

MEG – Magnetoencephalography

MRI – Magnetic Resonance Imaging

MTI – Magnetic Transfer Imaging

NAWM – Normal Appearing White Matter

NIH – National Institutes of Health

NFTs – Neurofibrillary Tangles

NMR – Nuclear Magnetic Resonance

PA – Physical Activity

PET – Positron Emission Tomography

PET Amyloid – PET scan examining cerebral amyloid load

PIB – Pittsburgh compound B

PVWMH – Peri Ventricular White Matter Hyperintensities

RF – Radio Frequency

SbsWMH – Side-by-Side (manually segmented) White Matter Hyperintensities

SITs – Sit to stand test

SMC – Subjective Memory Complaints

SPECT – Single Photon Emission Computed Tomography

T1 – T1 Weighted image

T2 – T2 Weighted Image

T (Unit) – Tesla

TUG – timed up and go

VRF – Vascular Risk Factor

WMH – White Matter Hyperintensities

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CHAPTER 1 LITERATURE REVIEW

1.1 Introduction

1.1.1 Introduction and overview

With an ageing society come changes of disease prevalence. The most common dementia, Alzheimer's disease will be presented before discussing physical activity and the relationship between the two. Medical Imaging followed by white matter hyperintensities will then be discussed, finishing with the study design and hypothesis.

1.1.2 Ageing

Ageing represents change over time. As we grow old, we deteriorate independently of disease (Bowen and Atwood 2004). "Healthy ageing" requires functional mobility, conserved mental capacity and being a productive member of society (Rowe and Kahn 1997). Normal ageing includes muscle mass loss, worsening coordination, slowing metabolism, and diminishing senses (Besdine, 2013). Slower memory and forgetfulness is normal, however dementia is not.

1.1.3 Dementia

Dementia is a chronic neurodegenerative syndrome affecting memory, orientation, learning and comprehension, encompassing different brain pathologies. Not every ageing patient gets dementia (Price and Morris 1999 and Jack et al. 2010). Patients with subjective memory complaints (SMC) and mild cognitive impairment (MCI) are at increased risk. SMC patients feel they have deteriorating cognition but have no objective deficit on cognitive testing (Van Oijen et al. 2007). MCI requires testing deficits, but not enough to be classified as dementia (Petersen 2011). Also, not every SMC or MCI patient gets dementia.

Dementia affects approximately 35.6 million people worldwide and will triple by 2050 (Alzheimer's disease International 2009). In Australia between 2003 and 2012, dementia rose from 6th to 3rd commonest mortality (Australian Bureau of Statistics 2014). The only untreatable in the top 10 most prevalent conditions, globally cost US$604 Billion in 2010 (Lanctôt et al. 2009, Alzheimer's disease International 2010). Upsetting for patients and family, it was labelled as a public health priority in 2012, recognising "research evidence should underpin actions and is a critical element of the overall package of global dementia efforts" (World Health Organisation 2012, Alzheimer's disease International 2013).

1.2 Alzheimer's Disease

1.2.1 Introduction and definition

First described by Alois Alzheimer, it was named after him after he described a patient suffering from short term memory loss, and behavioural problems. She slowly deteriorated and after her death in 1906 he examined her brain. After staining microscope specimens, he noted senile plaques and neurofibrillary tangles (NFTs), which became synonymous with the condition. He presented the case of memory loss and behavioural problems, coupled with the observed neuropathological changes. The condition was named after him in 1910 (Berchtold et al. 1998).

AD is defined classically as gradual onset memory impairment, apathy and depression, coupled with senile plaques and neurofibrillary tangles. Macroscopically there is hippocampal and cortical atrophy, with dilation of ventricles (Serrano-Pozo et al. 2011). It represents around 75% of dementias and is common to have mixed dementia (Alzheimer 's disease International 2009). There is controversy defining mixed dementia, but is generally accepted as more than one dementia in a patient (Alzheimer's Association 2011, Massoud 2012).

Patients can be classified as Late Onset Alzheimer's (LOAD), those over 65, around 95% of cases, and Early –Onset Alzheimer's (EOAD) around 5% of cases and under 65(Reitz and Mayeux 2014). Those with genes that invariably cause AD have Familial AD (FAD), the majority of whom are younger patients. Non-familial AD occurs from sporadic mutations and can be LOAD or EOAD.

1.2.2 Clinical phenotype

Division into clinical stages gives diagnostic and prognostic information (Reisberg et al. 1982). The 7 stage Global Deterioration Scale for Dementia is common. Representing typical AD progression, stages 1 to 3 are pre-dementia and 4-7 dementia.

(1): No cognitive decline

(2): Subjective memory complaints

(3): Mild cognitive impairment

(4): Mild Dementia: difficulty with memory of events and gaps in personal history, starting to affect daily life (finances, travel). Flattening affect and difficulty recognising faces. Denial now dominant to cover this up

(5): Moderate Dementia: defined now as inability to live unaided. Further memory deterioration, now forgetting close family. Often getting lost and disoriented. Starts to dress inappropriately

(6): Moderate-Severe Dementia: Now unaware of surroundings and close relatives. Diurnal disturbance and incontinence emerge. Delusional and aggressive behaviour emerge.

(7): Severe dementia: Loss of speech and continence. Often bedbound, loss of basic motor abilities such as feeding self, flat affect. Death often from other causes: pneumonia, sepsis.

1.2.3 The Cause of Alzheimer's disease

AD is a neurodegenerative disease, taking decades to appear, which results in difficulty in characterising pathology and diagnosis (Bateman et al. 2012). Although invariably involving amyloid (senile) plaques and neurofibrillary triangles, the exact pathological process is unknown, it is not known whether they primarily cause AD or are a marker of another process. The relation of each to cognition is also unclear and variable due to cognitive plasticity and likely other parts of the disease pathway are yet to be identified (Katzman et al. 1988). Differentiating AD from other dementias is difficult as they can be clinically similar and mixed dementia is common.

Amyloid and tau are present in AD, but it is not clear which is present first, therefore being the cause of the other. There are groups of thought, those who believe Amyloid appears first and those who believe tau appears first. Each is supported by a number of experimental and observational studies, but there is no clear consensus despite increasingly finer details about each area being uncovered. Currently, amyloid appearing first has more popularity than tau, but this may change in future with further progress in each field. Despite the controversy, this stage of the pathogenesis is important to know as amyloid and tau are both present in the disease and are so integral to classifying AD, biomarker development and its prognosis.

1.2.4 Amyloid

In 1984 amyloid protein was identified by Glenner and Wong and later shown to be the main component of senile (amyloid) plaques (Masters et al. 1985). There has since been much research into it (Masters and Dennis 2012). In 1987 Kang et al. identified that amyloid is formed from a trans-membrane protein, called amyloid precursor protein (APP). APP is thought to be involved in neural activity, plasticity and memory (Priller et al 2006, Westmark 2013) but its exact role is unknown (Nalivaeva and Turner 2013). APP is cleaved by beta-secretase then gamma-secretase to give the protein known as beta amyloid, Aβ (Vassar et al, 1999, Chen et al. 2006). Cleavage by alpha secretase is the main process acting on APP, resulting in a soluble product which does not form plaques.

The creation of plaques from insoluble Aβ resulted in some classifying AD as a "storage disorder disease". As well as alpha secretase breakdown, Amyloid beta is normally cleared by astrocytes/microglia, plasmin/neprisylin and transported (actively and passively) into the blood and Cerebrospinal fluid (CSF). Failure of breakdown and clearance is a commonly proposed mechanism of how amyloid accumulates and contributes to the pathogenesis of AD (Zlokovic and Frangione 2003). Aβ is an amino acid protein (Hartmann et al. 1997), varying from 36 to 43 amino acids. The 40 variant is most prevalent *in vitro* while the 42 variant is most common in plaques (Jarrett et al. 1993). The exact mechanism of plaque formation is not yet understood.

Amyloid plaques are deposited in a hierarchical manner, commencing in the entorhinal cortex, the junction between the hippocampus and neocortex (Serrano-Pozo 2011). It then spreads to areas adjacent to the neocortex followed by diencephalic nuclei, striatum and cholinergic nuclei in the basal forebrain. Next are brainstem nuclei and it finally spreads to the cerebellum (Thal et al. 2002).

Roughly mirroring this is the deposition of amyloid in blood vessels, termed cerebral amyloid angiopathy (CAA). Thal et al. demonstrated in 2003 that CAA commences in the cortical and leptomeningeal vessels of the neocortex. Next allocortical vessels (cingulate gyrus, entorhinal cortex and hippocampus), cerebellum and midbrain vessels are involved. Later, basal ganglia, thalamus and lower brainstem vessels are affected. In contrast to this, arteriosclerosis and lipohyalinosis (AD/LH) starts with the basal ganglia or cerebral white matter. It then progresses to deep white matter, cortical leptomeningeal arteries, thalamus and cerebellum. Finally it involves the vessels of the brainstem and hypothalamus.

Beta amyloid originates inside neurons then transported extracellularly, resulting in plaque formation. Whether these are reactionary to another factor or primary is the subject of many theories. The most popular theory is the “Amyloid Cascade” theory in which it is stipulated that the primary cause of AD is amyloid followed by Tau. The amyloid cascade hypothesis (ACH) was first put forward by Hardy and Higgins in 1992 and has remained the dominant hypothesis ever since. ACH states that the main causative aetiology for AD is the deposition of amyloid beta protein. It is proposed that this is followed by NFT and subsequently cellular damage, loss and then finally dementia. This is backed up by observations that APP is present on chromosome 21 and trisomy 21 patients exhibiting early AD, thought to be due to the extra copy of APP encoding genes (Goldbager et al. 1987, Robakis et al. 1987, Tanzi et al. 1987). It has been found that plaques contain a mixture of beta amyloid, and chronic inflammatory mediators and innate immune system mediators. This mixture has led to differing lines of investigation to whether AD is immune or inflammation related.

It is thought that there are multiple stages of plaque formation, going from active to “burnt out”. The difficulty in teasing out the mechanism of AD lies in the fact that the disease occurs “silently”, progressing with chronic amyloid deposition. Over these years the amount deposited increases but the brain is able to “work around” the dysfunctional circuitry by rewiring and connecting via alternate pathways (neuroplasticity). Once this plasticity is overcome, there is no cognitive reserve left and the patient starts to exhibit the signs of memory loss and dementia (Stern 2002).

However, there are some normal patients with high amyloid load and some patients with minimal load but debilitating cognitive changes. There must be more to AD than amyloid. AD is a multifactorial disease, caused by multiple factors and exacerbated by lifestyle and environmental factors. The presence of tau adds another layer of complexity to AD as there is not clear order of amyloid and tau deposition and they are also separated anatomically. A decrease in CSF level of Aβ has been shown to correlate with AD (Dubois et al 2014).

1.2.5 Tau

Tau is the main component of NFT (Grundke-Iqbal et al. 1986, Kosik et al, 1986 and Wood et al. 1986). It is part of the microtubule assembly complex (MAC) within cells, being integral to microtubule assembly with other microtubule assembly proteins (Weingarten et al. 1975). Microtubules are part of the cytoskeleton, dictating cellular shape, movement and function (Maccioni and Cambiazo 1995). Tau is normally soluble and as part of the MAC it stabilises microtubules (Bré and Karsenti 1990). Phosphorylated Tau is unable to join the MAC and microtubules disassemble. This is part of normal cellular activity (Cleveland et al., 1977). Phosphorylating many of Tau's phosphorylation sites creates "hyperphosphorylation" aggregate formation (Jameson et al. 1980 and Lindwall and Cole, 1984). Tau is present in another number of conditions (tauopathy) including post head-trauma so it is thought that tau is reactionary than causative in AD.

Tau is deposited in a reproducible manner, which lead to Braak and Braak staging. This staging follows the distribution from entorhinal (stages I/II), to limbic (stages III/IV) and finally neocortical (V/VI) areas (Braak and Braak 1991). The stages mirror the progression for normal cognition, through cognitive impairment and through to AD. The Braak and Braak stage progression correlates with increasing cortical atrophy. An increase in tau protein in the CSF (total tau, T-tau or phosphorylated tau, P-tau) correlates with the presence of AD (Dubois et al 2014).

1.2.6 Other Aetiologies

It is still unclear what causes AD and work is ongoing. The cholinergic hypothesis first appeared after a loss of cholinergic activity in the brains of AD patients was observed (Davies and Maloney, 1976 and Perry et al. 1981). It was suggested that reduced cholinergic activity could trigger AD but age-matched normal patients also showed a decline (Perry et al. 1992). It is more now widely accepted as a phenomenon of ageing. Growing consensus supports simultaneous aetiologies acting together (Craig et al. 2011). There is additionally growing opinion that AD pathology is closely linked with vascular disease, and perhaps even a vascular disorder (De la Torre, 2010). There is much work being done to identify the pathological pathway, which is likely multifactorial.

1.2.7 Risk Factors

The single highest risk factor for AD is age, with the vast majority of AD patients being over 65. The prevalence of AD markedly increases over 65, from approximately 2% at 65, doubling every 5 years to being approximately 30% chance of having AD at 85 and older. Figures vary with participant makeup (e.g. white vs Hispanic or blacks) and how AD is diagnosed (diagnostic criteria, CSF marker use or if using census data) but patterns are similar (Prince et al. 2013, Ott et al. 1995, Rizzi et al. 2014). Diabetes, hypertension and obesity, depression, low education, low mental activity, physical activity and smoking are also risk factors (Barnes and Yaffe 2011). Often multiple factors co-exist, even so, these are together responsible for 28.2% of cases of AD (Norton et al. 2014).

1.2.8 Genetics

Genes are divided into 'risk' genes that increase the likelihood of AD but do not guarantee it will occur and 'deterministic' genes, those that guarantee those with the genetic changes will get AD. The true nature of interactions with genes, environmental factors and pathology is complex and far from being fully understood.

The risk gene with strongest influence is a variant of Apolipoprotein E – Epsilon 4 variant (APOE-e4 the 4/4 genotype). It has been implicated in up to 64 % of sporadic late onset AD and 80% of familial AD cases (Corder et al. 1993). Other variant of ApoE have normal risk while the genotype ApoE 2,3 is considered lower than normal risk of contracting AD (Corder et al. 1994). Risk genes numbers are growing, including PICALM, CLU, CR1, BIN1, MS4A, CD2AP, EPHA1, ABCA7, SORL1 and TREM2 (National Institutes of aging 2014). Genome wide association studies (GWAS) are continuing to yield more results. These studies will continue to probe for further genes, which can give insight into some pathways that cause AD (Kim et al. 2014a).

Deterministic genetic mutations include APP (and trisomy 21), PSEN1, PSEN2 genes (Bertam and Tanzi, 2012). These mutations use Mendelian transmission, the presence of which results in familial AD.

1.2.9 Diagnosis

Diagnosis of AD is made primarily on clinical grounds, requiring typical or atypical AD phenotypes, and exclusion of other causes of dementia and cognitive impairment. A few diagnostic criteria exist but the current consensus accepts National Institute on Aging-Alzheimer's Association workgroups criteria (Jack et al. 2011, Budson and Solomon 2012). These include diagnosis of MCI due to AD, familial AD and dementia due to AD. Another common criteria is the IWG criteria, that mainly differs in definition of pre AD dementia phases (Morris et al. 2014). These diagnoses remain presumptive as the gold standard is still post-mortem histopathology.

Biomarkers such as decreased CSF Amyloid or increased CS T-Tau or P-Tau can be used to clarify difficult or mixed diagnoses. Newer imaging modalities can also be used, but both are usually used at specialist centres only. Even the routine use of CT or MRI remains controversial in cases of clinically likely AD (Health Quality Ontario 2014). "Preclinical AD" remains research definition rather than diagnosis, but enables recruitment of patients to study early AD pathology and treatment (Dubois et al. 2014). As research criteria become better validated, they will be incorporated into clinical use.

1.3. Physical Activity

1.3.1 Introduction and why it is important

Physical Activity (PA) results in energy expenditure, and includes daily activities. Exercise is a subtype used to get fit. Physical fitness can mean cardiovascular capacity, muscle mass, strength or balance (Caspersen et al. 1985). Physical inactivity often refers to lack of exercise, rather than lack of performing activities of daily living.

For simplicity of description and comparison, PA is often divided into low, medium and high intensity levels. Low intensity includes walking, household chores and daily living. Medium includes jogging, and similar energy activities. High includes running and higher energy expenditures. There are minimum PA levels recommended (usually 150 minutes of moderate PA per week) to achieve positive outcomes; which result in improved cardiac and respiratory health, bone health, reduction in cancer incidence (World Health Organisation 2011).

1.3.2 Effects of PA

PA reduces vascular risk factors impact, including hypertension, obesity, diabetes and dyslipidaemia (Kraus et al. 2002 and World Health Organisation 2011). It improves stability, balance, mobility, mental health and reduces depression; especially in older individuals (Netz et al. 2005, Podewils et al. 2005). It is potentially a simple intervention to reduce dementia progression (Blondell et al. 2014 and Netz et al. 2011). The evidence promoting PA is growing in the literature and in addition, PA has been shown to:

* Increase brain blood flow (Maass et al. 2014)

* Increase brain volume (Colcombe et al 2006)

* Increase brain derived neurotrophic factor (BDNF) which is important for neurogenesis and neuron health (Gomez-Pinilla et al 2008)

* Decrease amyloid deposition (Adlard et al 2005)

* Increase brain connectivity which suggests improved neuroplasticity (Voss et al 2010)

While we can calculate PA expenditure accurately, it is cumbersome and expensive. Whilst It is possible to calculate PA expenditure accurately in a laboratory setting, this is not possible in everyday life and so activity levels (low, medium and high) are currently in use.

1.3.3 PA and cognition

Cognition is our higher thought processes. Usefully defined from the NIH toolbox for the Assessment of Neurological and Behavioural Function (NIH-TB), it includes executive function (the overall control or "top down" thoughts), episodic memory (autobiographical events), language, processing speed and attention, and often global score (Weintraub et al. 2013). PA has been shown to the reduce rate of cognitive decline, an effect that is more pronounced with higher amounts of activity (Laurin et al. 2001, Lautenschlager et al. 2008, and Steinberg et al. 2014). This was supported with a number of meta-studies (Colcombe and Kramer 2003, Heyn et al. 2004). Others were unable to demonstrate significance due to lack of standardisation among cognitive testing, type of PA and length of follow up (Snowden et al. 2011).

Molecular and animal models showing remodelling in response to exercise (reviewed by Phillips et al. 2014), and increasing imaging studies show a positive effect (Ahlskog et al. 2011). The specific effect of PA on MCI and SCM is an area that needs further work, but some preliminary studies are showing a positive effect on cognition in this subgroup (Baker et al. 2010, Heyn et al. 2004, and Lautenschlager et al. 2008).

1.3.4 PA and dementia

Increasing number of studies show preservation of cognition in exercising demented patients (Ahlskog et al. 2011, Laurin et al. 2011). Focus is shifting toward pre-dementia as once dementia is diagnosed, cognitive reserve is overcome and it is often too late to effectively intervene.

1.4. Medical imaging in dementia

1.4.1 Introduction

Neuroimaging includes structural and functional imaging. Structural neuroimaging includes CT and structural MRI. Functional imaging includes modalities such as PET, SPECT, fMRI and DWI. In the initial work up of progressive memory impairment, it is recommended structural neuroimaging be included (CT or MRI) to ensure reversible causes such as space occupying lesions and subdural haematomas are not missed (Sitohet al. 2006, Ishikawa et al. 2002). The role of functional imaging in dementia imaging is transforming from its use in excluding other conditions to being a biomarker of disease and diagnosing dementia (Dubois et al. 2014).

1.4.2 Computed Tomography

Computed Tomography (CT) involves taking a slice of anatomy with rotating x-ray beams and reconstructing it with Fourier Transform (FT) mathematics (Preim and Bartz 2007). To get whole sections, many slices are required. CT is readily available, cheaper than MRI, has short acquisition times, and can be used in patients with metallic devices and an advantage in demented and confused elderly patients (Pasi et al. 2011). Disadvantages include exposure to ionizing radiation and limited soft tissue resolution compared with MRI. CT is therefore best restricted to initial workup rather than diagnosis, and best used to exclude other causes of impairment in a clinical workup of dementia.

1.4.3 Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) uses a strong magnetic field, magnetic gradients and Radio Frequency (RF) pulses to produce images. Elements with an uneven quantum spin act as magnetic dipoles, the most abundant in humans being hydrogen ions (protons), which is on average 63% hydrogen atoms, mainly from water and lipids (CH_2) in fat (Ghatak 2011, Stoller 2007, McCance et al 2014). They align with the strong magnetic field (B_o, conventionally the Z axis), usually 1.5T or 3T in clinical MRI scanners, most commonly created with superconducting coils (Jorgen Smith 1995, Marchiori 2014). After selectively tipping protons 90° (towards x or y) by RF pulse matching their resonance, they realign with B_o, inducing current in the RF coil that can be measured.

Realignment can be divided into the decay of transverse magnetic component (T2 or spin-spin relaxation) and the growth of net magnetization towards Z (T1 or spin-lattice relaxation). Different tissues have different T1 and T2 values, enabling differentiation between tissue types. MRI images area created by firstly selecting a slice of tissue in the z-plane, and then using phase shifts and gradient coils to determine the individual x and y voxel (image component) of that slice. By varying the strong MRI magnetic field across the z-direction with the addition of a magnetic gradient, only a very thin slice of tissue will have an exact resonance and therefore be selected. By varying the phase and gradient across this slice, detail within that slice (x and y co-ordinates with their subsequent T1/T2 values) can be detected and an image constructed of that slice. This is required because unlike CT, whole (z direction) slices are detected simultaneously, so varied x and y gradients enable calculation of coordinates and images to be produced with FT (Preim and Bartz 2007). After the data from a single slice is collected, the RF pulse is varied to detect
the next slice along (in the same field). By varying gradients, RF timing, phase and imaging weighting, many different imaging modes are possible.

1.4.4 Functional Imaging

Functional imaging is integral to research and increasingly used to support AD diagnoses even before consensus guidelines agree.

Positron Emission Tomography (PET) is providing multiple insights into the disease with different radiotracers (Rabinovici et al. 2011). Fludeoxyglucose (FDG) PET shows AD specific glucose metabolic, while PET C^{11}-PIB (Carbon 11 Pittsburgh compound B) demonstrates amyloid load. PET can reveal deeper insights into the brain including functional relationships and associations with other conditions such as depression (Ishii 2014).

Single Photon Emission Computed Tomography (SPECT) uses radio-nuclides and detects photons. SPECT gives a representation of cerebral blood flow. Common tracers include ^{99m}Tc-HMPAO and ^{99m}Tc-ECD, which can differentiate AD from other dementias, but not strongly enough to enable clinical use (Yeo et al. 2012).

Functional MRI (fMRI) detects the slightly paramagnetic property of deoxygenated haemoglobin, Blood Oxygen Level Dependent (BOLD) signal. BOLD represents neuronal activity by detecting increased blood flow. Using fast scanning techniques, real time inference into neuronal activity is possible. It can reveal disconnected networks in regions of amyloid load (Sperling 2012), and some proponents argue that it is more useful when combined with other imaging modalities such as such as PETC^{11}-PIB (Sperling et al. 2009).

fMRI can probe a number of other factors in dementia research. In addition to demonstrating a decrease in the "default mode network" (Grecius et al. 2004), It can also show compensatory increases of activity in other brain regions (Celone et al. 2006), and may precede changes on other structural imaging modalities such as MRI and CT. The number of applications are increasing, including assessing the effects of new pharmacologic therapies (Sperling et al. 2002).

Diffusion Tensor (MRI) Imaging (DTI) is a measure of the direction and magnitude of water diffusion. A normal tract (or group of neuronal axons) that are intact will act like a cylinder and allow diffusion along its path (longitudinal flow, termed Axial Diffusivity) but not perpendicular to this (Radial Diffusivity). When there is damage to the axons from a pathological process, water can escape the axon which results in the DTI appearance closer free water, that is, water can diffuse freely no longer limited to flow in one direction. As white matter consists of tracts of fibres coursing throughout the brain between the regions of the brain, knowledge of the tract DTI signal indicates if there is damage (Le Bihan et al. 2001, Kitamura et al. 2013, Huston and Field 2013). While not used in our study, DTI will be considered in parts of the discussion as it can be used to discuss tract and white matter integrity which can be interrupted in white matter hyperintensities (WMH).

1.5. White Matter Hyperintensities

1.5.1 Introduction

White Matter Hyperintensities (WMH) are observed in white matter of T2 and fluid attenuated inversion recovery (FLAIR) MRI sequences. They appear hyperintense due to free water, a property of many pathological processes (Wilson and Rofe 2010). FLAIR appears similarly but suppresses the hyperintense CSF signal in the ventricles, enabling better visualisation of WMH (Rydberg et al. 1994).

1.5.2 WMH terminology in the literature

They are sometimes incorrectly called leukoaraiosis, a term for hypodense white matter abnormalities seen on CT (Hachinski et al 1987). Strictly speaking, WMH are changes on MRI (due to hyperintense appearance). In practice however, WMH and leuocoaraiosis do not overlap in site, number, extension and even time of onset (Pantoni and Garcia 1995). To remain inclusive yet precise, lesions will be referred to as WMH but include research on MRI changes called leukoaraiosis.

1.5.3 WMH effects and frequency

WMH were originally considered benign. Studies now suggest associated decreased executive function and gait/balance, mortality and dementia (Ylikoski et al. 1993, Debette et al 2010). They are also associated with falls, hand incoordination and a large risk of future stroke (Ovbiagele and Saver 2006).

Although common, there has always been inaccuracy describing frequency of WMH due to differing ages, conditions being studied, vascular risk factors, MRI field strength and number/classification of lesions (Pantoni and Garcia 1995). A recent literature review found reported elderly patient WMH varies between 50% and 98%, with 67 to 98% in stroke patients, 28.9-100% in AD patients and 30-55% of Parkinson's disease with WMH (Xiong and Mok 2011).

1.5.4 WMH location

WMH often appear around the ventricles (peri-ventricular) and are also found further away from the ventricles (deeper) into the white matter, the "deep" (subcortical) white matter. Periventricular WMH (PVWMH) changes are seen as a pattern of caps on ventricular horns, more often anteriorly, and thin strips lateral to the ventricles. Deep WMH (DWMH) appear as punctate to confluent, merging with PVWM once widespread (Fazekas et al. 1987).

1.5.5 WMH pathology

PVWMH and DWMH represent differences in pathology (Fazekas et al. 1987). DWMH classification of punctate, early confluent and confluent lesions has been shown to correlate with a continuum of increasing ischaemia: mild perivascular changes, loss of fibres, arteriosclerosis and finally small cavitations (Fazekas et al. 1993). In the same study, PVWMH revealed demyelination and subepedymal gliosis with disruption of the ependymal lining but represents non-ischaemic change, a different aetiology to DWMH. Braffman et al. 1988 demonstrated heterogeneity of WMH lesions, identifying them as either white matter infarctions, gliosis or demyelination plaques. It has also been shown that WMH are more common in women, implicating oestrogen as a possible contributing factor (De Leeuw et al. 2001).

Different diseases associated with WMH suggest multiple different pathways can result in the same final outcome. WMH have been demonstrated with cerebral oedema, hypertension, demyelination and blood pressure dysregulation. WMH associations with depression, bipolar disorder, schizophrenia, stress, hypertension and stroke also support this (Thomas et al. 2002, Anh et al 2004, Brown et al 1995, Neelum et al 2014, Gottesman et al. 2010 and Debette et al. 2010). While there might be some common elements in histology of all these lesions, there will also be differences in their cause. It is more accurate to focus on WMH pathology in cognitive impairment as different initial pathologies may cause WMH in the different associated medical conditions.

1.5.6 WMH and cognitive impairment

It is known that WMH cause cognitive impairment (Carmichael et al. 2010), however cognitive function overall is highly complex (Miyaki et al. 2000) and influenced by many additional factors including education level, age, gender, AD pathology load and cognitive reserve (Doraiswamy et al. 1997, Cloutier et al. 2015, Brickman et al. 2011). Cognitive impairment is also associated with grey matter volume change (Manard et al. 2016) and cortical atrophy (Jokinen et al. 2012), and hippocampal atrophy being specifically associated with memory impairment (Godin et al. 2010, Kramer et al. 2007). In addition, medial temporal lobe atrophy is associated with cognitive dysfunction (Overdorp et al. 2014) and along with WMH has a synergistic effect on cognitive decline (Van der flier et al. 2005). While some studies found associations with WMH and global cognition (Longstreth et al. 2005), others found associations with executive function and psychomotor speed only (de Groot et al. 2000, Kloppenborg et al. 2014), and further studies were able to find associations with sub regions of WMH (de Groot et al. 2000, de Groot et al. 2002, Van den Heuvel et al. 2000, Seo et al. 2012). From this, it can be concluded that while WMH causes specific cognitive impairment, it is also location dependent and affects some components of cognition more than others. It can also be seen that overall, cognition is a complex entity composed of multiple interacting factors.

Dissecting the contributions of two chronic and insidious pathologies to cognition is difficult and making links between the two without solid neuropathological correlation data is not possible. As the majority of investigation into WMH is image based, caution is needed in extrapolating the findings beyond correlations. The expansion of DTI and functional image will hopefully enable more detailed understanding of the relationships between WMH damage and outcome (not just the damage visible as T2 hyperintensity), but interactions between WMH and AD at the cellular and molecular level are unfortunately still unknown. WMH may provide the second insult to exacerbate underlying AD effects on cognition (but be unrelated), WMH and AD may influence each other by middle (but yet unidentified) risk factor or they may be mutually exclusive. Further work is needed to clarify this.

1.5.7 WMH and AD

Progression of WMH has also been associated with AD. This is suggestive of changes to white matter integrity, additionally supported by DTI (Radanovic et al. 2013). WMH and AD have been associated in a large number of prospective studies. The cardiovascular health cognitive study, Rotterdam scan study and Framingham Offspring study all associated the two (Kuller et al. 2003, Prins et al. 2004a, and Debette et al. 2010). While presumed to be related to vascular disease exacerbating AD pathology, it is still speculative (Hommet et al 2011).

1.5.8 WMH versus Normal Appearing White Matter

Changes occurring elsewhere in the white matter which are not visible on MRI are called Normal Appearing White Matter (NAWM). Areas of (MRI) NAWM have been shown to contain post-mortem abnormalities, and it is estimated that damaged white matter which appears normal on MRI is on average 54% larger than MRI estimated WMH volumes (Bronge et al. 2002). Huang et al. used Diffusion Tensor Imaging (DTI) and showed NAWM is functionally different despite normal MRI (Huang et al. 2007). NAWM is also present in other white matter diseases, including multiple sclerosis. (Filippi et al. 1999). It is therefore unclear if the cognitive and clinical associations made with WMH are due to the MRI visible pathology or larger “invisible” burden within the (MRI) NAWM.

1.5.9 WMH risk factors

The largest risk factor is age. Over 85, virtually 100% of individuals will have WMH (Ovbiagele and Saver 2006). The next highest risk is hypertension. In addition, large vessel atherosclerosis and endothelial dysfunction are associated with WMH. It would seem logical that diabetes would be associated with WMH, but this relationship is inconclusive (Ovbiagele and Saver 2006). ApoE is a genetic factor possibly related to WMH occurrence, but there is ongoing debate surround its effect (Schmidt et al. 2011). These risk factors don’t always associate WMH changes, so more genome-wide association studies should enable further exploration of WMH risk factors, which are likely polygenic rather than being caused by a single genetic factor (Assareh et al 2010, Paternoster et al. 2009).

1.5.10 WMH and PA

Studies have previously related WMH to physical disability and gait/balance disorders (Baezner et al 2008, Zheng et al 2013). WMH are also lower in physically fit adults (Tseng et al 2013b). The effect of PA on WMH is yet to be evaluated in older patients at risk of Alzheimer's disease, one reason for the AIBL Active trial, which will supply data for this thesis (Cyarto et al 2012).

1.5.11 Cerebrovascular disease and WMH as a biomarker

Cerebrovascular disease is a disturbance of the blood flow of the brain resulting in transient or permanent change in one or more areas of the brain. It includes macrovascular changes such as stroke (including cerebral infarction and cerebral haemorrhage), trans ischaemic attack (TIA), subarachnoid haemorrhage (in some cases defined as part of stroke), cerebral vessel atherosclerosis, thrombosis or stenosis, vessel aneurysms and malformations and small vessel disease (Good 1990,Sacco et al 2013, Yu et al. 2016).

Small vessel disease (also known as microvascular disease) by definition is also heterogeneous and includes a number of entities on imaging such as white matter hyperintensities, lacunar infarcts, cerebral microbleeds, haemosiderin deposition, incomplete infarcts and hereditary arteriopathies (Craggs et al. 2014). For the purpose of this thesis, cerebrovascular disease refers to the changes of vessel hyalinization, pallor of adjacent periventricular spaces and astrocytic gliosis as found on neuropathological studies. As the WMH outlined are high signal on T2 Weighted (FLAIR) imaging, they exclude non-hyperintense but MRI visible pathology such as lacunar infarcts, perivascular spaces and haemosiderin deposition.

WMH are an accepted diagnostic and prognostic marker in cerebrovascular disease however, that is also associated with stroke, lacunes, dementia and vascular cognitive impairment. Although mechanisms remain to be discovered, its use as a biomarker is now widely accepted (Chutinet and Rost 2014). In this thesis, WMH progression volumes are required for determining the effect of the physical activity program, while baseline WMH volumes and WMH progression volumes will be analysed (in both correlation and general linear models) to enable detailed comparison between traditional and side-by-side segmentation

1.5.12 Segmentation of WMH

In order to analyse the volume of WMH and therefore effects associated with clinical endpoint, a number of WMH evaluation methods have been developed. These methods range from qualitative (visual) scales that give a rating to WMH volume burden, to quantitative methods which aim to best calculate the volume of WMH by segmentation. The Quantitative methods range from fully automated, semi-automated to full manual segmentation of volumes.

The visual rating scales, even though requiring input from a human rater, still allow a relatively rapid throughput of images and have the advantage of being robust to image artefacts (Yoshita et al 2005), which has obvious advantages when needing to process a large number of scans. The disadvantages however, are that they can suffer from a floor and ceiling effect (Gao et al 2012, Van Straaten et al. 2006) and are limited in their ability to detect longitudinal changes (Prins et al. 2004b).

The use of dedicated progression scales can improve longitudinal change detection (Gouw et al. 2008a) but the presence of a floor effect still indicates that small and possibly clinically significant changes are not detectable (Van Straaten et al 2006).Their statistical inferences possible are also reduced because visual rating scale outputs are not continuous like segmentation methods (Yoshita et al. 2005), and there is still some debate regarding inter and intra-rater reliabilities (Mäntylä et al. 1997, Gouw et al. 2008a).

Fully and semi-automated methods of segmentation remain an intensely interesting area of ongoing research as methods evolve using various techniques. Similarly to visual rating scales, their value lies in the analysis of very large datasets in which it would be too cumbersome to manually segment every image (Brickman et al. 2011). Computed methods rely on thresholds to classify what is hyperintense (Yoshita et al. 2005) with variations in further processing depending on which algorithm is used (Caligiuri et al. 2015). Without any manual input, this can render the threshold classification susceptible to false positives, classifying image artefact and bone as true WMH lesions (Caligiuri et al 2015). Fully and semi-automated methods can also suffer from reduced ability to detect WMH in reduced grey-white MR contrast (Caligiuri et al 2015) images, which has been shown to occur with ageing (Jernigan et al. 1991, Magnaldi et al. 1993). Finally, although methods are evolving to integrate contrast changes (Csapo et al. 2013), the majority of software suites currently only register images spatially and not to a standard intensity.

As indicated above, (even though the most laborious) manual still segmentation remains the standard that all other methods are compared to (Clerx et al 2015, Klöppel et al. 2011). The viewer can also be trained to exclude MR artefacts (Lavdas et al. 2014) that would normally affect computerised assisted methods as outlined above. In addition to be the best method for detecting WMH volumes in isolation, manual segmentation remains the most accurate method for detecting longitudinal volumetric changes (Gouw et al. 2008a).

1.5.13 Side-by-side segmentation

Some studies have utilised a side-by-side method of analysing images to approach results obtainable by manual segmentation. The technique has been utilised to both improve the accuracy of rating scales (Longstreth et al. 2005, Gouw et al. 2008a) and as a pre-processing step before automated segmentation (Switzer 2014). Some studies have allowed side-by-side rating of WMH unblinded (Yamauchi et al 2002) with Prins et al (2004b) measured its impact and found no bias in their outcome. Interestingly, paired reading has been shown to improve accuracy in a number of other areas of radiology (Aulely et al 2000, Nogami et al 2007 and Weissman et al 2001), and has been used in MR brain studies to compare MRI images with vessel atlases (Duering et al 2013) and post-mortem photography (Bartlett et al. 1994). Side by side comparison of large MR brain imaging data sets with other techniques is actively encouraged (Wyman et al. 2013) but despite this, side by side manual segmentation of white matter hyperintensities has not previously been described in the literature.

1.6. Aims and expected outcome (hypothesis)

The aim of this single blinded randomised controlled trial is to determine if physical activity can slow the progression of cerebrovascular disease in older adults with vascular risk factors who have subjective memory complaints or mild impairments.

A model based on the current literature and data collected will be developed and following interactions examined:

1. Does physical activity affect white matter disease progression?
2. What are the interactions with baseline WMH volume? How does this compare with progression volumes?
3. Does ApoE or PET amyloid status affect progression?
4. Are there any effects with age, gender or level of education previously attained?
5. Does cognitive diagnosis of subjective memory complaint or mild cognitive impairment have any bearing on the outcome?
6. Are there any associations with individual vascular risk factors in our cohort?
7. Does the metric of "number of vascular risk factors" have a stepwise effect in the data?
8. Does baseline functional fitness affect the final outcome?
9. How does white matter progression and the above factors associate with the neurocognitive assessments?

The primary hypothesis is that physical activity slows the progression of white matter hyperintensites and that this correlated to a decrease rate of cognitive decline. Secondary hypotheses predict that PET amyloid negative and ApoE negative patients will have a slower rate of WMH and cognitive decline. It is predicted that an increased number of vascular risk factors will correlate positively with WMH accumulation. It will also be predicted that this will be mirrored in the cognitive assessments, with WMH accumulation negatively correlated with executive function. It is predicted that side-by-side segmentation will give more precise results than individually segmented hyperintensities, resulting in stronger statistical significance in the hypotheses stated above.

CHAPTER 2 MATERIALS AND METHODS

2.1 Introduction

The study population (participants from AIBL Active study) will first be described, followed by the study design. The acquisition of clinical data, that was obtained other members of the study, will then be discussed. The role of imaging will then be discussed: Position emission tomography (PET) imaging (obtained by other research members) will briefly be described, ending with our contribution of magnetic resonance imaging and our methods including statistics.

2.2 Study population (The AIBL Active study)

2.2.1 Introduction and ethics

This study investigated the longitudinal differences in White Matter Hyperintensities on MRI over 24 months in older adults with vascular risk factors and either subjective memory complaints (SMC) or mild cognitive impairment (MCI) who were randomised to either a monitored physical activity program or to their normal daily activities. MCI and SMC patients with vascular risk factors were chosen because they are at higher risk of developing to dementia, but still had potential to slow this process with physical activity (De la Torre 2010, Li et al. 2011, and Peterson 2004). The rationale behind this was that once a patient already has clinical dementia, the underlying process is very advanced due to brain plasticity compensating for underlying pathology and the potential to slow this progression is limited (Blondell et al. 2014 and Netz et al. 2011).

The data used in this thesis was prospectively obtained as part of an NHMRC funded trial, the AIBL (The Australian Imaging, Biomarkers and Lifestyle Flagship of Ageing) Active trial. The main hypothesis tested was that physical activity slows progression of cerebrovascular disease in older adults as evidenced by a decreased rate of white matter hyperintensity accumulation; and that this correlates to a decreased rate of cognitive decline. The WMH volumes acquired for this thesis will form part of the main outcome of the trial.

Ethics approval for the AIBL Active trial had been obtained from the Melbourne Health Human Research Ethics Committee. This project complied with human research ethical principles outline in Declaration of Helsinki. Ethics approval had also been granted this author to work with the data, along with the use of data in this thesis.

2.2.2 Pilot/previous studies

The Australian Imaging, Biomarkers and Lifestyle (AIBL) study (Ellis et al. 2009) was a progressive longitudinal study that studied ageing in 1112 Volunteers in Melbourne and Perth. The data from this thesis was obtained from the a subset of the AIBL study, the AIBL Active study, which recruited participants from Melbourne only. At the commencement of AIBL active, 40% of SMC and 61% of MCI patients from AIBL demonstrated clinical progression on MMSE after 18 months. In addition, 4% of SMS progressed to MCI/AD and 25% of MCI progressed to AD at follow up, showing SMC and MCI patients to be at risk of cognitive decline. Of the Melbourne AIBL study arm, 66% of the SMC and MCI patients had at least one VRF, suggesting an association with vascular pathology (Cyarto et al. 2012).

SMC/MCI progression was first shown to be slowed with PA in a RCT that randomised 170 community members to either home-based PA or usual activity (Lautenschlager et al. 2008). After 24 weeks of PA or usual activity, PA ceased and follow-up assessments at 6, 12 and 18 months were performed. The primary outcome measure was the cognitive section of the Alzheimer Disease Assessment Scale (ADAS-cog, Rosen et al. 1984), participants in the PA group improved and those in the usual care group deteriorated at the end of the intervention. This difference continued to be significant for another 12 months.

2.2.3 Statistics for study design

Power was calculated based on the primary study outcome, the change in WMH over 2 years between intervention and control groups. As there were no previous studies investigating WMH change in older adults with SMC and MCI in response to exercise, calculations were based on a randomised controlled trial by Richard et al(2010). In this study, WMH progression was compared in 123 participants who received either vascular care of normal care over 2 years. Vascular care meant that their vascular risk factors were treated as well as possible, an analogy to exercise which decreases the modifiable risks.

Between group differences were estimated for an *a priori* Effect Size = 0.5 and aimed for a power of 80 %, equating to an ability to see something significant in 80% of the cases with a 15% included dropout rate (at p = 0.05, two tailed). Based on this calculation, this meant that we would have had to recruit 148 subjects at baseline (74 each). For the AIBL Active study, 98 patients were eventually recruited who satisfied the study criteria.

2.2.4 Inclusion criteria

Participants were included if they satisfied the following:

(i) Aged 60 years or over at last birthday

(ii) Diagnosis of SMC or MCI

(iii) Community dwelling

(iv) Presence of at least one Vascular Risk Factor (VRF) (such as obesity, hypertension, heart disease, type II diabetes, smoking, hypercholesterolemia)

(v) Understands written and spoken English.

2.2.5 Exclusion criteria

Participants were excluded if they had:

(i) Baseline Standardized Mini-Mental State Examination score (SMMSE) < 24 [36] or diagnosis of dementia

(ii) An inability to have MRI scans

(iii) Limited mobility (e.g. unable to walk or require a walking aid for balance)

(vi) Evidence of pervasive depression

(v) Current alcohol dependence at the time of recruitment

(vi) Unstable or life-threatening medical conditions

(vii) Medical condition that contraindicates PA

(viii) Severe visual or hearing impairment

(ix) Inability to attend the follow-up visits

(x) Already been enrolled in another RCT (apart from the larger AIBL Study).

2.3 Assessments

2.3.1 Introduction

Patients were assessed over the 24 month period. Assessment periods were divided into baseline, 6 month, 12 month and 24 months. The major assessments occurred at baseline and 24 months (cognitive tests, physical function/PA assessment, MRI scanning and fasting blood sample). 6 and 12 month assessments involved cognitive and physical function/PA assessment only. At baseline, participants underwent beta-amyloid PET scanning.

Blood tests included lipid profile (total cholesterol, LDL-C, HDL-C and triglycerides), fasting insulin, glucose, homocysteine, hs-CRP and biomarkers. The biomarkers included IL-6, TNF-α, sICAM-1, sVCAM-1, and sP-selectin, sE-selectin.

Separate research assistants performed the PA assessments and cognitive assessments. A physical activity research assistant (PA RA) performed PA assessments with the addition of the SMMSE (A modified version of the mini-mental state examination, MMSE) in order to exclude patients with possible dementia (Folstein et al. 1975, Molloy et al. 1991). SMMSE was used rather than MMSE due to greater objectivity from more specific scoring examples and uses alternatives for repeated testing of the registration and delayed recall items.
The PA RA also collected demographic and health information in the participant interview. A neuropsychology research assistant then performed the battery of cognitive tests required.

2.3.2 Screening criteria

Participants from the AIBL study who satisfied the relevant criteria were invited to contact an assessor by phone for possible inclusion in the AIBL Active trial. The assessor then checked the patient against the inclusion/exclusion criteria with a screening protocol. The screening protocol included the 15-item Geriatric Depression Scale (GDS – 15) to exclude patients with clinically relevant depression (score of 6 and above, Almeida and Almeida, 1999). As part of recruitment patients and their physicians also signed a release of medical information form to enable a geriatrician AIBL Active research member to confirm inclusion eligibility. Once inclusion was confirmed, a formal written consent was filled by the participant.

2.3.3 Measures obtained from the physical activity research assistant

The PA RA collected biometric data, baseline functional fitness assessment measurements and measured compliance with the physical activity program.

The biometric data included the assessment of vascular risk factors, with either a score of normal or elevated above a given threshold (0 or 1, dichotomous). Individual scores were obtained along with combined scores as outlined below:

Obesity measures

*waist circumference (elevated if >80cm in females or >94cm in men, median of 3 measures at baseline)
*Central obesity (elevated if BMI >25kg/m^2 at baseline)
*Obesity combined (positive if either of the above are positive)

Blood pressure

*History of hypertenstion (from the questionnaire at baseline)

*High systolic blood pressure: Blood pressure was measured at rest after a 2 minute rest period. 5 repeat measurements were taken and an average calculated. Considered abnormal if the average systolic blood pressure was over 140mmHg)

*High diastolic blood pressure: Blood pressure was measured at rest after a 2 minute rest period. 5 repeat measurements were taken and an average calculated. Considered abnormal if the average diastolic blood pressure was over 90mmHg)

*On antihypertensive medications (If on any antihypertensive medications)

*Hypertension combined (Positive if any of the above values are positive)

Dyslipaemia

* Cholesterol (positive if serum level is above 6.22mmol/L)

* Triglycerides (positive of serum level is above 2.26mmol/L)

* Lipid lowering agent (positive if on any lipid lowering agent)

* Dyslipidaemia (Positive if any of the above is positive)

Diabetes

* Fasting glucose (positive if fasting level >7mmol/L)

* Diabetes history (from questionnaire at baseline)

* Diabetic medication (positive if on any diabetic medication)

* Diabetes combined (positive if any of the above are positive)

Smoking

* current smoking (from the questionnaire at baseline)

* smoking ever? (>1 cigarette/day for 1 year. From the baseline questionnaire)

* smoking combined (positive if either of the two above are positive)

Atherosclerotic disease

* Heart disease (baseline questionnaire, 'do you have heart disease or angina?')

* Stroke (baseline questionnaire, 'have you had a stroke or TIA?')

*Atherosclerosis combined (positive if any of the above are positive)

Vascular risk factors combined

A combined score of all of the above, tabulating the number of "combined" scores positive. As having vascular risk factors are an inclusion criteria, the minimum score is 1, to a highest possible score of 6 (obesity, blood pressure, dyslipidaemia, diabetes, smoking and atherosclerotic disease).

Physical activity measurements (as per the AIBL Active protocol) were obtained at baseline, 6, 12 and 24 months. As only the baseline data was processed and available at time of writing these were termed baseline functional fitness assessment measurements and include:

* The step test (Hill et al. 1996).

The participant stepped up onto a 7.5cm wooden block unaided as many times as possible within 15 seconds. Each leg was tested separately and lowest score recorded. The test assessed participant dynamic balance. The unit is number of steps, with more steps corresponding to a better score.

* The Timed up and go test (Podsialo and Richardson, 1991)

Participants started from a sitting position in a chair with arms resting on the arm rests. They were then be instructed to get up, walk three metres, turn around and walk back and sit in the chair as fast and safely as they could. This test was used to measure mobility and was measured in seconds, a lower time corresponding to a better score.

* Maximum voluntary grip strength (Gore and Edwards, 1992)

The participant stood up against a wall, with a (Smedley's) dynamometer vertically above the head. The patient was then asked to squeeze as hard they could while bringing their arm down by their side. The test was repeated for both arms and recorded in terms of dominant and non-dominant hand results. Units are in kilograms, with a larger score indicating a stronger grip.

*Five times chair stands (the Sit to Stand test), (McCarthy et al 1994)

Participants were asked to stand up and sit down as quickly as possible. The test was performed with or without the use of arms. This test measured functional lower limb strength. Units are in seconds and measurement is the total time taken for 5 repetitions. A lower score corresponded to a better score.

* The 6 minute walk test (Rikli and Jones 1998)

This score measured the cardiovascular ability of the participant. The distance covered in 6 minutes of walking was then recorded. The units are in metres and a larger distance corresponded to a better score.

The details of each as described above are available (with yet more detail) in the fitness for Ageing Brain Study II (FABS II), (Cyarto et al. 2011), with the exception of the six minute walk test which is described by Rikli and Jones only (1998).

As part of the compliance to the prescribed physical activity program in the exercise treatment arm (and to check activity in the control arm), all participants answered questionnaires related to physical activity and wore a pedometer.

The questionnaires administered by the PA RA included:

* Community Healthy Activities Model Program for Seniors (CHAMPS) physical activity questionnaire (Stewart et al. 2001)
* Stages of Change Instrument (SCI) (Marcus et al. 1992a)
* Self-Efficacy Questionnaire (SEQ) (Marcus et al. 1992b)
* Satisfaction with Life Scale (Pavot et al. 1991)

Following each visit, subjects were asked to wear a pedometer (Digi-walker SW-200, Yamax inc., Tokyo, Japan) for 1 week. They were shown how to wear and use the pedometer, and how to complete the diary. This measured their weekly PA and subjects were asked to perform at their usual activity levels (Cyarto et al. 2004).

From the questionnaires at baseline, amounts of activity usually performed at baseline were recorded and categorised for level of activity and expenditure. From this, we can assess:

* Minutes per week of activity (including exercise) performed (all intensities)
* Frequency per week of all intensity activity performed at baseline
* Caloric expenditure per week of all intensity activity

The addition of these measures taken at baseline gave a quantification of usual activity, which is in addition to the baseline functional fitness assessment data. From this we could gauge how active the participants usually were at baseline and whether this impacted upon the progression of WMH. Whilst amounts exercised at different levels (low, moderate, high and very high) were available, there were heterogeneous results and many results where patients performed zero minutes/kCal of each different type, reducing statistical power. It was therefore more appropriate to use total amounts as they include all participants and give continuous results.

Both pedometer and questionnaire activity were used to measure compliance over the course of the study and ensure each participant adhered to their prescribed treatment. The self-reported questionnaire data was used for compliance purposes only and not used as a physical activity measure because this could have introduced reporting bias into the results.

2.3.4 Measures obtained from the neuropsychologist research assistant

At the time of writing, only the baseline cognitive data was available from the neurocognitive team. Baseline neurocognitive assessments were compared against baseline imaging outcomes and longitudinal changes. Each test has been previously validated for their individual roles, and the details of each test can be viewed in their individual references. The domains tested and reason for choosing each test are presented:

* The Alzheimer's Disease Assessment Scale - Cognitive section (ADAS-Cog) (Rogen et al. 1984)

This test is widely used to assess patients with AD and can be utilised for patients at risk for AD (Marsico et al. 2014), although not a substitute for a full neuropsychological battery it was considered the more comprehensive than other rating scales (Pena-Casanova 1997). The ADAS Cog measured 11 components (word recall, word recognition, orientation, naming objects and fingers, constructional praxis, ideational praxis, remembering test instruction, spoken language, word finding and comprehension), hence the ADAS Cog 11 score (Cano et al. 2010). The ADAS cog covers a broad range of cognition: The ability to orientate to time, place and person, language, memory, the construction of simple behaviours in pursuit of a basic predefined role and construction of simple designs and planning (Rosen, Mohs and Favis, 1984).

* The Behaviour Rating Inventory of Executive Function – Adult Version (BRIEF-A) (Rabin et al. 2006)

The BRIEF-A is a standardised measure that explores the adult's view of their executive function and self-regulation within their everyday environment. It is composed of 75 self-reported items that are divided up into non-overlapping empirically derived clinical scales that measure various aspects of executive function. It is for this reason that we examined subgroups as well as total score. The Behavioural Regulation Index (BRI score), along with the Metacognition Index (MI score) as well as total of both was utilised. This divided the executive function up into "cool executive function" and "Hot executive function" (Giancola, Godlanski and Roth, 2012). This theoretical construct used to divide executive function has some use to determine differences between the more metacognitive (problem solving and planning) aspects of "cool" executive function and the affective and motivational "hot" aspects.

* The Hospital Anxiety and Depression Scale (HADS-A) -Anxiety component (Zigmond and Snaith 1983)

The HADS is a self-rating instrument designed to assess the presence of anxiety and depression in medical patients. The Anxiety component (HADS-A) consisted of 7 item sub scale questions which normally has utility in outpatient, primary care patients and in the community.

*The Memory Complaint Questionnaire (MAC-Q) (Crook, Feher and Larrabee 1992)

It is a self-reported six item scale of memory decline, where the participant compared current memory ability with past performance for given situations. The participant was given scores from 7 to 35, with higher scores representing a perceived cognitive decline on behalf of the participant. T he above neurocognitive measures were chosen for their complete coverage of Alzheimer's spectrum disease, executive function and self-reported participant concern regarding anxiety and memory complaints.

2.3.5 Diagnosis of subjective memory complaints and mild cognitive impairment

The diagnosis of SMC is made by a neuropsychologist. In order to make this diagnosis, participants need to answer "yes" to "Do you have any difficulty with memory?" and score in the normal range for their age and sex on the Cognitive Battery of the Consortium to Establish a Registry for Alzheimer‟s Disease (CERAD).

The diagnosis of MCI is made by a neuropsychologist. To be diagnosed as MCI, the patient was diagnosed according to Winblad et al. (2004): where the patient needs (1) memory complaints, (2) impairment on objective tasks (as measured by being lower than 1.5 Standard deviation in comparison to normal control group scores on any of the CERAD subtests), (3) preserved basic activities of daily living (ADL) and only minimal impairment in complex instrumental functions (IADL) and (4), not demented. All subtypes of MCI are included in the diagnosis of MCI in the study cohort.

2.4 Study intervention

2.4.1 Introduction

The study intervention examined is a physical activity program, which is compared to participants that underwent their usual daily activities. Following an explanation of randomisation, the physical activity program prescribed to the intervention arm will be outlined, ending with the behavioural intervention program.

2.4.2 Randomisation

Randomisation occurred in blocks of six (three participants in each treatment arm), generated using STATA 10 (StataCorp, Texas, USA). A member not participating in assessment or recruitment allocated participants to groups. Due to it being readily apparent if a participant was exercising or not, participants could not be blind to the intervention. As PA was performed at home it was not feasible to create a sham exercise. Clinical staff who gathered endpoint data were unaware of group allocations, enabling the single blind study design. Blinding was further achieved by splitting the locations that cognitive and physical assessments were performed at. Staff and participants were given strict instruction to not discuss their PA program.

2.4.3 The physical activity program

Subjects performed at least 150 minutes of moderate intensity exercise per week. For those already performing this, they were advised to add one 50 minute session per week. Walking was the preferred exercise, but the program was customised to each patient, taking into account their interests, questionnaire data and health problems that may have limited mobility. Participants started gently and increased to full intensity exercise over an 8 week period. It was recommended that the 150 minutes be achieved in 3 x 50 minute sessions. Some subjects may have chosen to complete some activities in community centres which was acceptable as long as they reached the time and intensity levels required. To ensure standardisation, the programs were monitored by one of the study chief investigators.

Once a program was chosen for each participant, they were given instructions for their individual program. They were supplied with instructions on how to read their program plan, how to complete their exercises and how to record it later. Compliance and details of each activity was recorded in a diary which was returned back to the PA RA (by mail) each month. Compliance was calculated as a percentage of exercises completed, expressed as a percentage of the total prescribed exercise.

At the time of writing, the compliance data was not yet completed. The groups were therefore only analysed according only to their prescribed intervention groups.

2.4.4 Behavioural intervention

Each intervention subject received educational material for a healthy lifestyle (and the same given to the control subjects). The intervention group was also given a manual with the PA program and the behavioural intervention (BI) outlined.

The BI program promoted change by developing self-belief that the individual can achieve a goal. This goal directed confidence is based on the Stages of change model which has been modified for PA (Marcus et al. 1998a). Using practical steps to ensure self-monitoring and goal setting, better program adherence was hoped to be achieved. Over the 24 months this was reinforced with motivational newsletters, the 18 telephone calls and progress reviews when meeting with the PA RA, including a summary PA report given to participants after each follow-up session. In addition, midway through each 6-month period, participants recorded the number of their steps for 4 weeks while trying to reach a personalised goal. Individualised target setting and review has been shown to be successful in increasing program compliance (Rothman, 2000).

2.4.5 Control group

Control group (usual care) subjects were given educational material and recommendations towards living a healthy lifestyle (not including PA). Phone contact was of the same frequency as the intervention group. Phone contact focused on general health and did not discuss PA. After each follow-up visit, control subjects completed a short questionnaire covering their involvement in the study. Once the study was complete, control subjects were invited to attend an educational session on PA.

2.5 Medical Imaging

2.5.1 Introduction

PET imaging performed by other members of the AIBL Active team will first be discussed, followed by our work with MR Imaging. The MR image acquisition will be outlined, leading into our processing pipeline, our white matter hyperintensity volume acquisition methods and ending with a discussion of our statistical methods.

2.5.2 PET Image acquisition

Participants underwent PET scanning to ascertain the presence of amyloid plaques, a phenomenon normally expected in patients with AD. The PET Ligand F-18 Florbetapir (University of Pennsylvania and Avid Radiopharmaceuticals Pty Ltd, Philadelphia) was used to image in vivo amyloid. No adverse effects have been reported during the development of this compound in clinical use and it has completed Phase III clinical trials. Patients hadtheir head immobilised with a head strap and intravenous access obtained. 370MBq of compound was administered over 30 seconds, and scanning performed with a Phillips Allegro PET camera (Austin Hospital, Melbourne, Victoria).

The majority of patients underwent scanning with F-18 Florbetapir, but a few patients had Amyloid imaging with other ligands (11 had GE Flutemetamol, 1 had AV1 tracer and 1 had a scan with PIB tracer) due to some patients having been enrolled in another study and already underwent a PET scan with alternative ligand. For a binary yes and no result for amyloid load, the results of these tracers are comparable. As a result, patients were grouped into amyloid positive or negative based on their PET results.

Co-registration of each participant's baseline MRI with the PET images will be performed and an MRI ROI template transferred to the co-registered PET. Standardized uptake value ratios (SUVR) will be generated by normalizing to the cerebellar cortex. Beta-amyloid burden will be expressed as an average SUVR of the area-weighted mean of frontal, superior parietal, lateral temporal, lateral occipital, and anterior and posterior cingulate regions

In our data, the SUVR values are considered as dichotomous variables (high = Amyloid beta PET positive or low = Amyloid beta PET negative). For PET amyloid beta status, participants are classified as positive when the SUVR is ≥ 1.50 for PiB (Villemagne et al, 2011), positive when the SUVR is ≥ 1.10 for florbetapir (Clark et al. 2011), and positive when the SUVR is ≥ 0.62 for flutemetamol (Thurfjell et al. 2013).

2.5.3 MR Image acquisition

MRI scanning was performed on a Siemens 3T Tim Trio Scanner, utilising a 12-channel phased array coil at the Royal Melbourne Hospital (Melbourne, Victoria). High resolution data was obtained in order to evaluate white matter disease and brain atrophy. Patients underwent multiple sequences for evaluation of multiple imaging parameters during the AIBL Active trial, but results that pertained to this hypothesis are the MPRAGE and FLAIR sequences. Sagittal T1 weighted Magnetization Prepared Rapid Gradient Echo (MPRAGE) images were obtained with Isotropic 1mm voxels (TR/TE/TI of 1900/2.13/900ms) and 9° flip angle. Sagittal 3D Fluid Attenuated Inversion Recovery (FLAIR) images were obtained with isotropic 1mm voxel (TR/TE/TE of 5000/255/1800ms) and 120° flip angle.

2.5.4 MRI processing pipeline

Images from the MRI scanners were exported from MRI servers in DICOM format and securely stored in servers at the Brain Imaging Lab in the Department of Radiology, Royal Melbourne Hospital.

Image processing in the Brain Imaging Lab was run from computers with Ubuntu Linux (Canonical Ltd. London, United Kingdom). DICOM images were converted initially to Nifti (Neuroimaging Informatics Technology Initiative) format, which is more easily able to be processed by additional programs in the imaging pipeline. FLAIR and MPRAGE MRI images of participants were used. Images were all visually inspected at this point to ensure conversion did not result in any errors or warping.

Once converted to Nifti, images were all reoriented to standard space using the *fslreorient2std* function (FSL, FMRIB Software Library v5.0). This ensured that all images were processed the same way and reoriented to the same co-ordinates as the standard template images (MNI152 space). Again, images were all reviewed to ensure correct orientation before further processing.

Images were then de-skulled using the *BET* function (Brain Extraction Tool, FSL, FMRIB Software Library v5.0), with the -B option enabled, which attempts to reduce image bias, and residual neck voxels. In addition, the *BET* fractional intensity threshold was set to 0.25 on most images. Every image was reviewed after brain extraction, but some had portions of brain removed or skull left behind, so the fractional intensity threshold needed to be readjusted to get an optimised outcome in a minimal number of cases.

Next images were normalised using *fslmaths* (FSL, FMRIB Software Library v5.0), where the images were (mean) intensity normalised to a value of 100. After normalisation, images underwent bias field correction with the *N4BiasFieldCorrection* command (ANTs, Advanced Normalization Tools), to correct for artefacts produced by imperfections in field coils or magnetic susceptibility changes which occur at anatomical tissue/air boundaries.

The images were resampled to have 128 slices, using the c3d command (ITK-snap, www.itksnap.org, Paul et al. 2006). This was done to make it feasible to manually segment Regions of Interests (ROI), white matter hyperintensities using ITK-SNAP desktop software. After resampling, again all images were checked for any distortions or errors.

2.6 Conventional manually segmented white matter hyperintensities

2.6.1 Introduction

White matter hyperintensities were outlined with the following methods. These methods were followed to optimise the environment, education of the reader (myself) and method reproducibility. Following final review, a discussion of processing prior to final analysis will be briefly mentioned. The term conventional manually segmented is employed in this thesis to differentiate it from sided-by-side manual segmentation.

2.6.2 Processing environment

All images were viewed in a single room with lights turned off. Blinds covered the window to an internal hospital hallway and there were no external windows. There were no additional sources of light aside from the computer monitor, and a minimum period of 20 minutes was allocated to allow the viewer to become accustomed to the dark.

Images were processed on ITK-SNAP version 3.0.0 (Yushkevich et al. 2006). The same version was used for all segmentation for continuity of results, despite later versions becoming available. Viewing was performed on a single desktop computer running Ubuntu Linux (14.04), with no upgrade to hardware over the 2 year period. Care was taken to keep the screen resolution, contrast and brightness constant.

Each time images were viewed, the ITK-SNAP window was maximised, the "Toolbox" kept out of view and other application icons minimised to enable maximal viewing size and minimise distraction and light pollution of the viewer's eyes.

Each participant's brain was maximised to fill the screen and the screen was level with the viewer's eyes both laterally and in terms of elevation. The viewer sat approximately 50cm from the screen with controls comfortably at arm length. If fatigue or distraction occurred, a short rest followed by customisation to the dark once more was necessary to ensure optimal image processing.

Images were processed from superior to inferior, with segmentation performed only on subcortical white matter (excluding cerebellar and spinal white matter which is not involved in cognitive processing).

2.6.3 Region of interest segmentation

Lesions were outlined manually using ITK-SNAP, with brush size 3, isotropic voxels and in the same location. Manual segmentation was chosen, as although labour intensive, as it was the closest to a gold standard (Khan et al. 2008).To minimise outside ambient interference, all processing was performed in a darkened room and on the same computer. The screen resolution, refresh rate and brightness/contrast were kept constant and standardised for constant gray-white differentiation. A run of 10 images was processed, followed by a check by an expert neuroradiologist to ensure sufficient introduction and readings by the ROI marker. All images were then analysed by the marker (including doing the initial 10 images again) and lesions identified and marked. Each slice of every image was also checked by the same neuroradiologist. At the end of baseline image reading, 20 of the first images were marked again (with neuroradiologist overview once more) to ensure good intra-observer reliability with the ROI marker and neuroradiologist. With 91% intra-rater reliability, the follow up time point images were processed and checked with the same method.

2.6.4 Education

The viewer was educated from a number of methods. First the viewer was instructed of the methods by a previously trained colleague, another post-graduate student who had also analysed the AIBL Active data set (but the baseline MR Images only).
Following this the viewer performed segmentation on a set of 20 participants to become accustomed to processing images.

After discussion with the neuroradiologists, the following guidelines were obtained:

*Segment the periventricular hyperintensities, the anterolateral and posterolateral caps of white matter hyperintensities around the ventricles, and lateral walls if they are hyperintense and over 2 voxels in thickness.

*Segment the deep white matter hyperintensities and exclude deep lesions that become sulci in the next slice, as these regions are not hyperintensities but partial voluming of cortical grey matter, creating the illusion of white matter hyperintensities

*Exclude hyperintense regions in the anterior inferior surface of the brain (prefrontal cortex and gyrus rectus). These regions are very often inclusions of base of skull bone (so are very hyperintense and easy to distinguish from other hyperintensities).

*Exclude hyperintensities that occur as a result of bands of artefact due to RF interference (Iwama et al. 1989). These artefacts create horizontal lines across the image, most often in the inferior aspect of the images. These create false changes in intensity that may create relative hyper or hypointensities to the surrounding brain parenchyma.

*Exclude any hyperintensity that is part of an ischaemic process (infarct, i.e.: stroke), these are recognised by the continuation of hyperintensity from the white matter outwards to and including the cortex (grey matter), reflecting gliosis. Stroke (unlike lacunes, see below) are excluded as they represent macrovascular disease, which is a different entity from the chronic microvascular process occurring in WMH disease (Kim et al. 2014b)

*With these guidelines, the first 100 baseline images were processed and then viewed with a neuroradiologist and approved. After reliability measures were performed, the next 98 patients were segmented.

* Following all images being segmented for WMH, uniform selection of lacunar and periventricular hypointensities was also performed. Following identification of hypointense areas, review with the expert neuroradiologist enabled differentiation between true lacunar lesions and perivascular spaces. Those areas classified as lacunes were included in the volumetric assessment of WMH because these also represent MRI microvascular disease. Lacune selection was again reviewed when side-by-side segmenting to ensure consistent lesion selection and volume segmentation.

2.6.5 Reliability measurements

As mentioned above, the rater was first educated with a set of 10 cases before redoing them as part of a whole run. This ensured that the "learning" cases were not included in the final volume. Also as outlined, 20 first time point cases were segmented again to test intra-rater reliability (of 91%). This was performed on the initial data to check for drift in methods which was minimal at the time.

At the conclusion of collecting first point data, we also compared our volumes with the volumes segmented by another student in the lab (B. Merkel, a PhD student in the same lab). This student had segmented WMH lesions from the baseline (only), and was also had his segmentations reviewed by an expert neuroradiologist (With Professor P. Desmond, another neuroradiologist). In addition, he used a previous version of Freesurfer (5.2.0), a previous version of ITK-Snap, and completed his volumes on another computer with a different screen in a different room. Despite this, our values were found to have an intra-class correlation coefficient of 99.4% (for single measures, using a 2-way mixed model calculated with SPSS statistics, version 22). This suggested that despite different raters, program versions, computers and neuroradiologists, there is still a high degree of agreeance with volumes calculated in our lab on the same dataset.

2.6.6 Final volume review and evaluation

Following segmentation of all images, lacune correction and reliability measurements, it was apparent that there was a slight drift in methods. This was due to a slight under-filling of first time point segmentations. This was corrected for (by adding in the missing voxels to all baseline images in isolation to the second time point). The final volumes were again viewed with a neuroradiologist who was satisfied this drift had been corrected for as best as possible.

The baseline volumes were then compared to the volumes already completed by the other student in our lab and found to have an intra-class correlation coefficient of 99.4% (for single measures, 2 way mixed effect model calculated with SPSS Statistics, version 22).

2.6.7 Post volume acquisition processing

Volumes were obtained from ITK-SNAP, and adjusted for head volumes (Freesurfer) as outlines above. After WMH identification, their volume was output by ITK-SNAP (in mm^3), and this was converted to a percentage of Intra Cranial Volume (ICV). ICV was estimated with Freesurfer, (Martinos Center for Biomedical Imaging), using its Estimated Total Intracranial Volume (ETIV) output. The patient's scans were longitudinally processed in order to give a more precise estimation of ETIV. Automated volume estimation was used as it is an acceptable alternative to manually segmenting whole brains, which would be not feasible with the number of patients included in the study (Buckner at. Al 2004, Whitwell et al. 2001). The difference was then calculated (initial volume subtracted from first volume), and then change adjusted for variation between scan acquisitions by converting WMH progression to change per year.

2.7 Side-by-side white matter hyperintensity segmentation

2.7.1 Introduction

Side-by-side segmentation was performed on the cmsWMH data, creating a subsequent data set. The processing environment will be discussed first, along with the comparison method and changed performed. Next the post volume acquisition will be described, ending with comparison method and statistics.

2.7.2 Processing environment

The processing environment was identical to that used above. The same computer, screen, operating system and segmentation program were used. The same dark room was used for all segmentation and neuroradiologist review.

In this second method of segmentation however, participant's brains were viewed side-by side. Brains were still zoomed to fill the same amount of screen, and this was possible because a 16:9 aspect ratio screen was used. Both "toolboxes" were minimised and each slice compared between first and second time point and was adjusted.

2.7.3 Comparison method and changes performed.

Prior to performing corrections to images, a sample of 5 participants were viewed side by side with a neuroradiologist and the viewer given instructions on how to amend the segmentations and create a refined subset of white matter hyperintensity segmentations.

This method included:

* A method of scrolling up and down 1 to 2 slices to appropriately view lesions between patients to correct for differences in acquisition angles. Often there was a slight difference in angle of acquisition through the head anterior to posterior and left to right between the scans. This necessitated scrolling between slices to compare lesions. WMH present at baseline in one region (e.g. anterior of right) would line up with the follow up scan well, but the lesion in the opposing half of the image (e.g. posterior or left) would appear 1 to 2 slices deeper. Although time consuming, this method enabled the best comparison of manual segmentation with both scans.

* Segmenting over periventricular WMH lesions to the same extent, although both covering the periventricular caps on individual processing, a side by side comparison revealed some variability in segmenting sub-hyperintense white matter signal. This was corrected for by filling selecting the same degree of hyperintensity in each image.

* Consistently filling out the lateral ventricular walls was also performed. There was a slight tendency to segment walls at the second time point over the first, where both were legitimately hyperintense; the first time point was segmented to match the second.

* Using one time point to look for segmentations in the other. Single to double voxel size hyperintensities were overlooked on a few occasions. This was able to be corrected for with parallel scrolling through image stacks.

* Adjusting contrast of one image to match the other. Most MR Images performed were homogenous, but a number of these images (8) differed from the other as a result of contrast difference. Correcting for this difference enabled detection of white matter disease that was previously not detectable. While there was no standard "reference" image, images were corrected if they visually looked different to the others in terms of grey-white differentiation and overall "brightness" of the offending image. This was performed by comparing the abnormal image to a selection of other "normal" brains randomly from the accepted group of images. This approach was used as using a standard "curve" or window setting (contrast window of that image) still resulted in contrast and brightness differences. This is due to there being no intensity standard in MRI (unlike CT, Goerner et al. 2013), and some images obviously still being slightly abnormal despite the intensity normalisation step performed.

* Viewing of white matter lesions without segmentation images was also performed. At each comparison, both segmentations were turned off and the underlying hyperintensities viewed side by side. This enabled characterisation of appropriateness of the segmentations, which needed only minor sculpting at this stage.

Following the above methods, all volumes were reviewed once more by a neuroradiologist and confirmed to be satisfactory.

2.7.7 Post volume acquisition processing

Volumes were obtained from ITK-SNAP, and adjusted for head volumes and adjusted for time variation as outlined above. The same values for ETIV and years (between scans) as above were used for these volumes.

2.2.8 Comparison of segmentation methods

Both methods were compared in a number of ways. Distributions were compared qualitatively and quantitatively, followed by a comparison of clinical outcomes of each. This is summarised in the concluding chapter with methodological and clinical implications of the new method.

2.2.9 Statistics

All Statistical analyses were performed using SPSS version 22 (on a Windows 7 PC) apart from effect size calculations for independent t-tests and Mann U Whitney tests.

All models were checked by Statistical Consulting Centre, through the School of Mathematics and Statistics (The University of Melbourne).

CHAPTER 3 AN ANALYSIS OF BASELINE POPULATION DEMOGRAPHICS

3.1 Introduction

As the progression of white matter hyperintensities are being compared between two groups, it is necessary to outline the distribution of risk factors between these groups to determine whether a biased distribution may be contributing to any results. As the risk factors are all obtained at baseline only, and progression occurs over the 24 months between MRI scans, the effect of baseline factors on progression will only be tested. An outline of general demographics will first be examined, followed by a detailed breakdown of each vascular risk factor and their summed total. An outline of baseline functional fitness assessment followed by cognitive measures will then be presented, ending with discussion of their impact.

3.2 Results

3.2.1. General demographics

The general demographics are outlined in table 3.2.1. The numbers for each factor corresponding to the control, exercise and total cohort are presented, with absolute numbers and percentages of total displayed. P values are also presented, with a value below 0.05 to be taken as a significant result. There are a total of 48 participants in the control group and 50 in the intervention (exercise) group. Percentages are expressed in terms of these numbers, missing results will therefore not sum to 100% as in the case of PET amyloid status.

As can be seen from the above table, there was a slightly lower number of males versus females for both control (21 Males versus 27 Females) and exercise groups (22 Males versus 28 Females). As this pattern was upheld over both groups, there wasn't a significant difference in the distribution of genders at baseline (p=0.571 Fisher's exact test, 2-sided).

Participants were more often a non-carrier than a carrier of the ApoE ε4 gene. This was reflected in both the control (33 non-carriers versus 15 carriers) and exercise groups (37 non carriers versus 17 carriers). This was again not significant between exercise and control groups due to the even distribution (p=0.363 for Fisher's exact test).

With regard to the PET amyloid imaging, there were greatly reduced numbers of PET positive to PET negative results. This is the case across both control (35 amyloid negative versus 8 amyloid positive) and exercise groups (42 negative versus 5 positive). Again, due to this being spread evenly across both treatment arms, there is no statistical difference (p=0.22 Fisher's exact test). As 8 participants didn't undergo PET imaging (5 in control group versus 3 in the exercise group), subsequent tests with this risk factor would include 90 instead of the full cohort of 98 patients.

Years of education, with a very similar outcome among study groups. The mean values of education years were close for control and exercise groups (14.33 versus 14.12) as were the standard deviations (3.634 for control versus 3.707 for exercise groups). This resulted in a lack of detectable difference between groups (p=0.774) using the two-sample Wilcoxon rank sum for continuous variables.

Table 3.2.1 General Demographics

Demographics	Control		Exercise		Total		P-value *
	Number	% of total	Number	% of total	Number	% of total	
Gender							
Female	27	56.3	28	56.0	55	56.1	0.571
Male	21	43.7	22	44.0	43	43.9	
ApoE ε4 status							
Non-carrier	33	68.7	37	74.0	70	71.4	0.363
Carrier	15	31.3	13	26.0	28	28.6	
PET amyloid status ***							
Negative	35	72.9	42	84.0	77	78.6	0.22
Positive	8	16.7	5	10.0	13	13.3	
Cognitive group classification							
Subjective Memory Complaints	32	66.7	37	74.0	69	70.4	0.28
Mild Cognitive Impairment	16	33.3	13	26.0	29	29.6	
	Mean	SD	Mean	SD	Mean	SD	P value *
Years of education at baseline	14.33	3.634	14.12	3.707	14.224	3.654	0.77
	Mean	SD	Mean	SD	Mean	SD	P value *
Age at time of baseline MRI	74.67	5.709	72.71	5.718	73.66	5.769	0.09
Age at time of follow up MRI	76.67	5.704	74.76	5.771	75.79	5.79	0.10
* Fisher's exact test for dichotomous and two-sample Wilcoxon rank sum for continuous variables ** 90 patients had PET imaging, % expressed as out of 98 (and therefore won't add up to 100%)							

3.2.2. Vascular risk factors

The distribution of vascular risk factors (VRF) are shown in terms of number (and percentage of) each factor in control and exercise groups (and total numbers). Each vascular risk factor has a number of variables that equate to being "positive" for that factor. Individual constituent factors as well as "combined" factors are presented, along with any significance between groups. As there are six different overall risk factors and each have multiple sub-factors, the distribution is therefore presented in a table for each.

For each vascular risk factor, Fisher's exact test was used to look for any baseline differences between exercise and control group, while a Chi-Square test was used to examine differences in the number of vascular risk factors. As can be seen from Tables 3.2.1 through to 3.2.6, there were no statistically significant results between exercise and control groups, including when examining the constituent sub factors that make up each vascular risk factor. Table 3.2.2.1b demonstrates that there is no difference of distribution of obesity across gender and treatment groups.

Table 3.2.2.1a Obesity distribution

OBESITY MEASUREMENTS	Control		Exercise		Total		p-value*
Risk Factor (high)	Number	% of total	Number	% of total	Number	% of total	
Waist measurement							
No	11	22.9	17	34	28	28.6	0.267
Yes	37	77.1	33	66	70	71.4	
Body Mass Index							
No	22	45.8	14	28	36	36.7	0.093
Yes	26	54.2	36	72	62	63.3	
Obesity combined							
Negative	9	18.8	7	14	16	16.3	0.592
Positive	39	81.3	43	86	82	83.7	
* Fisher's exact test, 2 sided							

Table 3.2.2.1.b Obesity versus gender

OBESITY VS SEX VS GROUP	Control		Exercise		Total		p-value*
	Number	%M/F	Number	%M/F	Number	%M/F	
Obesity (combined) Men							
No	4	9.3	2	4.65	6	13.95	0.309
Yes	17	39.53	20	46.51	37	86.05	
Obesity (Combined) Women							
No	5	9.09	5	9.09	10	18.18	0.611
Yes	22	40	23	41.82	45	81.18	
Total	48		50				
p-value* (gender difference)	0.623		0.322		* Fisher's exact test		

Table 3.2.2.2 Hypertension

HYPERTENSION	Control		Exercise		Total		p-value*
Risk Factor (high)	Number	% of total	Number	% of total	Number	% of total	
Hypertension history							
No	35	72.9	43	86	78	79.6	0.14
Yes	13	27.1	7	14	20	20.4	
SBP high							
No	23	47.9	24	48	47	48	1
Yes	25	52.1	26	52	51	52	
DBP high							
No	43	89.6	43	86	86	87.8	0.76
Yes	5	10.4	7	14	12	12.2	
Hypertension medication							
No	29	60.4	27	54	56	57.1	0.547
Yes	19	39.6	23	46	42	42.9	
Hypertension combined							
Negative	17	35.4	11	22	28	28.6	0.181
Positive	31	64.6	39	78	70	71.4	
* Fisher's exact test, 2 sided							

Table 3.2.2.3 Dyslipidaemia

DYSLIPIDAEMIA	Control		Exercise		Total		P-value*
Risk Factor (high)	Number	% of total	Number	% of total	Number	% of total	
Cholesterol							
No	43	89.6	43	86	86	87.8	0.526
Yes	4	8.3	7	14	11	11.2	
Triglycerides							
No	43	89.6	49	98	92	93.9	0.195
Yes	4	8.3	1	2	5	5.1	
Lipid lowering medications							
No	30	62.5	27	54	57	58.2	0.420
Yes	18	37.5	23	46	41	41.8	
Dyslipidaemia combined							
Negative	26	54.2	23	46	49	50	0.545
Positive	22	45.8	27	54	49	50	
* Fisher's exact test, 2 sided							

Table 3.2.2.4 Diabetes

DIABETES	Control		Exercise		Total		P-value*
Risk Factor (high)	Number	% of total	Number	% of total	Number	% of total	
Fasting Glucose							
No	46	95.8	48	96	94	95.9	1
Yes	1	2.1	2	4	3	3.1	
Diabetes History							
No	44	91.7	46	92	90	91.8	1
Yes	4	8.3	4	8	8	8.2	
Diabetic medications							
No	46	95.8	47	94	93	94.9	1
Yes	2	4.2	3	6	5	5	
Diabetes combined							
Negative	44	91.7	46	92	90	91.8	1
Positive	4	8.3	4	8	8	8.2	
* Fisher's exact test							

Table 3.2.2.5 Smoking

SMOKING STATUS	Control		Exercise		Total		P-value*
Risk Factor (high)	Number	% of total	Number	% of total	Number	% of total	
Current Smoker							
No	46	95.8	48	96	94	95.9	1
Yes	2	4.2	2	4	4	4.1	
Smoking ever							
No	27	56.3	35	70	62	63.3	0.209
Yes	21	43.8	15	30	36	36.7	
Smoking combined							
Negative	27	56.3	35	70	62	63.3	0.209
Positive	21	43.8	15	30	36	36.7	
* Fisher's exact test, 2 sided							

Table 3.2.2.6 Atherosclerotic disease

ATHEROSCLEROTIC DISEASE	Control		Exercise		Total		P-value*
Risk Factor (high)	Number	% of total	Number	% of total	Number	% of total	
Heart disease history							
No	44	91.7	46	92	90	91.8	1
Yes	4	8.3	4	8	8	8.2	
Stroke history							
No	47	97.9	49	98	96	98	1
Yes	1	2.1	1	2	2	2	
Atherosclerosis combined							
Negative	43	89.6	46	92	89	90.8	0.738
Positive	5	10.4	4	8	9	9.2	
* Fisher's exact test							

Table 3.2.2.6 Combined vascular risk factor numbers

COMBINED VASCULAR RISK FACTOR TOTAL	Control		Exercise		Total		P-value*
	Number	% of total	Number	% of total	Number	% of total	
1	10	20.8	7	14	17	17.3	0.856
2	13	27.1	15	30	28	28.6	
3	16	33.3	18	36	34	34.7	
4	7	14.6	9	18	16	16.3	
5	2	4.2	1	2	3	3.1	
* Chi squared test							

3.2.3. Baseline functional fitness assessment

The biometric measures of physical activity are also compared between exercise and control groups. They are displayed in terms of mean values, standard deviation and any statistical significance between groups. The results are displayed below in Table 3.2.3. These results demonstrate that there are no statistically significant differences between control and exercise groups for all of the baseline measures that represent baseline functional fitness assessment and baseline weekly physical activity. 1 less patient in the non-dominant hand grip group will reduce subsequent statistical analysis by 1 participant.

Table 3.2.3 Baseline functional fitness assessment

BASELINE FUNCTIONAL FITNESS ASSESSMENT MEASURES	Control		Exercise		Total		P-value*
	Mean	SD	Mean	SD	Mean	SD	
Timed up and go	6.61	2.35	6.38	1.38	6.47	1.91	0.8
Dominant grip force	30.47	9.39	32.77	8.11	31.63	8.80	0.91
Non Dominant grip force**	28.32	9.46	30.28	7.71	29.32	8.62	0.21
Sit to stand test	11.18	3.50	11.57	2.95	11.38	3.22	0.25
6 minute walk test	498	97.49	488.6	83.68	493.2	90.21	0.29
Amount of all intensity activity/week (minutes)	795.6	358.8	800.7	427.2	724.1	289.1	0.82
Number of all intensity activity sessions per week	20.21	9.76	19.74	9.60	19.97	9.63	0.93
Total KCal energy expenditure per week	2611	1058	2715	1309	2664	1187	0.93
* 2-sample Wilcoxon rank sum (Mann-Whitney U). ** 49 (not 50) in exercise and 97 (not 98) in total groups							

3.2.4. Cognitive measures

The results of the neurocognitive tests taken at study commencement are provided below in Table 3.2.4. The mean and standard deviation results for control, exercise and total group values are displayed, along with the p-values for differences between groups.

The results did not demonstrate any statistical significance between baseline measures of cognition in the exercise and control groups. There were no missing values and all 98 patients imaged were tested with all neuropsychological tests.

Table 3.2.4 Baseline neuropsychological tests

BASELINE MEASURES OF COGNITION	Control		Exercise		Total		P-value*
	Mean	SD	Mean	SD	Mean	SD	
ADAS Cog 11	7.69	3.20	7.38	4.46	7.53	3.88	0.31
BRIEF-A BRI raw	42.27	8.5	42.98	7.46	42.63	7.95	0.50
BRIEF-A MI raw	60.31	10.88	61.1	13.91	60.71	12.46	0.77
CDR Score	0.208	0.25	0.19	0.25	0.20	0.25	0.71
HADS A	4.25	2.70	4.2	2.67	4.22	2.67	0.95
MAC- Q	26.73	3.26	26.72	4.28	26.72	3.79	0.82
*2-sample Wilcoxon rank sum							

CHAPTER 4 CONVENTIONAL MANUALLY SEGMENTED WHITE MATTER HYPERINTENSITIES

4.1 Introduction

This chapter will outline the results for WMH lesions obtained using manual segmentation. As two different methods of manual segmentation are being explored in this thesis, they will be defined with individual acronyms. The method employed in this section is the conventional method of manually segmenting WMH lesions, and thus will be designated cmsWMH (conventional manually segmented WMH), whereas the next chapter will use the term sbsWMH to indicate side-by-side WMH (using both time points for reference). When referring to WMH volumes in the literature, they will still be termed WMH instead of referring to them as cmsWMH. This is to avoid confusion between our results and what is reported literature results. Although WMH as a term used in the literature is more analogous to cmsWMH (than sbsWMH), heterogeneous methods in the literature (segmentation type, MRI acquisition/protocol, patient characteristics etc.) and the novelty of our study mean that our results are not verbatim to the literature anyway. Results will be outlined, with the inclusion of general linear models, ending with a discussion and conclusion of this method.

4.2 Results

4.2.1. Distribution and transformation

Distributions and transformations for cmsWMH are in the appendix (Chapter 10, section 10.1)

4.2.2. WMH and age

The distribution of baseline cmsWMH versus age is outlined below in Figure 4.2.2.1, with there being an increase in volume of (corrected) cmsWMH with increasing age (2 tailed Person's correlation p=0.007, r=0.270). There is also a positive correlation between cmsWMH progression and age (at baseline) as outlined in Figure 4.2.2.2. Progression per year was again used due to slight differences in length of time between initial and subsequent MRI scans. This relationship was less significant than age versus baseline cmsWMH but significant nonetheless (2 tailed Pearson's p=0.049, r=0.199). This equated to older patients having a slightly higher progression than younger patients.

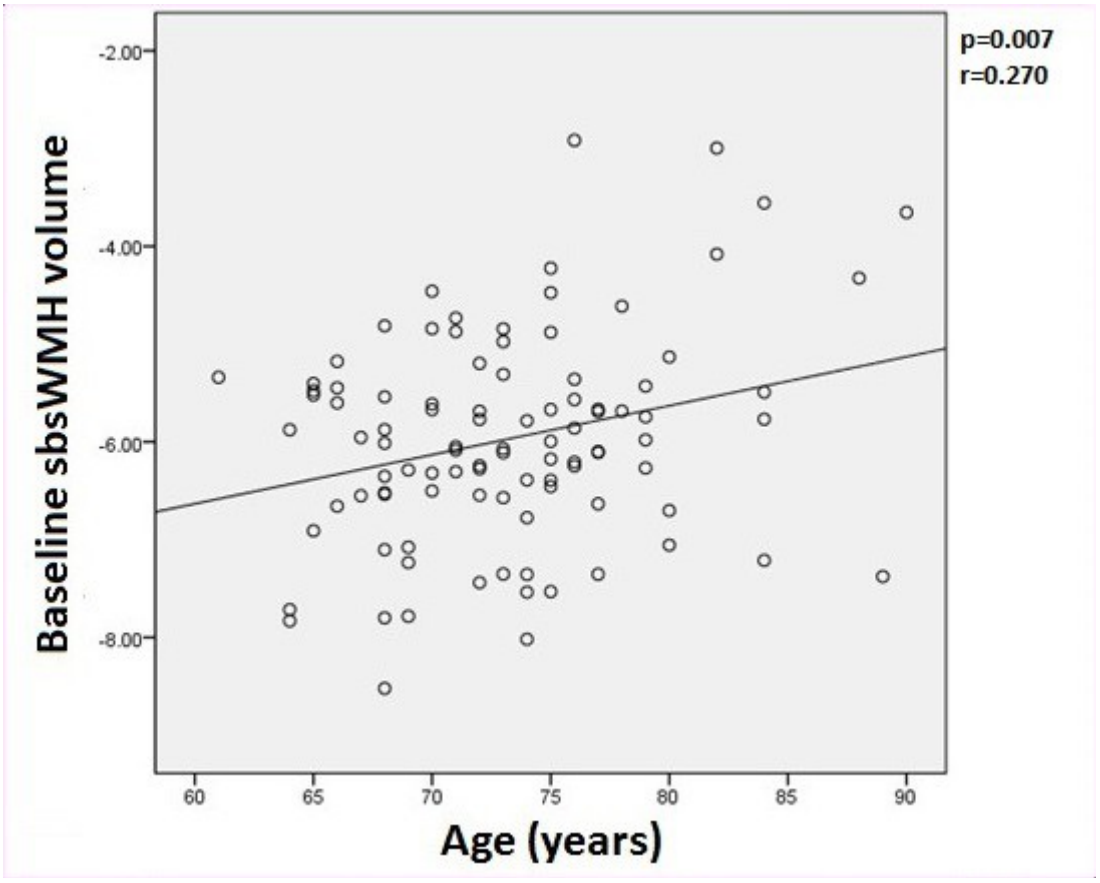

Figure 4.2.2.1 Age (years) versus baseline cmsWMH volume (natural log, ICV corrected)

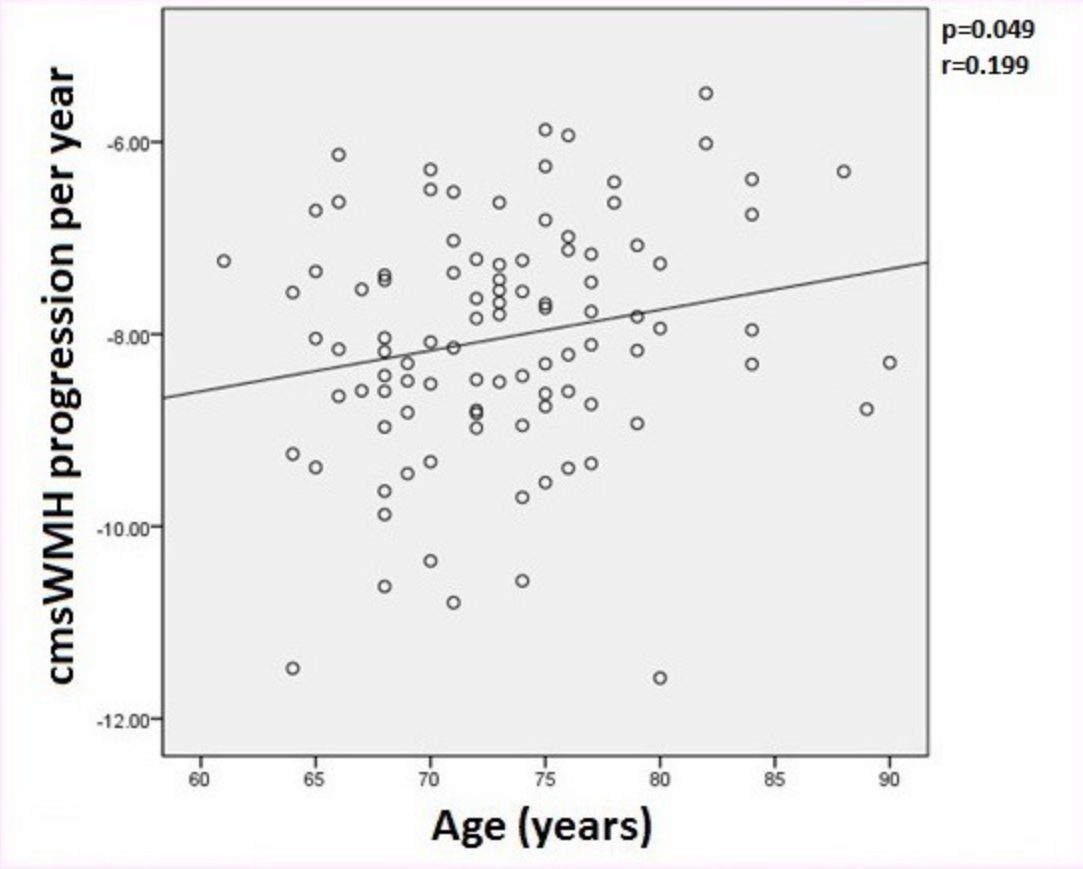

Figure 4.2.2.2 Age (years) versus yearly cmsWMH volume progression (natural log, ICV corrected)

4.2.3. Progression versus baseline volumes

Figure 4.2.3 shows a scatterplot of this relationship. It can be seen that there is a significant and positive correlation between the two (Two-tailed Spearman's correlation of p=0.000 r=0.651). This indicates that the baseline volume of cmsWMH is a strong predictor of the cmsWMH progression.

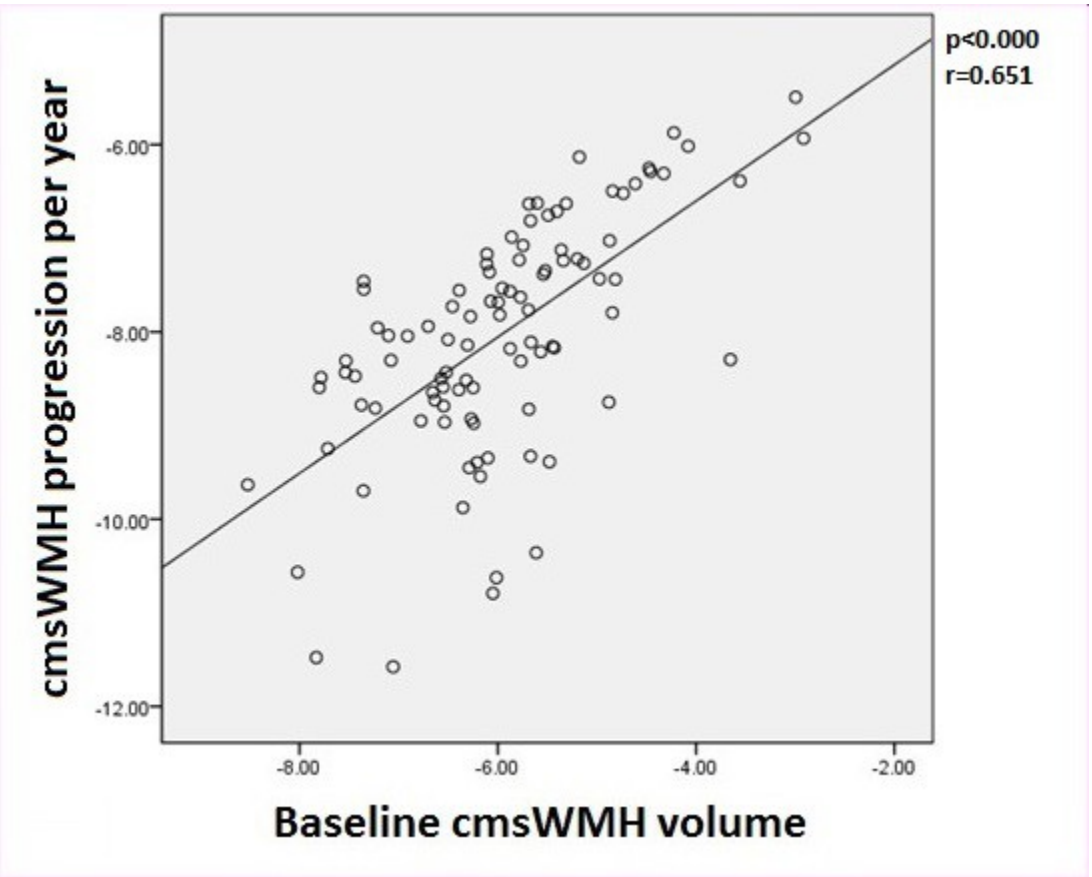

Figure 4.2.3 CmsWMH baseline volume versus yearly cmsWMH volume progression (natural log, ICV corrected)

4.2.4 Associations with baseline and progression data

Age and progression versus baseline cmsWMH values are outlined above, with other associations outlined below. Table 4.2.4.1 demonstrates associations of categorical factors and natural log Baseline cmsWMH values, using the independent sample t-test as cmsWMH is normally distributed. For baseline data, treatment group, gender, ApoE ε4, PET amyloid status and cognitive classification (SMC/MCI) were not significantly associated with cmsWMH volumes. There was also no association with most of the vascular risk factors, however a strong association between Systolic Blood Pressure (p=0.003) is present. Greater volumes of cmsWMH occur in the SBP high group (p=0.003, -5.67 mean natural log volumes in high SBP vs -6.30 mean natural log volumes in the non-elevated SBP), corrected for head size. This was again the case for high DBP (p=0.009, -5.28 mean natural log volume in the high group vs -6.07 mean volume in the low group) corrected for head size.

Table 4.2.4.1 Categorical factors versus cmsWMH baseline volume

Categorical factor versus log of baseline corrected cmsWMH volume. Independent sample t-test. *=Equal variance not assumed		
Factor	p-value*	Effect size (Cohen's D)
Treatment group	0.73	0.07
Sex	0.34	0.19
Pet amyloid status	0.21	0.44
ApoE ε4 status	0.35	0.21
Cognitive status (SMC/MCI)	0.97	0.01
Waist High	0.25	0.26
BMI High	0.58	0.12
Obesity combined	0.09	0.43
History of hypertension	0.89	0.03
High SBP	0.003**	0.62
High DBP	0.009**	0.82
Hypertension medication	0.87	0.03
Hypertension combined	0.20	0.29
Cholesterol high	0.14	0.54
Triglycerides high	0.32	0.60
on lipid lowering medication	0.28	0.23
dyslipidaemia combined	0.87	0.03
Elevated fasting glucose	0.96	0.04
History of Diabetes	0.88	0.06
On diabetic medications	0.71	0.14
Diabetes combined	0.88	0.06
Current smoker	0.37	0.33
Smoking combined (ex/current)	0.35	0.20
heart disease history	0.67	0.16
Stroke history	0.19	2.20
Atherosclerosis combined	0.30	0.43
** = p-value below 0.05		

Table 4.2.4.2 demonstrates the partial correlation of cmsWMH and continuous factors which are normally distributed (baseline functional fitness assessment measures). The measures of timed up and go and sit to stand test needed to be natural log transformed in order to satisfy normality. A partial correlation was used to correct for age and gender as both of these factors can have an impact on the performance in physical activity metrics. As can be seen in the data, there were no partial correlations between cmsWMH and baseline functional fitness assessment metrics. It can also be seen that there are no correlations against the baseline measures of weekly minutes of exercise, frequency of exercise of caloric expenditure.

Table 4.2.4.2 Relationship between cmsWMH baseline volume and continuous variables.

Partial correlation of baseline corrected cmsWMH volume with continuous factors, corrected for Age and Sex		
Continuous Factor	p-value	Effect size (r)
Step number	0.98	0.003
Timed up and go (natural log)	0.99	0.001
Dominant hand grip force	0.63	0.02
Non Dominant hand grip force	0.87	0.02
Sit to stand test (natural log)	0.49	0.01
6 minute walk distance	0.28	0.11
Minutes/week all intensity activity (natural log)	0.35	0.01
Frequency/week all intensity activity (natural log)	0.11	0.03
Caloric expenditure per week all activity levels	0.35	0.04

Table 4.2.4.3 outlines the Spearman correlation with baseline cmsWMH factors and other measures using a Spearman correlation. It was chosen in this case as these values could not be transformed to normality. Here the numbers of vascular risk factors were treated as a categorical and ordinal variable. This assumed an increasing effect with larger number of VRF and didn't analyse individual contributions of VRF in this group. As each factor could have a variable factor on each participant, be present for a variable amount of time and possibly have different strength of effects in certain combinations, a detailed analysis of this is beyond the scope of this thesis. As can be seen, there was no association with the cmsWMH values and either years of education, number of vascular risk factors or any of the cognitive measures. Age corrected scores where included where possible, but in further general linear models the raw scores (non-age corrected) will be used as age will be a covariate in modelling.

Table 4.2.4.3 Relationship between cmsWMH baseline volume and education, number of vascular risk factors and baseline cognitive scores.

Spearman correlation of baseline corrected cmsWMH volume with continuous factors		
Continuous factor	p-value	Effect size (r)
Education (years)	0.18	0.14
Number of vascular risk factors	0.13	0.16
ADAS Cog 11	0.32	0.10
BRIEF-A BRI T score*	0.22	0.13
BRIEF-A MI T score*	0.71	0.04
BRIEF-A total T score*	0.31	0.11
HADS A	0.48	0.07
MAC- Q	0.80	0.03

*= T scores used as they are age adjusted versions of BRIEF A. 7 patients excluded as they inconsistently answer, answer too infrequently or satisfy negativity criteria

The remaining tables in this chapter outline the relationships between study factors and change in cmsWMH over time (cmsWMH progression). Table 4.2.4.4 describes the relationship between cmsWMH progression and categorical factors. There is no effect of treatment group (main intervention) and there is no impact of gender, pet amyloid or ApoE ε4 or cognitive status. There is now a significant association with BMI, one of the obesity measures. There is more progression in the BMI group below 30 (mean = -5.89 natural log cmsWMH volume) compared to the high BMI group with values above 30 (mean = -6.02 natural log volume). A comparison of histograms between low BMI (figure 4.2.4.1) and high BMI (figure 4.2.4.2) are presented. Non-log transformed figures are shown in this case to better demonstrate the effect of low values on data distribution. It can be seen that a large number of low cmsWMH progression values are present in the BMI high group. It can also be seen that there is more patients with higher progression of cmsWMH in the high BMI group (above values of 0.010). Exclusion of patients with lower cmsWMH values results in loss of any significance (p=0.057), even when excluding the lowest 6 patients allowing only cmsWMH progression values above 100 (resulting in 35 in the low BMI group versus 57 in the high group). With statistical advice it has been confirmed that the association with BMI is an outlier and not significant. When excluding higher numbers (changing the lower threshold of cmsWMH progression from 100 to200, 500, 1000 and even 2000), there also is no significant difference among any of the subsequent values. From here onwards BMI will not be considered a significant result due to the above factors.

The p=0.004 significance of higher cmsWMH values in the higher SBP group (mean -7.70 natural log corrected volume) versus lower SBP group (mean -8.40 natural log corrected volume) was a true effect, with equal numbers in each group (47 low SBP and 51 high SBP) and an equal number of low cmsWMH values. For comparison to the above artefact, the non-log transformed distributions of low and high SBP values are presented in figures 4.2.4.3 and 4.2.4.4 respectively. Here is can be seen that the majority of cases are in the low cmsWMH progression but this is present in both cases. In the high SBP group it can also be seen that there are a larger number of cases above the 0.001 value.

Table 4.2.4.4 Categorical factors against Ln cmsWMH progression volumes.

Categorical factors versus log corrected cmsWMH progression volume. Independent sample t-test. P values given for equal variance not assumed.		
Factor	p-value	Effect size (Cohen's D)
Treatment group	0.61	0.10
Sex	0.71	0.08
Pet amyloid status	0.21	0.41
ApoE ε4 status	0.58	0.09
Cognitive status (SMC/MCI)	0.40	0.18
Waist High	0.60	0.12
BMI High	0.021*	0.36
Obesity combined	0.81	0.06
History of hypertension	0.71	0.09
High SBP	0.004*	0.60
High DBP	0.43	0.26
Hypertension medication	0.69	0.08
Hypertension combined	0.10	0.36
Cholesterol high	0.06	0.59
Triglycerides high	0.18	0.53
lipid lowering medication	0.52	0.13
dyslipidaemia combined	0.98	0.005
Elevated fasting glucose	0.54	0.43
History of Diabetes	0.87	0.06
On diabetic medications	0.69	0.16
Diabetes combined	0.78	0.06
Current smoker	0.25	0.59
Smoking combined	0.67	0.09
heart disease history	0.71	0.15
Stroke history	0.08	2.37
Atherosclerosis combined	0.38	0.36
** = p-value below 0.05		

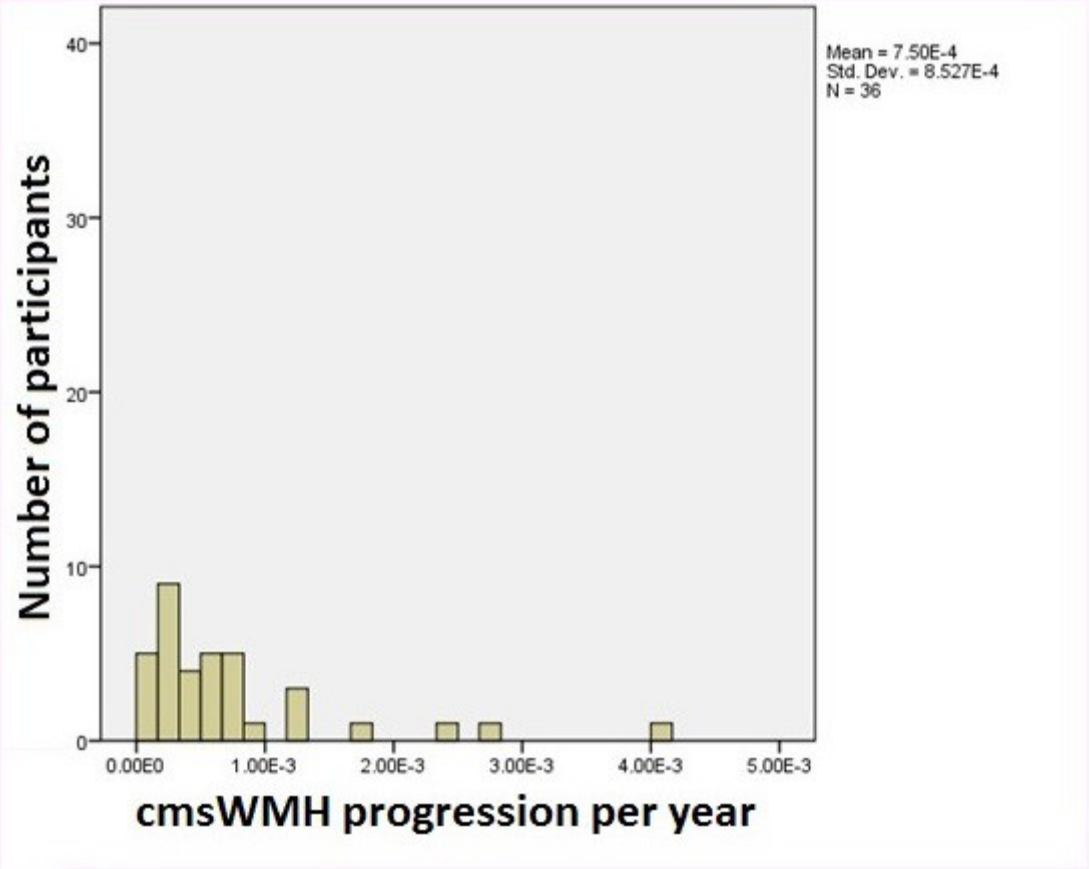

Figure 4.2.4.1 Distribution of yearly cmsWMH volume progression (ICV corrected) versus number of participants. BMI below 30 group.

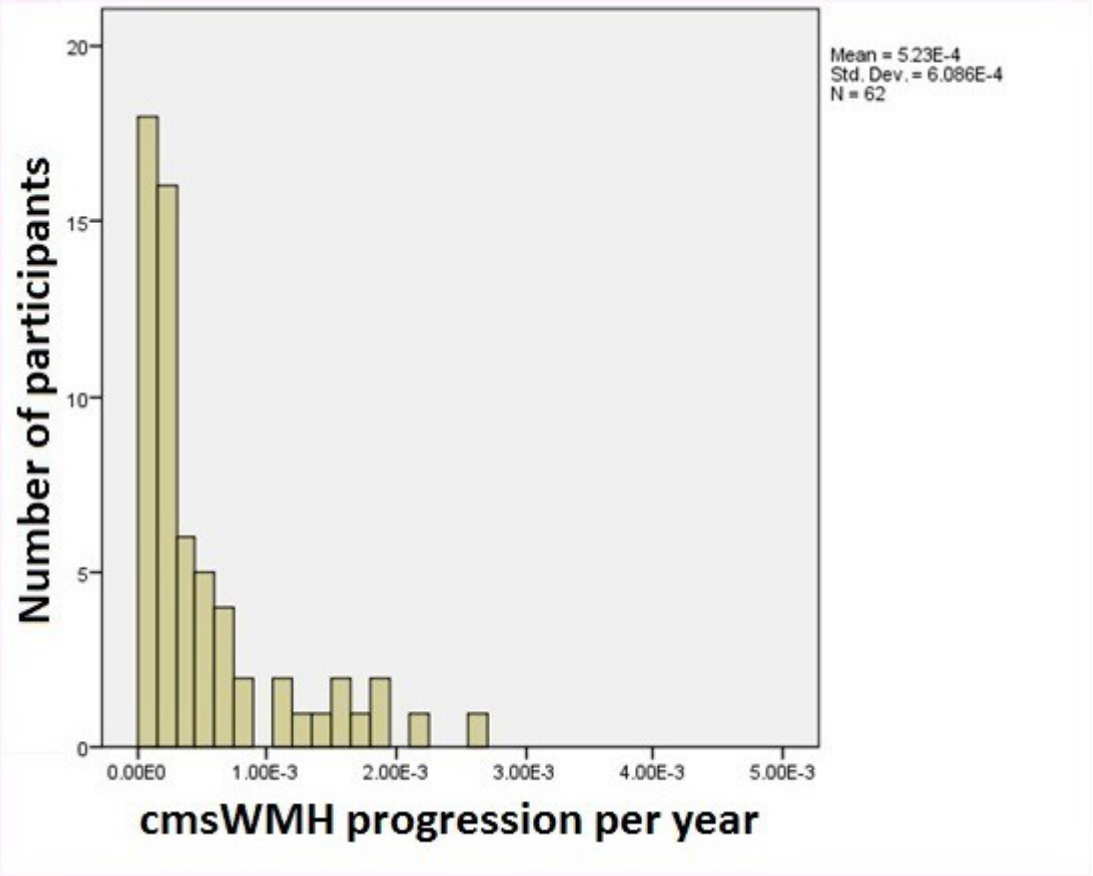

Figure 4.2.4.2 Distribution of yearly cmsWMH volume progression (ICV corrected) versus number of participants, BMI above 30.

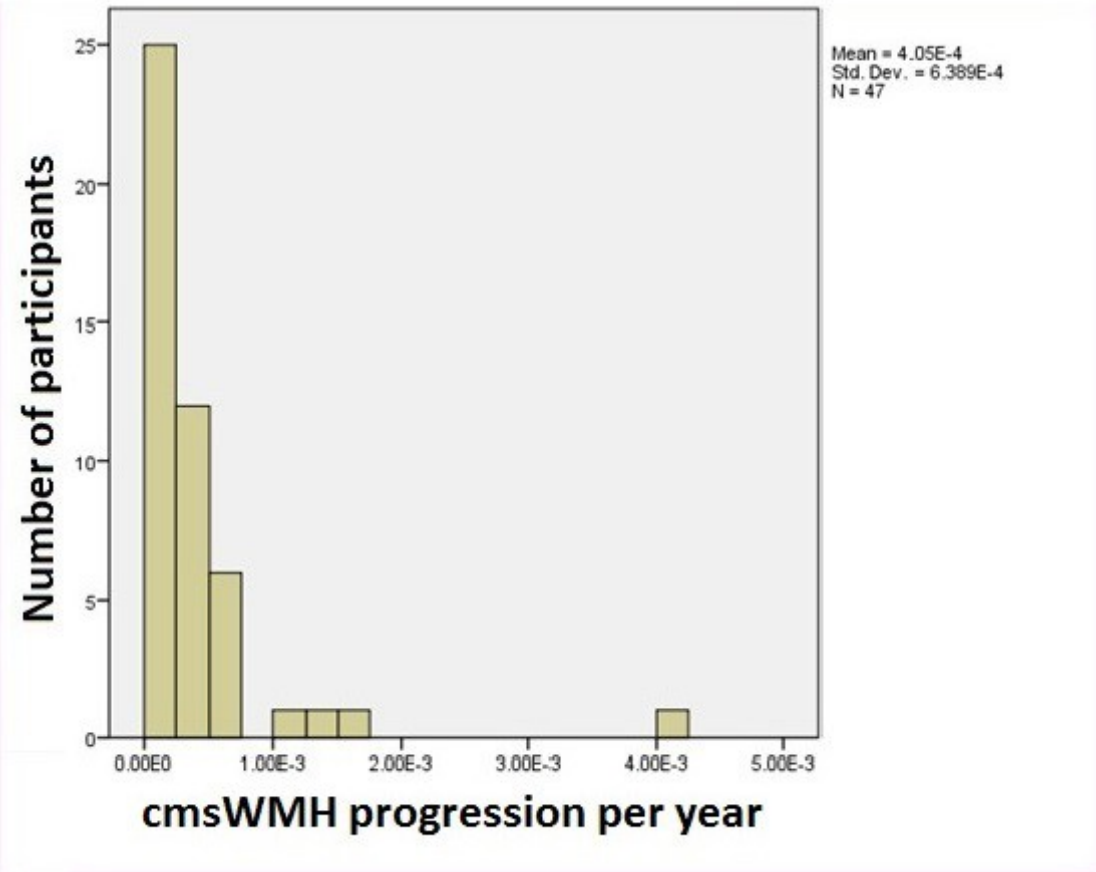

Figure 4.2.4.3 Distribution of yearly cmsWMH volume progression (ICV corrected) versus number of participants, low SBP group.

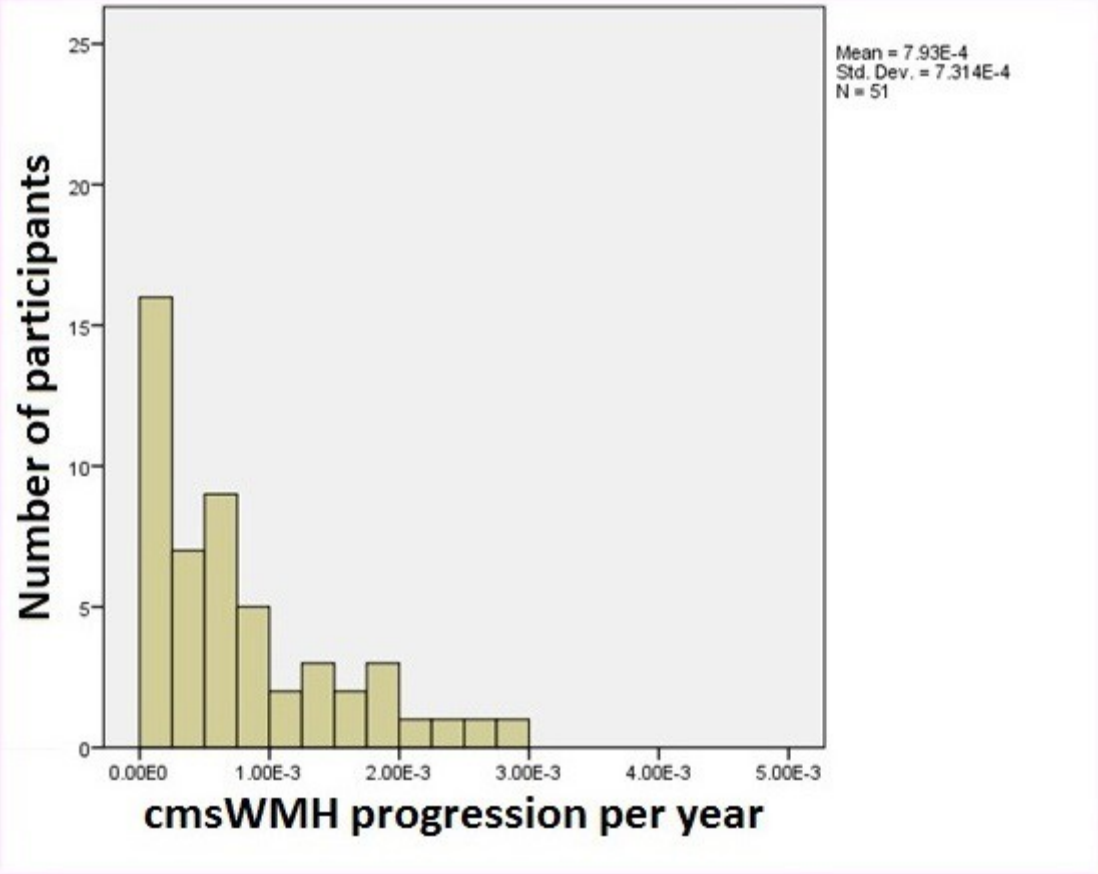

Figure 4.2.4.4 Distribution of yearly cmsWMH volume progression (ICV corrected) versus number of participants, high SBP group.

Partial correlations are next reported for cmsWMH progression volumes against baseline functional fitness assessment and baseline weekly physical activity measurements in Tables 4.2.4.5 and 4.2.4.6, with values corrected for age and sex (4.2.4.5) and age, sex and baseline cmsWMH volumes (4.2.4.6). Natural log of timed up and go and sit to stand test are presented, while remaining values are naturally distributed without transformation. In both sets of partial correlations, it can be seen that there is no partial correlation between both baseline functional fitness assessment measurements and baseline weekly exercise data against cmsWMH volumes.

Table 4.2.4.5 Relationship between sbsWMH progression values and baseline functional fitness assessment, corrected for age and sex.

Partial correlation of corrected log cmsWMH progression volume and continuous factors, corrected for Age and Sex		
Continuous variables	p-value	Effect size (r)
Step number	0.83	0.02
Timed up and go (natural log)	0.82	0.01
Dominant hand grip force	0.19	0.14
Non Dominant hand grip force	0.46	0.08
Sit to stand test (natural log)	0.96	0.000
6 minute walk distance	0.67	0.04
Minutes/week all intensity activity (natural log)	0.90	0.03
Frequency/week all intensity activity (natural log)	0.51	0.03
Caloric expenditure per week all activity levels	0.85	0.01

Table 4.2.4.6 Relationship between sbsWMH progression values and baseline functional fitness assessment, corrected for age, sex and cmsWMH volumes.

Partial correlation of corrected log cmsWMH progression volume and continuous factors, corrected for Age, Sex and baseline cmsWMH volume		
Continuous variables	p-value	Effect size (r)
Step number	0.80	0.22
Timed up and go (natural log)	0.78	0.03
Dominant hand grip force	0.21	0.13
Non Dominant hand grip force	0.41	0.08
Sit to stand test (natural log)	0.64	0.05
6 minute walk distance	0.76	0.04
Minutes/week all intensity activity (natural log)	0.38	0.03
Frequency/week all intensity activity (natural log)	0.70	0.05
Caloric expenditure per week all activity levels	0.33	0.12

Table 4.2.4.7 displays cmsWMH progression values against the remaining continuous variables. A Spearman correlation was performed as these variables could not be transformed into a normal distribution. There was no association with cmsWMH volumes (corrected) and education, number of vascular risk factors and most of the neurocognitive assessment results. The number of vascular risk factors was again treated as a categorical variable, assuming an increase of effect with increasing number of VRF, with further analysis being outside the scope of the thesis. All scores used the full 98 patients, whereas the BRIEF-A scores used 91 patients due to inconsistent, infrequent and negative answering (as tested by individual criteria for each of these factors). There was a correlation between total BRIEF A T-score and cmsWMH volume progression (with negative correlation, r=-0.226). Age corrected values were used where available (for BRIEF A scores). The relationship between BRIEF A total score and cmsWMH progression is also significant if raw scores (not corrected for age) are used (p=0.038, r=-.218 Spearman's correlation).For subsequent general linear modelling age will be a covariate so non age corrected (raw) values will be utilised.

Table 4.2.4.7 Relationship between cmsWMH progression and education, number of vascular risk factors and cognition.

Pearson correlation of corrected cmsWMH progression volume with continuous factors		
Continuous variables	p-value	Effect size (r)
Education (years)	0.23	0.12
Number of vascular risk factors	0.30	0.11
ADAS Cog 11	0.83	0.02
BRIEF-A BRI T score **	0.031*	0.23
BRIEF-A MI T score **	0.23	0.13
BRIEF-A Total T score* *	0.05	0.20
HADS A	0.08	0.18
MAC- Q	0.93	0.01

* = significant to 0.05 level

**= T scores used as they are age adjusted versions of BRIEF A. 7 patients excluded as they inconsistently answer, answer too infrequently or satisfy negativity criteria

4.2.5. General linear models

This chapter will investigate the correlations with cmsWMH progression as the dependent variable, first investigating effects of exercise, followed by ApoE ε4 status, PET amyloid status and baseline functional fitness assessment. Models will conclude with an examination of the effect of neurocognitive baseline results. Each outcome was examined against all other factors, including in multiples, with a heuristic inclusion and exclusion method adopted based on hypotheses of possible effects. Although some data being investigated is not normally distributed, all residuals have been confirmed to be normally distributed. Logarithmic cmsWMH volumes were chosen as the dependent variable as they resulted in better fitting models with regard to examining normality of residuals. All models have been checked with the Department of Mathematics and Statistics consultancy service at the University of Melbourne.

As the main research outcome is the effect of factors on WMH progression, the dependent variable will be cmsWMH volumes. The majority of tables will examine the effect upon cmsWMH progression with a brief examination of factors upon baseline cmsWMH volumes. P-values below 0.05 were deemed significant, with all p-values in each model to be displayed to indicate possible interactions.

In addition, age and gender was included in all models as this can influence the impact of physical activity. With a large number of possibilities of other covariates are possible, only the relevant general linear models (GLM) will be displayed, with the other possible combinations tested being mentioned in text. Interactions investigated and noted in the tables as a "No" rather than p-value were performed as a separate model and the displayed p-values are the only interactions being tested in each case. Where there is a "No", it can be assumed that all other p-values did not reach significance and interactions did not exist against the factor being investigated.

Table 4.2.5.1 investigates the outcome of exercise against cmsWMH progression, all taking into account age, gender and baseline cmsWMH volumes. Model A1 examines these factors alone, models A2 through A6 investigate the individual effect of VRF number, ApoE ε4 status, PET amyloid status and the cognitive group patients were classified into at baseline (SMC/MCI) and education. Model A7 investigates all these factors together. Other combinations of these factors were investigated with no change in results.

Models A1 through A7 have no interaction with age and gender in any of the models. All models (in addition to other combinations tested) do not show any effect of exercise upon cmsWMH progression. Other covariates tested were also insignificant, including checking every model with the addition of each vascular risk factor individually. Although ApoE was close to significant (p=0.077), other combinations of above factors including ApoE achieved a similar result and all had no impact upon the contribution of exercise in these models. It can be seen that across all models (A1 to A7), that there is a persistent and very strong influence of baseline functional fitness assessment ($p<0.001$, positive B values) upon cmsWMH progression. There were a few instances where SBP reached significance, but did not alter the outcome being investigated, so is presented in its own table as a special case (table 4.2.5.3 mentioned later), as our data is being presented in a hypothesis driven fashion. In addition, analyses were also performed against the exercise and control groups alone, but didn't result in any outcomes. This method of testing halved the number of covariates that could be included in each model, and therefore didn't enable the complexity of analysis needed.

Table 4.2.5.2 (models B1 and B2) are the only models in this chapter to examine interactions with baseline cmsWMH volumes as the dependent variable. When examining B1 we can see that there is an association with age with cmsWMH baseline volume (p=0.005, B=0.053). There was no gender effect upon cmsWMH baseline volumes, and there was no gender interaction with age when cmsWMH baseline volumes were the dependant variable. In Model B2 there was also a significant association with SBP and baseline cmsWMH (p=0.013, B=0.529), and between age and baseline cmsWMH (p=0.023, B=0.279) without any interactions between gender, age and SBP.

As alluded to previously, model C1 (Table 4.2.5.3) investigates an interaction between SBP and cmsWMH progression. Once correcting for an interaction between systolic blood pressure and baseline cmsWMH volumes (non-significant at p=0.71), systolic blood pressure is then significantly associated with cmsWMH progression (p=0.046 B=2.39). As a part of this model, age and gender was tested and found to be non-significant, with baseline cmsWMH volumes remaining strongly significant (p<0.001, with B being positive in the SBP*baselineWMH covariate, but not stated for baselineWMH alone as it is already being corrected for when examining this interaction). All other vascular risk factors along with VRF total, education, ApoE ε4 and PET amyloid status, age and gender were checked for the same interaction (with baseline volume upon cmsWMH progression) but none existed. In the case of model C1, the interaction between SBP and cmsWMH baseline volume approach significance (p=0.077), but once this interaction was taken into account, SBP alone had a significant effect upon cmsWMH progression. This effect also existed in other models, but it did not have an impact upon significance of the other factors so this phenomenon is only mentioned in isolation. Where it is indicated "other VRF effects" or "other effects", it refers to a significant result where both the outcome of interest and that particular factor (or one in isolation) became significant. Again there was no interaction between gender, age and SBP in this scenario. In this model, baseline cmsWMH was very strongly associated with cmsWMH progression.

Table 4.2.5.4 examines the interaction of various factors with ApoE ε4 status. As exercise was already examined previously against ApoE in Model A3 above, this was not displayed again. Across all models displayed here (models D1 to D6), ApoE ε4 did not become significant. In fact the strongest (but not significant) result was in Model A3 (p=0.077) and further investigation with other factors (including investigation of all vascular risk factors) did not influence this outcome nor the models in table 4.2.5.4. Once again, age and gender were not significant while baseline cmsWMH had a persistent and strong effect (p<0.001, B=positive in all models).

Table 4.2.4.5 displays models investigating PET amyloid beta. This set of models is shorter yet again as the interaction with exercise is already displayed in Table 4.2.5.1 (Model A4) and for ApoE ε4 status in Table 4.2.5.4 (D3). As there are 8 patients who did not undergo a PET scan, (Table 3.2.1 for General Demographics), all general linear models are for 90 participants. None of the models were significantly influenced by PET amyloid status (Models E1 through E5). Similarly, age and gender did not have an impact while baseline cmsWMH volume did (strongly, $p<0.001$, positive B values).

Tables 4.2.5.6a and 4.2.5.6b examine the interaction with baseline physical activity measures recorded at baseline and cmsWMH progression. Unlike the previous tables (Tables 4.2.5.1, 4.2.5.4 and 4.2.5.5) which report multiple factors against one covariate, these tables (as well as subsequent ones) summarise all these factors investigated against multiple physical activity measures. Models F1 to F6 represent examinations for separate baseline functional fitness measurements, whilst models F7 to F9 represent the baseline weekly activity as calculated from questionnaires. In all models, there was no effect of any baseline functional fitness assessment measurement on cmsWMH progression when taking into account age, sex and baseline cmsWMH volume. Age and gender were not significant but baseline cmsWMH remained strong ($p<0.001$, positive B values). There was no significant effect of exercise groups, ApoE ε4 or PET amyloid status, number of VRF or any individual VRF investigated.

Table 4.2.5.7 investigates interactions between neurocognitive outcomes and cmsWMH progression. Similar to Table 4.2.5.6, models G1 through G6 investigate individual covariates for each model and are a summary of all investigations undertaken. All models showed a sustained effect of baseline cmsWMH volume on cmsWMH progression, without any significant effect of age and gender. Non age and gender corrected models were also run without significance (but age-corrected alternatives needed to be used in the case of BRIEF-A results as age appropriate corrections are needed for function).

The Alzheimer's disease Assessment Scale-Cognitive (ADAS-Cog) did not show any relationship with cmsWMH progression (Model G1). This was again the case with the BRIEF A BRI, MI and total raw score executive function assessments (Models G2, G3 and G4), using data with 7 patients excluded due to inconsistency and infrequency of answering plus negativity scores taken into account. The Hospital Anxiety and Depression (Anxiety) test (HADS A), a measure of anxiety was associated with progression of cmsWMH volumes (p=0.038, Model G5), with a negative correlation (B=-.077). There were no interactions with HADS A and age, gender or baseline cmsWMH volume. This negative correlation implies that those with a lower anxiety score had more cmsWMH progression and those with a higher HADS A score had less progression. Having a "diagnosis" of anxiety is defined as a HADS A score of 8 and above, this was present in only 11 of the patients and the binary yes/no diagnosis was not associated with WMH progression (not significant for all correlations and GLM significance p = 0.364 in a model including baseline cmsWMH, age, gender, and not significant with any other factors in additional GLM combinations tested).

4.3 Summary of cmsWMH statistics:

There was no significance of physical activity with both baseline and progression cmsWMH volumes across both correlation and GLM statistics. The same was true for ApoE ε4 and PET amyloid status. In all models, there was also no effect of baseline PA measures, gender, years of education, cognitive (SMC,MCI) group and number of VRF.

Age was significantly associated with baseline cmsWMH for both correlation and GLM, and was associated with cmsWMH progression volumes for correlation statistics only.

Of the VRF tested individually, SBP was significant across correlation and GLM for both baseline and progression cmsWMH volume. DBP was only significant in correlation with baseline cmsWMH volume. BMI was only significantly correlated with cmsWMH progression volume only and this did not carry over to the GLM.

There was no association with neurocognitive assessments with both types of baseline cmsWMH statistics. BRIEF A BRI score was significantly correlated with cmsWMH progression volume, but not a significant covariate in the GLM. The reverse is true for HADS-A score, not significant with cmsWMH progression volume in correlation but significant in the GLM.

Baseline volume was a significant factor across correlation and GLM for all models investigating cmsWMH progression volume.

Table 4.2.5.1 GLM of factors against exercise intervention group, dependent variable natural log cmsWMH (corrected) volume progression.

	Model A1		Model A2		Model A3		Model A4		Model A5		Model A6		Model A7	
	F	Sig	F	Sig	F	Sig	F	Sig	F	Sig	F	Sig	F	Sig
Corrected model	16.142	<0.001	12.803	<0.001	13.599	<0.001	10.169	<0.001	12.912	<0.001	13.127	<0.001	5.643	<0.001
Age	0.245	0.515	0.28	0.598	0.307	0.581	0.218	0.642	0.263	0.0.609	0.187	0.666	0.264	0.609
Sex	0.04	0.708	0.05	0.0.824	0.134	0.715	0.096	0.757	0.007	0.933	0.023	0.881	0.034	0.855
Baseline WMH	56.402	<0.001	55.036	<0.001	58.942	<0.001	43.501	<0.001	54.785	<0.001	56.581	<0.001	41.823	<0.001
Number VRF	-	-	0.082	0.776	-	-	-	-	-	-	-	-	0.003	0.959
ApoE	-	-	-	-	2.433	0.077	-	-	-	-	-	-	0.508	0.478
Abeta	-	-	-	-	-	-	0.327	0.569	-	-	-	-	0.087	0.769
Education	-	-	-	-	-	-	-	-	0.403	0.527	-	-	0.104	0.748
SMC/MCI	-	-	-	-	-	-	-	-	-	-	1.038	0.311	737	0.393
Exercise treatment	1.041	0.372	1.071	0.303	1.279	0.308	0.865	0.355	1.075	0.302	1.184	0.279	0.952	0.332
Other VRF effects?	No		No		No		No		No		No		No	

Table 4.2.5.2 GLM of Age, Sex and Systolic Blood Pressure (SBP), Dependent variable natural log cmsWMH baseline volume

	Model B1		Model B2	
	F	Sig	F	Sig
Corrected model	4.688	0.011	5.429	0.002
Age	8.433	0.005*	5.354	0.023*
Sex	1.175	0.189	1.1825	0.18
SBP	-	-	6.38	0.013*
Age x Sex interaction?	No		No	
SBP x Age interaction?	-		No	
SBP x Sex interaction?	-		No	

Table 4.2.5.3 GLM of SBP effect of cmsWMH progression taking into account SBP and Baseline cmsWMH interaction

	Model C1	
	F	Sig
Corrected model	14.092	0
Age	0.121	0.729
Sex	0.015	0.902
Baseline WMH	49.104	<0.001
SBP * baseline WMH	3.327	0.071
SBP	4.088	0.046*
Age x Sex interaction?	No	
SBP x Age interaction?	No	
SBP x Sex interaction?	No	

Table 4.2.5.4 GLM of factors against ApoE ε4 status, dependent variable natural log cmsWMH (corrected) volume progression.

	Model D1		Model D2		Model D3		Model D4		Model D5		Model D6	
	F	Sig	F	Sig	F	Sig	F	Sig	F	Sig	F	Sig
Corrected model	16.63	<0.001	13.167	<0.001	10.116	<0.001	13.258	<0.001	13.35	<0.001	6.233	<0.001
Age	0.132	0.717	0.142	0.708	0.184	0.669	0.141	0.709	0.092	0.762	0.161	0.69
Sex	0.15	0.699	0.156	0.693	0.134	0.715	0.081	0.777	0.115	0.735	0.035	0.853
Baseline WMH	58.916	<0.001	57.131	<0.001	44.287	<0.001	57.239	<0.001	58.613	<0.001	41.839	<0.001
Number VRF	-	-	0.019	0.892	-	-	-	-	-	-	0.001	0.97
Abeta	-	-	-	-	0.052	0.82	-	-	-	-	0.043	0.837
Education	-	-	-	-	-	-	0.284	0.595	-	-	0.077	0.782
SMC/MCI	-	-	-	-	-	-	-	-	0.551	0.46	0.656	0.42
ApoE ε4 Status	2.205	0.141	2.158	0.145	0.698	0.406	2.105	0.15	1.843	0.178	0.506	0.479
Other VRF effects?	No		No		No		No		No		No	

Table 4.2.5.5 GLM of factors against PET amyloid status, dependent variable natural log cmsWMH (corrected) volume progression

	Model E1		Model E2		Model E3		Model E4		Model E5	
	F	Sig	F	Sig	F	Sig	F	Sig	F	Sig
Corrected model	12.515	<0.001	9.894	<0.001	9.9	<0.001	10.148	<0.001	7.093	<0.001
Age	0.136	0.713	0.132	0.717	0.137	0.712	0.123	0.726	0.123	0.727
Sex	0.094	0.76	0.092	0.762	0.076	0.784	0.037	0.848	0.016	0.9
Baseline WMH	42.751	<0.001	42.11	<0.001	42.878	<0.001	44.209	<0.001	41.592	<0.001
Number VRF	-	-	0	0.999	-	-	-	-	0.001	0.981
Education	-	-	-	-	0.018	0.894	-	-	0.077	0.783
SMC/MCI	-	-	-	-	-	-	0.798	0.374	0.839	0.362
PET Amyloid status	0.231	0.632	0.228	0.634	0.221	0.639	0.194	0.661	0.176	0.676
Other VRF effects?	No		No		No		No		No	

Table 4.2.5.6a GLM of factors against baseline functional fitness assessment, dependent variable natural log cmsWMH (corrected) volume progression

	Model F1		Model F2		Model F3		Model F4		Model F5		Model F6	
	F	Sig	F	Sig	F	Sig	F	Sig	F	Sig	F	Sig
Corrected model	15.728	<0.001	15.714	<0.001	16.255	<0.001	16.027	<0.001	15.836	<0.001	15.761	<0.001
Age	0.046	0.831	0.056	0.814	0.66	0.419	0.429	0.509	0.211	0.647	0.173	0.678
Sex	0.07	0.791	0.062	0.803	0.809	0.371	0.336	0.563	0.02	0.889	0.024	0.876
Baseline WMH	56.032	<0.001	56.01	<0.001	55.937	<0.001	56.262	<0.001	56.507	<0.001	55.975	<0.001
Step test (number steps)	0.052	0.819	-	-	-	-	-	-	-	-	-	-
TUG (natural log) (s)	-	-	0.018	0.894	-	-	-	-	-	-	-	-
Grip Dom (kg) Grip	-	-	-	-	1.632	0.205	-	-	-	-	-	-
nonDom (kg) SitS	-	-	-	-	-	-	0.765	0.384	-	-	-	-
(natural log) (s)	-	-	-	-	-	-	-	-	0.31	0.579	-	-
6 min walk test (m)	-	-	-	-	-	-	-	-	-	-	0.13	0.719
Other effects?*	No		No		No		No		No		No	

* Other effects investigated include exercise group, ApoE ε4 status, PET amyloid status, number of VRF and all other VRF.

Table 4.2.5.6b GLM of factors against baseline weekly exercise measurements, dependent variable natural log cmsWMH (corrected) volume progression

	Model F7		Model F8		Model F9	
	F	Sig	F	Sig	F	Sig
Corrected model	16.036	<0.001	15.770	<0.001	16.102	<0.001
Age	0.088	0.767	0.085	0.771	0.090	0.764
Sex	0.015	0.903	0.021	0.885	0.007	0.933
Baseline WMH	57.248	<0.001	55.553	<0.001	57.470	<0.001
Min/week exercise (natural log)	0.787	0.377	-	-	-	-
Frequency/week exercise (natural log)	-	-	0.152	0.698	-	-
Weekly Kcal expenditure	-	-	-	-	0.946	0.333
Other effects?*	No		No		No	

* Other effects investigated include exercise group, ApoE ε4 status, PET amyloid status, number of VRF and all other VRF.

Table 4.2.5.7 GLM of factors against baseline functional fitness assessment, dependent variable natural log cmsWMH (corrected) volume progression

	Model G1		Model G2		Model G3		Model G4		Model G5		Model G6	
	F	Sig	F	Sig	F	Sig	F	Sig	F	Sig	F	Sig
Corrected model	16.281	<0.001	14.212	<0.001	13.738	<0.001	14.078	<0.001	17.558	<0.001	15.71	<0.001
Age	0.197	0.658	0.101	0.751	0.132	0.717	0.115	0.736	0	0.999	0.107	0.745
Sex	0.045	0.833	0.172	0.172	0.035	0.852	0.061	0.806	0.176	0.676	0.054	0.816
Baseline WMH ADAS Cog	54.047	<0.001	48.754	<0.001	49.201	<0.001	48.646	<0.001	58.035	<0.001	55.716	<0.001
11 score BRIEF A BRI	1.372	0.244	-	-	-	-	-	-	-	-	-	-
raw score** BRIEF A MI	-	-	1.963	0.165	-	-	-	-	-	-	-	-
raw score** BRIEF A total	-	-	-	-	1.189	0.279	-	-	-	-	-	-
raw score** HADS A	-	-	-	-	-	-	1.633	0.205	-	-	-	-
score	-	-	-	-	-	-	-	-	4.421	0038*	-	-
MAC Q score	-	-	-	-	-	-	-	-	-	-	0.008	0.928
Other effects?*	No		No		No		No		No		No	

* = Other effects investigated include exercise group, years of education, ApoE ε4 status, PET amyloid status and all other VRF

** = Patients rejected if they fail inconsistency of answering, infrequency score or negativity scoring positive (7 patients rejected as a result)

CHAPTER 5 SIDE BY SIDE WHITE MATTER HYPERINTENSITIES

5.1 Introduction

This chapter will outline the results for WMH lesions using manual segmentation with the side by side method. The distribution of baseline and progression sbsWMH volumes will be presented, along with the relationship to age. The effect of baseline volumes on sbsWMH change will then be discussed. The general linear models will follow a similar pattern to how models were presented above in chapter 4. The results will then be followed by a discussion and conclusion of these results, with comparisons between the two manual segmentation methods being presented in the following chapter.

5.2 Results

5.2.1. Distribution and transformations

Distributions and transformations for cmsWMH are provided in the appendix (Chapter 10, section 10.1)

As volumes of sbsWMH (normally in units of mm^3) are all corrected for intracranial volume (also in mm^3), the units cancel out and results represent a ratio of sbsWMH volume to head size (absolute in the case of baseline volumes and per year in the case of progression volumes).

The baseline distribution of sbsWMH is presented below in Figure 5.2.1.1. This relationship has a strong positive skew (of 4.3), with the majority of participants having low volumes of sbsWMH at baseline. Due to this, baseline sbsWMH volumes are not normally distributed (Kolmogorov Smirnov value of 0.000). The volumes corrected for head size are small because they are corrected for head size, which involves dividing the sbsWMH volume by the much larger volume of estimated intracranial volume results (obtained from Freesurfer). Once the baseline sbsWMH volumes were log transformed (using natural log), it can be seen that the distribution changes towards normality (Figure 5.2.1.2). This was confirmed with a Kolmogorov Smirnov value of 0.200.

Progression values are not only corrected for intracranial volume, but for time elapsed between each scan. This creates progression values as volume change (corrected) per year, and corrects for potential further sbsWMH progression with a larger time elapsed between scans. The distribution of corrected sbsWMH volume progression is shown in Figure 5.2.1.3. This distribution is also positively skewed (skew of 2.3) and not normally distributed (Kolmogorov score of 0.000). A natural log transform of sbsWMH progression is presented in Figure 5.2.1.4. This distribution resembles a normal distribution but appears to suffer from a negative skew. This was confirmed with a skewness value of -0.853. Despite its appearance, this distribution is not normally distributed (Kolmogorov-Smirnov value of 0.003). Using all other possible transformations to normality failed to transform the sbsWMH volume to normality. As such, subsequent simple correlations will be performed using non-parametric measures. The natural log values will still be used as these values provided a better fit of residuals (being normally distributed) later in the chapter.

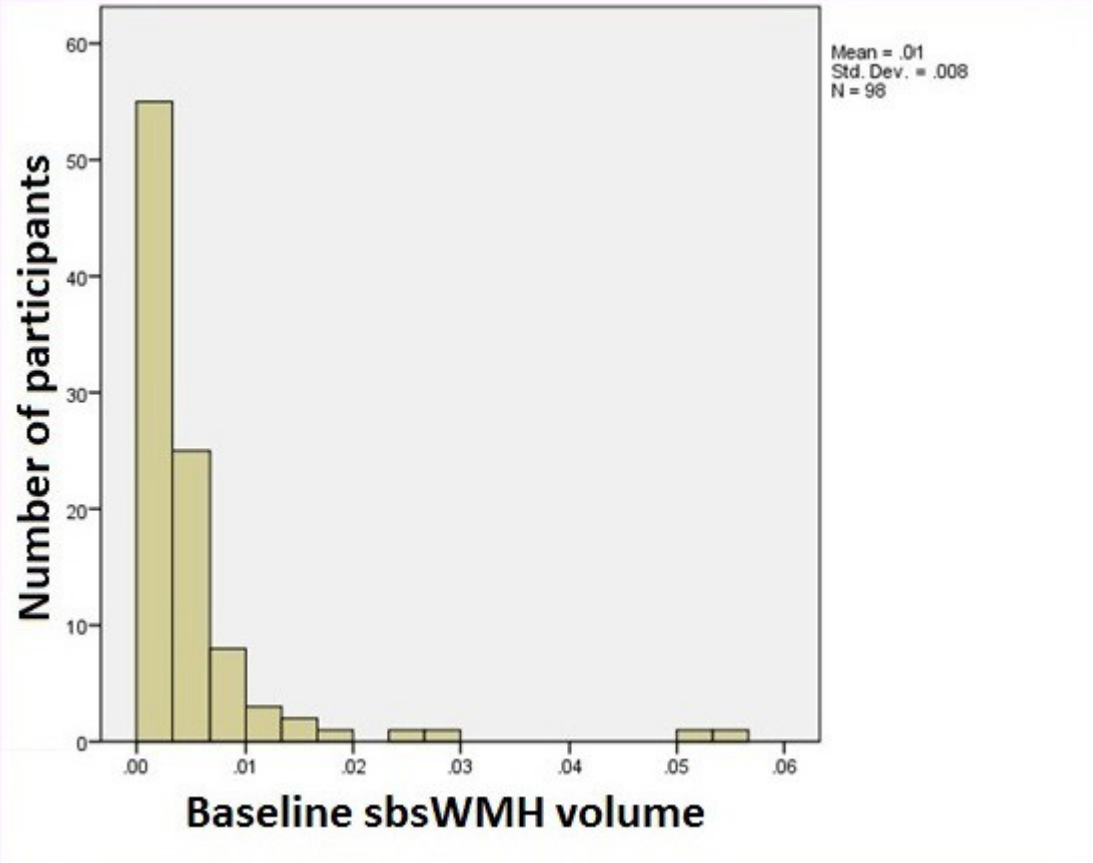

Figure 5.2.1.1 Baseline sbsWMH volume (ICV corrected) versus number of participants.

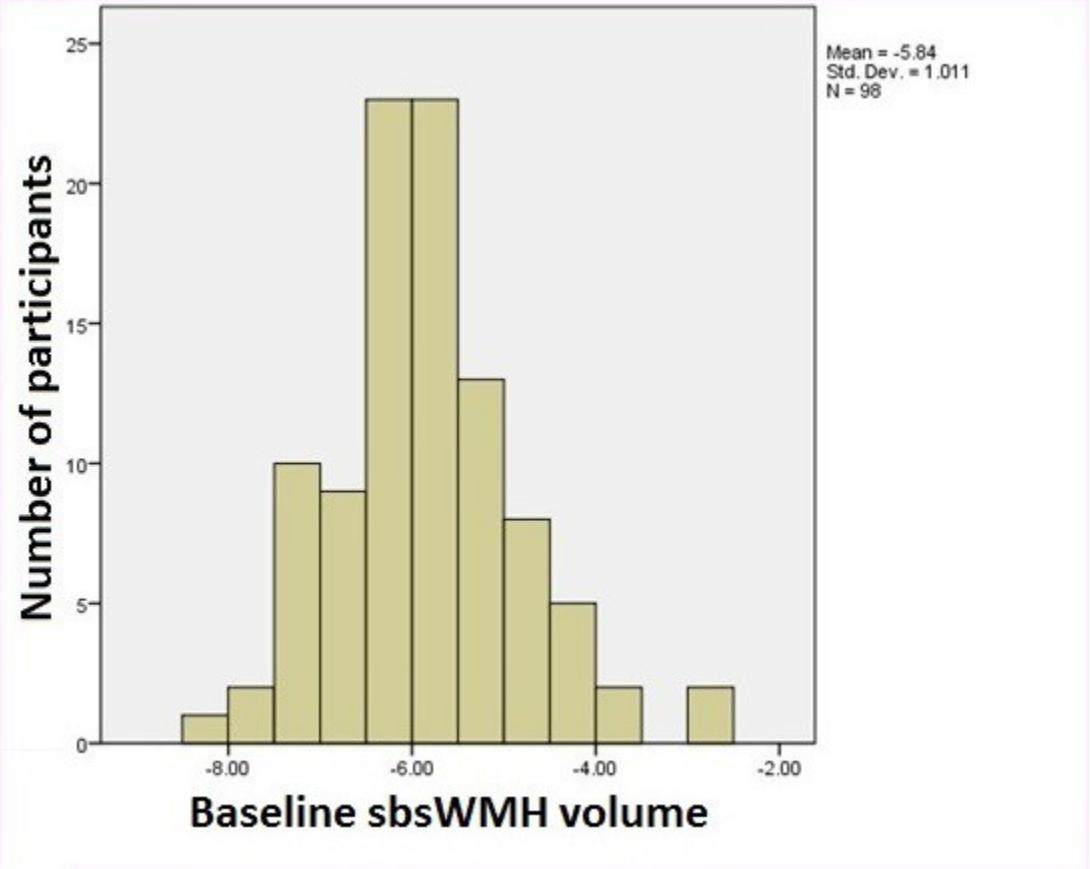

Figure 5.2.1.2 Baseline sbsWMH volume (Natural log, ICV corrected) versus number of participants.

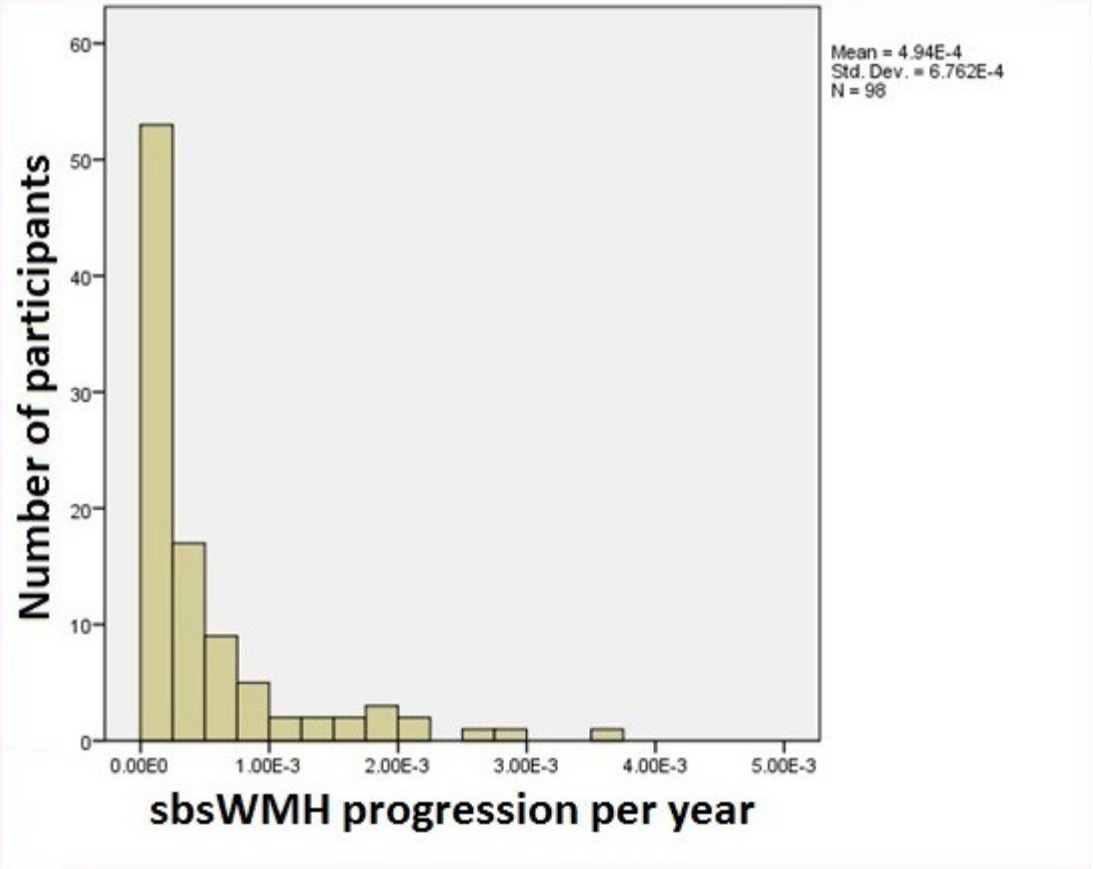

Figure 5.2.1.3 Yearly SbsWMH volume progression (ICV corrected) versus number of participants.

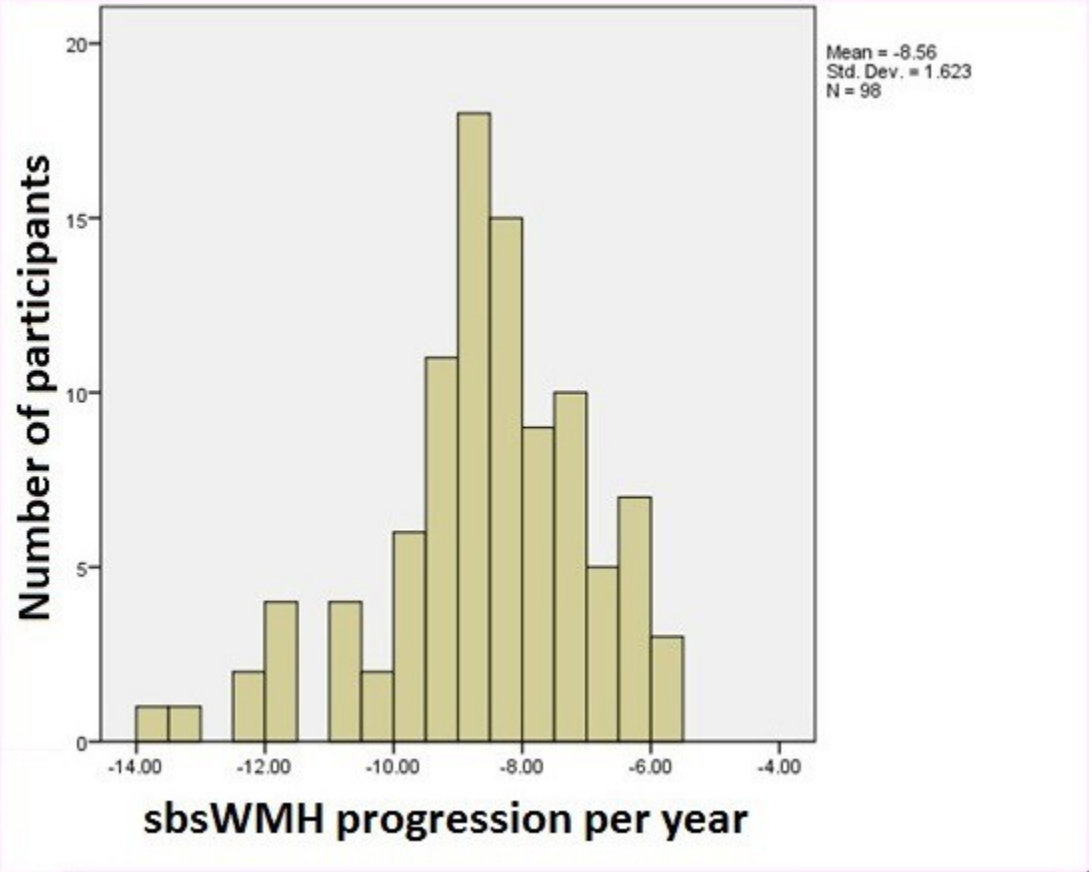

Figure 5.2.1.4 Yearly SbsWMH volume progression (natural log, ICV corrected) versus number of participants.

5.2.2. Side-by-Side WMH and age

The relationship between corrected baseline sbsWMH volume and age is shown in Figure 5.2.2.1. There is a positive correlation between age and baseline sbsWMH volume and this reached statistical significance (Pearson's correlation p=0.005, r=0.281). There is also a positive correlation seen between age and sbsWMH progression volume as outlined in Figure 5.2.2.1. This relationship also reached significance (Spearman's correlation p=0.034, r= 0.215). Non parametric correlations were required for sbsWMH progression volumes for reasons as outlined above.

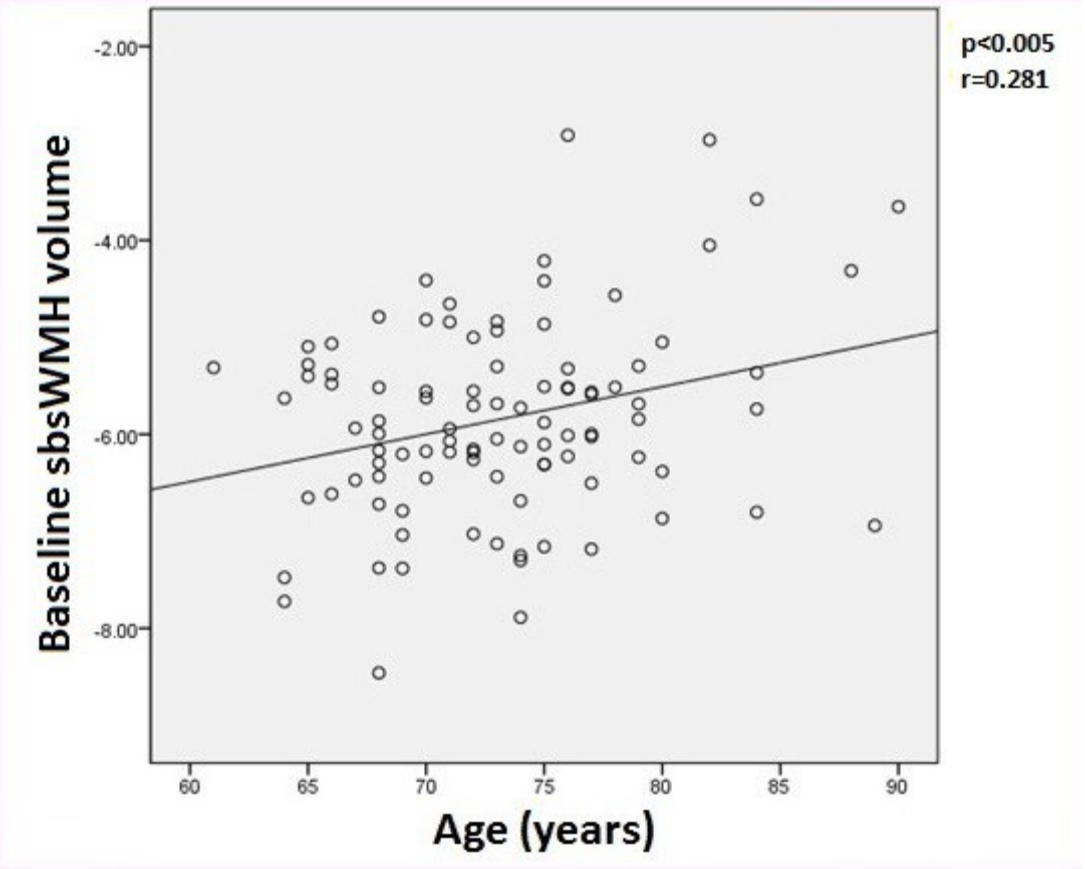

Figure 5.2.2.1 Age (years) versus baseline sbsWMH volume (Natural log, ICV corrected).

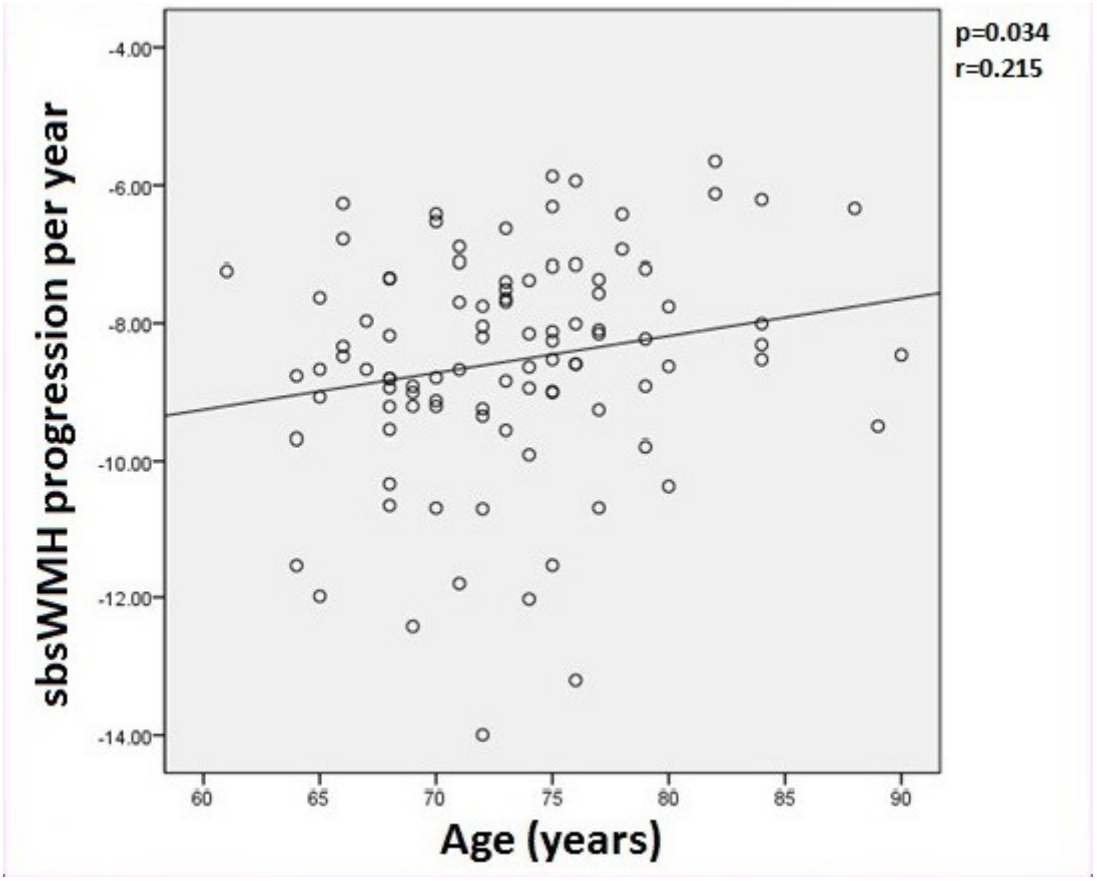

Figure 5.2.2.2 Age (years) versus yearly sbsWMH volume progression (natural log, ICV corrected).

5.2.3. Progression versus baseline volumes

Figure 5.2.3.1 demonstrates the relationship between baseline sbsWMH volume and progression volume. There is a significant positive correlation between the two (Two-tailed Spearman's correlation of p=0.000 and r=0.651). This indicates that sbsWMH baseline volume is a significant predictor of sbsWMH volume progression.

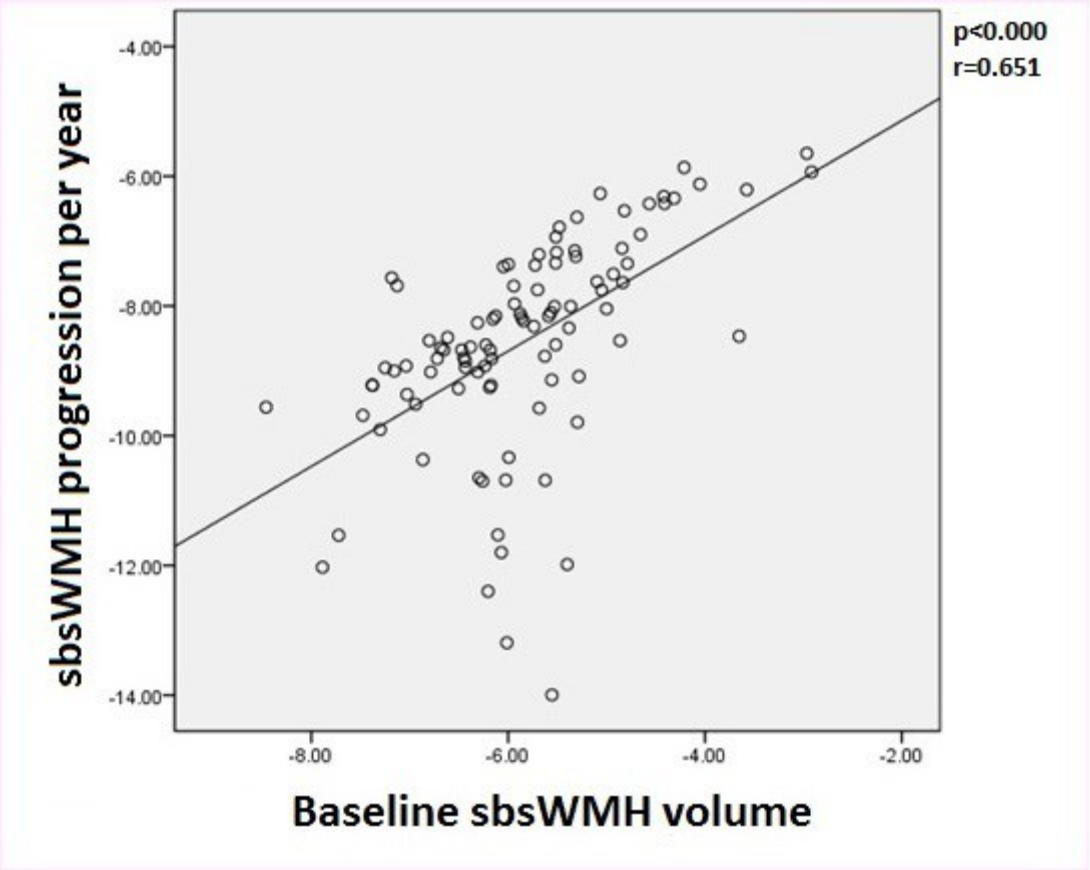

Figure 5.2.3.1 SbsWMH baseline volume versus sbsWMH volume progression correlation (natural log, ICV corrected).

5.2.4 Associations with baseline and progression data

Age and progression versus sbsWMH values are outlined above, with other associations outlined below. Table 5.2.4.1 presents categorical factors against corrected sbsWMH baseline volumes, using an independent sample t-test. Data is presented as p-values where equal variance is not assumed. There is not significant relationship between treatment group and baseline sbsWMH volume. Similarly, no relationship is present against gender, PET amyloid status, ApoE ε4 status or cognitive status (as assessed as baseline). There is a significant association between sbsWMH progression and both systolic and diastolic measures of blood pressure, with the high readings corresponding to higher progression in both cases (Log sbsWMH volume mean of -6.15 for low SBP and -5.56 for high SBP, and Log sbsWMH volume mean of -5.93 for low DBP and -5.22 for high DBP). Interestingly this did not result in a significant outcome for hypertension combined. All other vascular risk factors were not significantly related to baseline sbsWMH volume.

Table 5.2.4.1 Categorical factors versus sbsWMH baseline volume

Categorical factor vs Log corrected baseline sbsWMH volume. Independent sample t-test *equal variance not assumed		
Factor	p-value*	Effect size (Cohen's D)
Treatment group	0.70	0.08
Sex	0.39	0.17
PET amyloid status	0.20	0.46
ApoE ε4 status	0.37	0.19
Cognitive status (SMC/MCI)	0.90	0.03
Waist High	0.29	0.24
BMI High	0.46	0.16
Obesity combined	0.11	0.45
History of hypertension	0.94	0.02
High SBP	0.003**	0.61
High DBP	0.013**	0.73
Hypertension medication	0.86	0.04
Hypertension combined	0.18	0.30
Cholesterol high	0.12	0.54
Triglycerides high	0.34	0.57
Lipid lowering medication	0.32	0.21
Dyslipidaemia combined	0.92	0.02
Elevated fasting glucose	0.92	0.08
History of Diabetes	0.80	0.09
On diabetic medications	0.76	0.11
Diabetes combined	0.80	0.09
Current smoker	0.30	0.36
Smoking combined (ex/current)	0.31	0.22
Heart disease history	0.74	0.13
Stroke history	0.20	2.20
Atherosclerosis combined	0.33	0.40
** = p-value below 0.05		

Table 5.2.4.2 demonstrates the partial correlation between sbsWMH baseline volumes and continuous measures that are normally distributed. These consist of the baseline functional fitness assessment measures and weekly activity performed at baseline, of which timed up and go, sit to stand, and minutes/frequency of weekly exercise results are log transformed to give a normal distribution, allowing correction for age and sex which may have an impact upon physical activity metrics. As the results show, there was no correlation between baseline sbsWMH volumes at baseline and any of the physical activity measures obtained at baseline after correction of age and sex.

Table 5.2.4.2 Relationship between sbsWMH baseline volume and continuous variables.

partial correlation of baseline corrected sbsWMH volume with continuous factors, corrected for Age and Sex		
Continuous Factor	p-value	Effect size (r)
Step number	0.98	0.001
Timed up and go (natural log)	0.91	0.01
Dominant hand grip force	0.63	0.05
Non Dominant hand grip force	0.84	0.02
Sit to stand test (natural log)	0.54	0.07
6 minute walk distance	0.32	0.10
Minutes/week all intensity exercise (natural log)	0.49	0.08
Frequency/week all intensity exercise (natural log)	0.15	0.11
Caloric expenditure per week for all exercise levels	0.50	0.06

Table 5.2.4.3 outlines the spearman correlation between sbsWMH baseline volumes and continuous variables which could not be transformed to normality. The number of vascular risk factors was again treated as a categorical variable, assuming an increase of effect with increasing number of VRF. It is beyond the scope of this thesis to quantify the amount of effect of each VRF and whether there is a non-linear effect with the number of VRF and sbsWMH progression. From Table 5.2.4.3 it can be seen that there was no correlation with sbsWMH baseline volume and education, number of vascular risk factors. Age corrected scores where included where possible (T score in BRIEF A scores), but in further general linear models the raw scores (non-age corrected) will be used as age will be a covariate in modelling. There were no correlations with BRIEF A BRI and MI T Score (however BRI T score was very close at p=0.050, r=-0.206), there was also no correlation with HADS A score and MAC-Q with progression sbsWMH volumes. None of the raw (not age matched) scores were significant in BRI BRI, MI and total scores. The BRIEF A total score was statistically significantly associated with the progression of corrected sbsWMH volume (p=0.048, r=-0.208). This equated to participants with better BRIEF A (total) scores having lower progression in sbsWMH volumes.

Table 5.2.4.3 Relationship between sbsWMH baseline volumes and education, number of vascular risk factors and baseline neurocognitive measures.

Spearman correlation of baseline corrected sbsWMH with continuous factors		
Continuous factor	p-value	Effect size (r)
Education (years)	0.21	0.13
Number of vascular risk factors	0.10	0.17
ADAS Cog 11	0.28	0.11
BRIEF-A BRI T score*	0.16	0.15
BRIEF-A MI T score*	0.65	0.05
BRIEF- A total T score*	0.26	0.12
HADS A	0.36	0.09
MAC- Q	0.70	0.04

* T scores used as they are age adjusted versions of BRIEF A.

The remaining tables in this chapter outline the interaction between variables and the progression of sbsWMH volumes. Table 5.2.4.4 describes categorical factors against natural log corrected sbsWMH progression, using the Mann-U Whitney test. The Mann-U Whitney test is used as sbsWMH progression is not normally distributed, and log values utilised as these provide a better fit in the general linear model so will be presented for consistency. There is no effect of treatment group, gender, pet amyloid or ApoE ε4 or cognitive status. There are also no effects of any of the combined or constituent vascular risk factors for obesity, dyslipidaemia, diabetes and smoking. There is a statistically significant difference in sbsWMH for both systolic blood pressure and hypertension combined categories. As the distributions for low and high SBP were not similar (Figures 5.2.4.1 and 5.2.4.1), mean rank was compared. Log sbsWMH progression volumes for high systolic blood pressure (mean rank=58.55) was statistically significantly higher than the non-elevated systolic blood pressure group (mean rank 39.68), U= 737, Z =-3.282, p=0.001. Mean ranks was again used to interpret the hypertension combined results as these do share the same distribution shape (Figures 5.2.4.3 and 5.2.4.4). There is more progression of log sbsWMH volumes in the hypertension combined positive group (mean rank 53.23) than in the negative group (mean rank 40.18), U=719, Z=-2.053, p=0.40. There is no difference in log sbsWMH progression volumes with remaining hypertension measurements. Of the atherosclerotic measurements, heart disease and atherosclerotic disease combined were not significant, while stroke history reached significance at p=0.005. As there are only two patients with a positive history of stroke, interpretation of this result is questionable due to very low participant numbers factor. Despite this, it will still be considered as a covariate in subsequent general linear models where both effect size and number of patients will be taken into consideration.

Table 5.2.4.4 Categorical factors against natural log sbsWMH progression volumes.

Categorical factor versus log corrected sbsWMH Progression volume. Mann-U Whitney test.		
Factor	p-value	Effect size (Cohen's D) **
Treatment group	0.65	0.05
Sex	0.57	0.06
Pet amyloid status	0.23	0.13
ApoE ε4 status	0.42	0.08
Cognitive status (SMC/MCI)	0.55	0.06
Waist High	0.48	0.07
BMI High	0.09	0.17
Obesity combined	0.67	0.04
History of hypertension	0.32	0.09
High SBP	0.001*	0.33
High DBP	0.21	0.13
Hypertension medication	0.97	0.04
Hypertension combined	0.04*	0.21
Cholesterol high	0.08	0.18
Triglycerides high	0.16	0.14
lipid lowering medication	0.12	0.16
dyslipidaemia combined	0.34	0.10
Elevated fasting glucose	0.59	0.06
History of Diabetes	0.92	0.01
On diabetic medications	0.67	0.04
Diabetes combined	0.92	0.01
Current smoker	0.28	0.11
Smoking combined	0.77	0.03
heart disease history	0.31	0.10
Stroke history	0.005*	0.23
Atherosclerosis combined	0.12	0.16
* = p-value below 0.05 ** = Effect size is calculated as Z value divided by sample size		

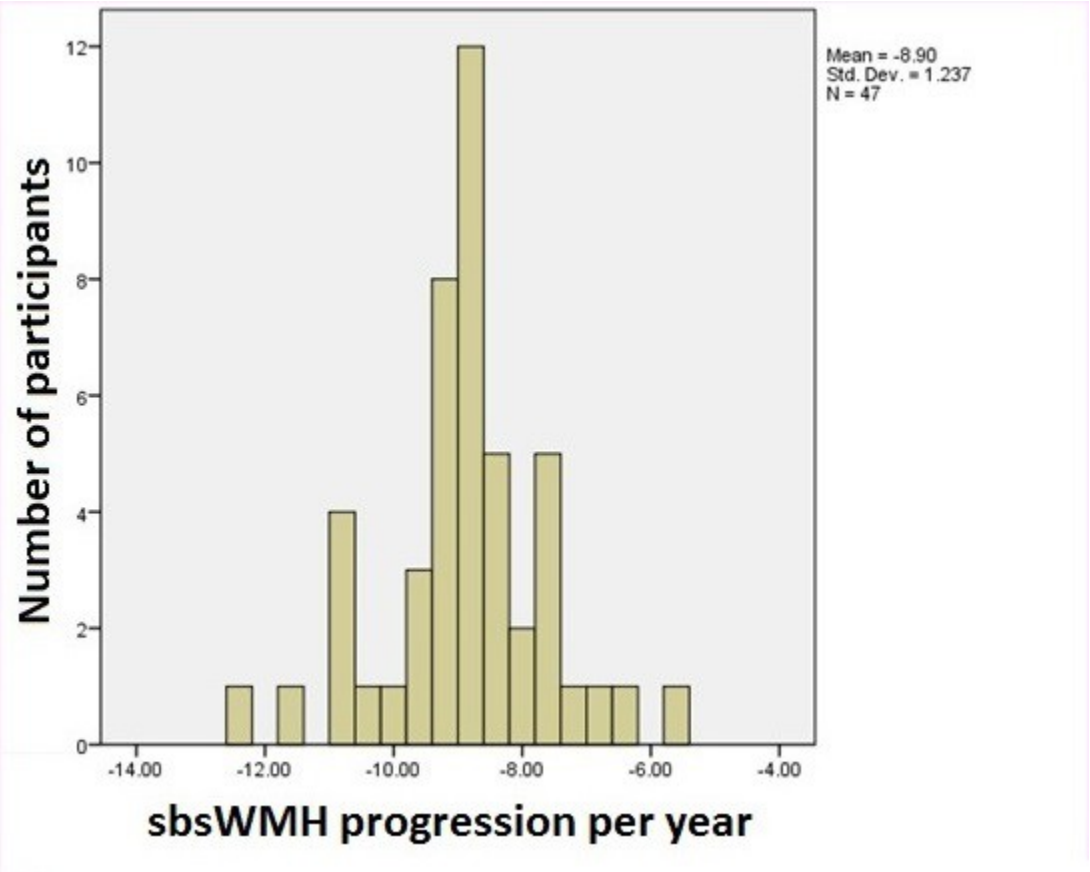

Figure 5.2.4.1 Distribution of yearly sbsWMH volume progression (natural log, ICV corrected) in non-elevated systolic blood pressure group

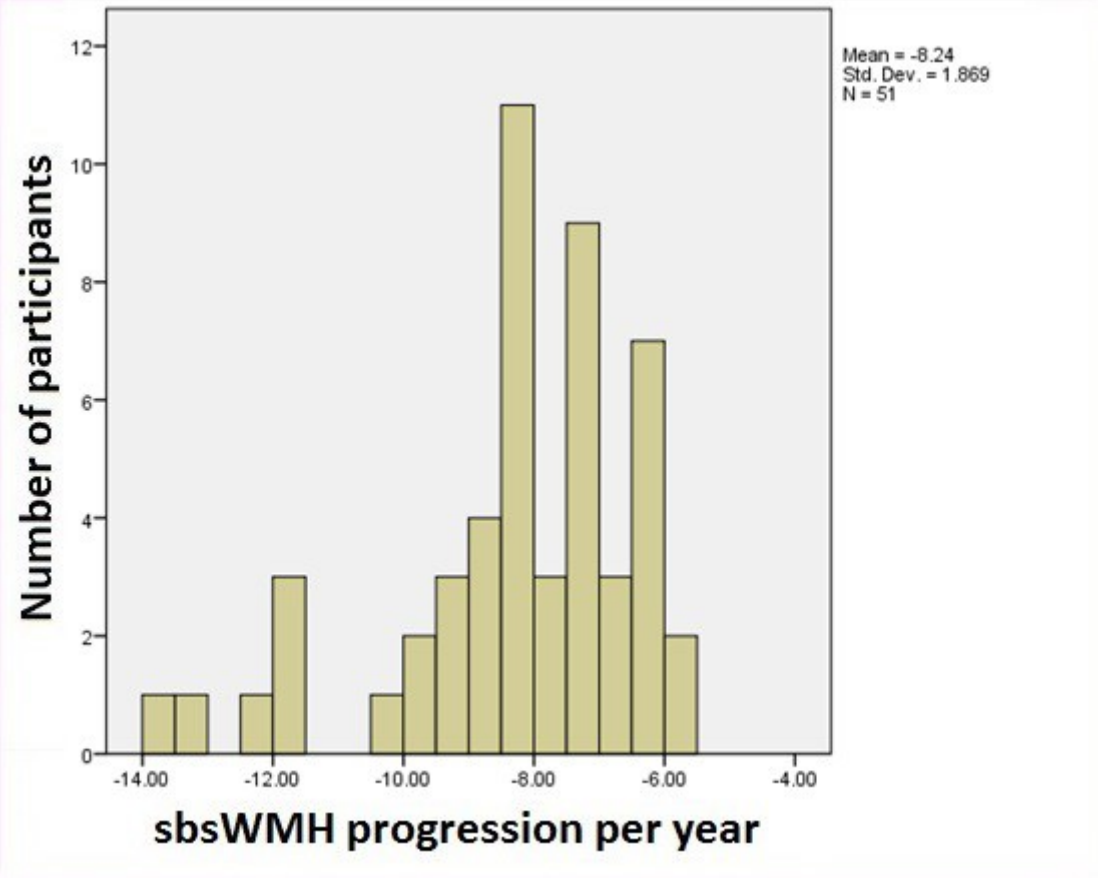

Figure 5.2.4.2 Distribution of yearly sbsWMH volume progression (natural log, ICV corrected) in elevated systolic blood pressure group.

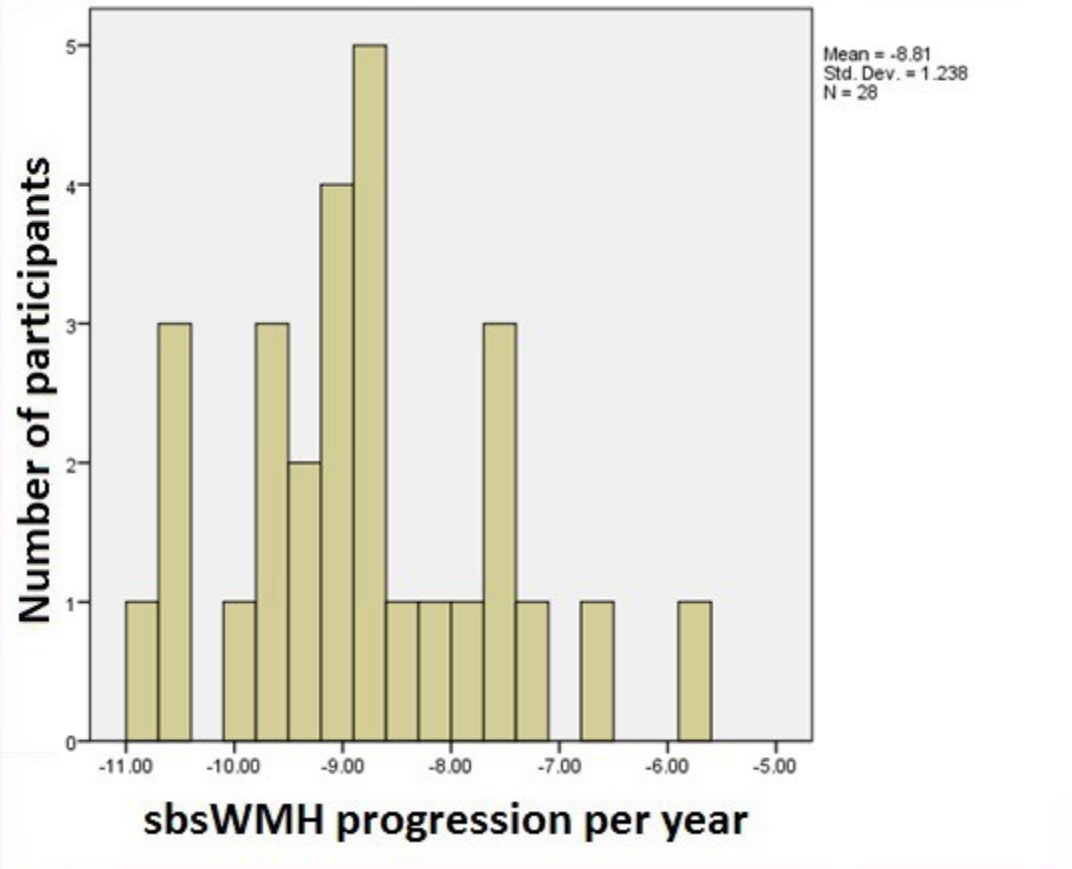

Figure 5.2.4.3 Distribution of yearly sbsWMH volume progression (natural log, ICV corrected) in hypertension combined negative group.

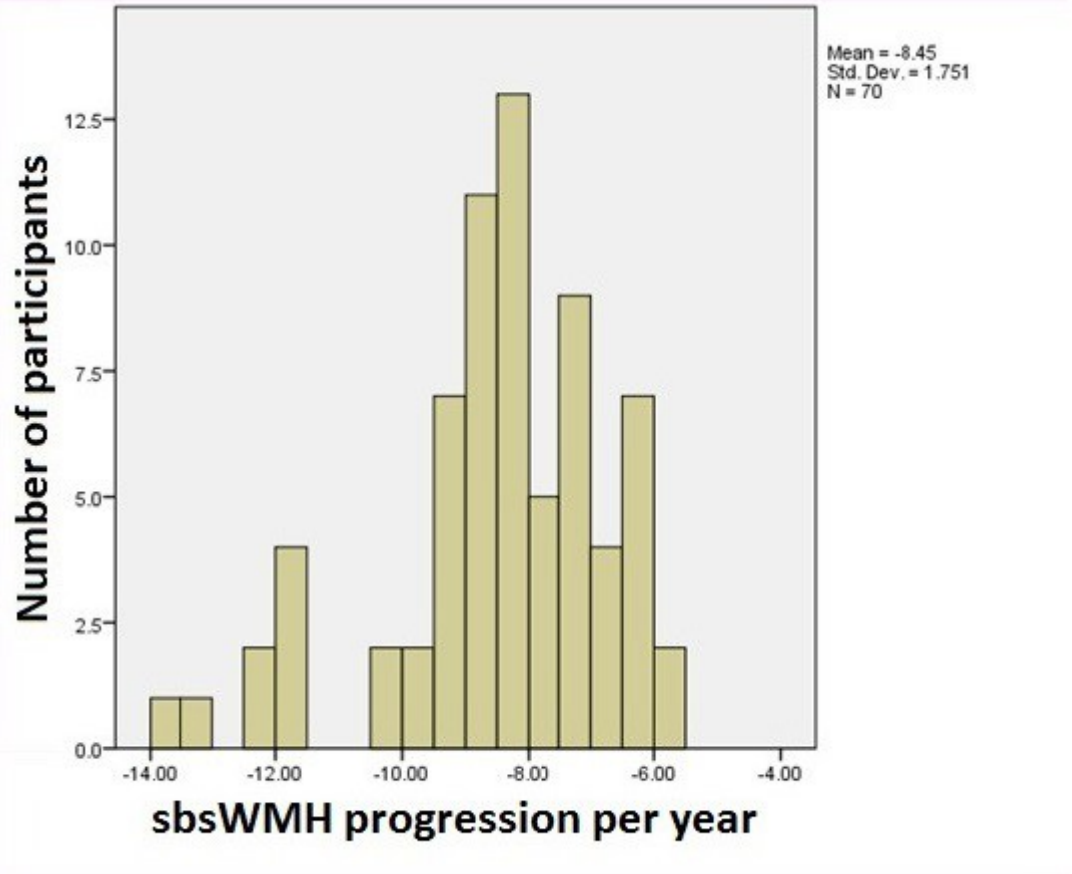

Figure 5.2.4.4 Distribution of yearly sbsWMH volume progression (natural log, ICV corrected) in hypertension combined positive group.

Table 5.2.4.5 outlines the relationship between sbsWMH progression and the baseline functional fitness assessment measurements. Spearman correlation was used as sbsWMH is not normally distributed, and none of the physical activity functional measurements or baseline weekly activity amounts was significantly associated with sbsWMH progression. Unmodified variables were presented for step number, grip force and 6 minute walking distance and log transformed timed up and go and sit to stand measures are presented to be consistent with cmsWMH and sbsWMH tables, and as these results are also used in the general linear models. Unmodified timed up and go and sit to stand results were also non-significant (p=0.35 and p=0.60 respectively).

Table 5.2.4.5 Relationship between sbsWMH progression values and baseline functional fitness assessment.

Spearman correlation of log corrected sbsWMH progression and continuous baseline functional fitness assessment factors		
Continuous variables	p-value	Effect size (r)
Step number	0.29	0.11
Timed up and go (natural log)	0.35	0.10
Dominant hand grip force	0.72	0.04
Non Dominant hand grip force	0.72	0.04
Sit to stand test (natural log)	0.60	0.05
6 minute walk distance	0.19	0.13
Minutes/week all intensity activity (natural log)	0.37	0.09
Frequency/week all intensity activity (natural log)	0.19	0.13
Caloric expenditure per week for all activity levels	0.62	0.04

Table 5.2.4.6 demonstrates the spearman correlation between sbsWMH progression and education, number of vascular risk factors and cognition. The number of vascular risk factors was again treated as a categorical variable, assuming an increase of effect with increasing number of VRF, and further analysis outside the scope of this thesis. There were no significant correlations between sbsWMH progression and education years, number of vascular risk factors or any of the cognitive scores tested. The BRIEF A used age-normed variables, although raw scores also failed to reach significance. Non-age scores will be used for subsequent general linear models as age will be used as a covariate in all models.

Table 5.2.4.6 Relationship between sbsWMH progression values to education (years) and cognitive scores.

Spearman correlation of log corrected sbsWMH progression against continuous education and baseline cognition scores		
Continuous variables	p-value	Effect size (r)
Education (years)	0.09	0.17
Number of vascular risk factors	0.54	0.06
ADAS Cog 11	0.74	0.03
BRIEF-A BRI T score *	0.05	0.26
BRIEF-A MI T score *	0.23	0.13
BRIEF-A Total T score *	0.048*	0.21
HADS A	0.06	0.19
MAC- Q	0.43	0.08

* BRIEF A T-score used as they are age adjusted versions of BRIEF

5.2.5. General linear models

This chapter will utilise the general linear model to investigate the effects on sbsWMH volumes. The majority of analysis will surround sbsWMH progression volumes with some consideration of relationships against sbsWMH baseline volumes. As the main research outcome is the effect of exercise on WMH progression, sbsWMH progression will be the dependent outcome for all models. The major hypothesis of the effect of exercise on sbsWMH progression will first be examined, followed by consideration of some factors against sbsWMH baseline volumes. Following this the next hypotheses of ApoE ε4 status and PET amyloid status effect upon sbsWMH progression will then be analysed. The baseline functional fitness assessment measures will then be examined, concluding with models analysing the baseline neurocognitive assessment outcomes.

Each outcome was examined against all other covariates, with a hypothesis driven approach adopted and heuristic inclusion and exclusion approach to model selection employed. With a large number of models possible, tables have been constructed demonstrating models in groups of effect with one particular outcome. Each other covariate was then added and removed, with all displayed together at the end. Despite some data being included is not normally distributed, all residuals were checked for normality and passed this assumption. This was achieved by utilising the (natural) logarithmic transform of sbsWMH volumes. All models have been checked with the Department of Mathematics and Statistics consultancy service at the University of Melbourne.

P-values below 0.05 were deemed significant, with all p-values included in each model displayed in the results table. Age and gender was included in all models as both factors may have an impact upon physical activity measurements. Age is also required as an adjusting factor for neurocognitive assessments, and gender is included in these models for continuity and to ensure there are no gender specific differences. With a large number of possible models, only relevant combinations to each hypothesis are displayed, along with varying the remaining factors one by one to explore possible interactions. In each model, only the p-values presented are used as variables. Where "No" is displayed rather than a p-value, this represents other combinations of models that was explored but didn't return a significant result or interaction with any of the remaining variables. This technique is employed to represent multiple other GLMs being performed, for example; Other VRF represents a testing of that model plus each VRF in turn, and in later models to represent exercise group, ApoE ε4 status, PET amyloid status, number of VRF and all other individual VRF. Where each VRF is tested against a model already containing VRF total number, this is tested for interactions only as VRF total includes the individual VRF being tested and this would test the same factor twice by differing means.

Table 5.2.5.1 displays models for exercise against sbsWMH progression, all corrected for age, gender and baseline sbsWMH volumes. Model H1 examines these alone in a single model, models H2 to H6 examine this with the addition of VRF number, ApoE ε4 status, PET amyloid status, education and cognitive classification (SMC/MCI) each in turn. Model H7 tests all these factors together at the one time.

There is no significant interaction with exercise and any of the models tested (Models A1 through A7). All models also fail to show any significant contribution of age and gender, likewise with each individual vascular risk factor tested individually. Reflecting the correlation above in 5.2.3.1, baseline smsWMH was very strongly related to the progression of sbsWMH volume in all cases ($p<0.001$). In all models in table 5.2.5.1, this represented a positive correlation (positive B values). All additional covariates failed to reach significance, however ApoE came close ($p=0.077$). Other combinations of individual VRF, number of VRF, Abeta, education and cognition did not alter this result with ApoE status remaining non-significant. Number of vascular risk factors, PET amyloid status, years of education and cognitive group all failed to reach significance, as did all the data presented together.

Table 5.2.5.2 (models I1 and I2) are the only models in this chapter to examine interactions with baseline sbsWMH volumes as the dependent variable. In Model I1 there is a significant interaction between age and baseline cmsWMH volume (mirroring the correlation shown above in Figure 5.2.2.1). This is positively correlated ($B=0.052$), with no interaction existing between age and sex found in an additional model. Model I2 examines the interaction of these factors with the addition of systolic blood pressure upon baseline sbsWMH volume. In this model, both Age ($p=0.017$, $B=0.042$) and systolic blood pressure ($p=0.015$, $B=0.490$) were significantly associated and positively correlated with baseline sbsWMH. There were no interactions found with any combination of age, gender and systolic blood pressure.

Model J1 (Table 5.2.5.3) examines the interplay with age, gender, baseline sbsWMH and systolic blood pressure upon sbsWMH progression once the interaction between systolic blood pressure and baseline sbsWMH volume are taken into account. Both the interaction and systolic blood pressure do not reach statistical significance against (and are positively correlated with) sbsWMH progression. Examining combinations of age, gender and systolic blood pressure fail to show any interaction in this model. Additionally, there was no effect when adding other factors to this such as PET amyloid status, ApoE ε4 status, treatment group of any other the vascular risk factors (individually or summed up). This interaction with baseline sbsWMH being examined against sbsMWH progression also failed to show any significance when examining interactions against PET amyloid status, ApoE ε4 status, treatment group of any other the vascular risk factors in isolation.

Table 5.2.5.4 consists of models with ApoE ε4 status, age, baseline sbsWMH and various factors against sbsWMH progression. As exercise was already examined in the presence of ApoE status in model H3, this interaction won't be retested. Model K1 examines these factors in isolation, K2 through K5 present models with the respective one by one addition of number of VRF, PET amyloid status, years of education and cognitive group. K6 represents all factors included together. All models also examine the additional of individual vascular risk factors. In all models, there is no significant interaction with ApoE ε4 status, age or gender. There is also no interaction with number of VRF, PET amyloid status, years of education, cognitive group and each individual VRF tested. Baseline sbsWMH volumes remain strongly significant in all models ($p<0.001$, B=positive), including all additional tests including individual risk factors.

Table 5.2.5.5 contains models examining combinations involving PET amyloid status and various covariates against sbsWMH progression, all corrected for age, gender and baseline sbsWMH volume. Models were not repeated that examined either exercise group or ApoE ε4 status as these had both been examined in above models. Again, each individual VRF was tested as an addition to each model with results displayed (but not included in the presented models). Model L1 tests these covariates in isolation; L2through L4 tests this model with the addition of VRF number, education years and cognition while model L5 tests all of them in combination. None of the models resulted in statistical significance with respect the PET amyloid status, nor with any of the added covariates. Similar to the above model, Age and gender were non-significant with strong effects of baseline sbsWMH volume ($p<0.001$, B=positive in all models). The addition of individual VRF did not change the outcome, nor were there any interactions identified (not significant for all correlations and GLM significance $p = 0.894$ in a model including baseline sbsWMH, age, gender, and not significant with any other factors in additional GLM combinations)

Tables 5.2.5.6a and 5.2.5.6b present the models dealing with the baseline functional fitness assessment measurements and baseline weekly activity data as a covariate against sbsWMH progression volume. Each model also has age, gender and baseline sbsWMH as a covariate. Each model tests a separate baseline functional fitness assessment outcome, with an indication underneath each model if there are any interactions when performing that model with the addition of exercise group, ApoE ε4 status, PET amyloid status, education, cognition or vascular risk factors (together or combined). None of the baseline functional fitness assessment measurements (Models M1 through M6) reached statistical significance, and neither did age, gender or any additional covariates examined. There was a constant presence of baseline sbsWMH being statistically significant ($p<0.001$, B = positive in all cases). Natural log values were again used in the case of timed up and go and sit to stand measurements, as they resulted in a better fit of residuals. Non logarithmic versions of these two measurements were also non-significant.

Finally, Table 5.2.6.7 explores the relationship between the baseline neurocognitive assessments with sbsWMH progression volumes. As before, each model is corrected for age, gender and baseline sbsWMH volume with each model exploring a different assessment result. Underneath each model is also an exploration of any other interactions that were performed. While the ADAS COG, HADS-A and MAC Q all utilise all 98 patients, the BRIEF-A measurements use 91 as 7 were rejected due to either answering inconsistently, infrequently responding or having a positive negativity score.

Every neurocognitive assessment aside from HADS-A were insignificant, with all models having the familiar pattern of no effect of age and gender with a strong ($p<0.001$, all B values positive) effect of baseline sbsWMH volume. In the presence of age, gender and baseline sbsWMH volume as covariates, HADS-A is significantly associated with sbsWMH progression volume ($p=0.035$, $B=-0.111$). This correlation suggests that participants with more anxiety have less sbsWMH progression. None of the other variables tested in addition to shown models became significant. Having a "diagnosis" of anxiety is defined as a HADS A score of 8 and above, this was present in only 11 of the patients and the binary yes/no diagnosis was not associated with WMH progression.

5.3 Summary of sbsWMH statistics:

There was no significance of physical activity with both baseline and progression sbsWMH volumes with both correlation and GLM statistics. The same was true for ApoE ε4 and PET amyloid status.

In all models, there was also no effect of baseline PA measures, gender, years of education, cognitive (SMC,MCI) group and number of VRF.

Age was significantly associated with baseline sbsWMH for both correlation and GLM, and was associated with sbsWMH progression volumes for correlation statistics only.

Of the VRF tested individually, SBP was significant across correlation and GLM for sbsWMH baseline volume, but only significant for correlation with sbsWMH progression volume. DBP was only significant in correlation with baseline sbsWMH volume. In addition, HTN combined and a history of stroke was significantly correlated with sbsWMH progression volume, but like SBP, were not significant in any GLM.

There was no association with neurocognitive assessments with both types of baseline sbsWMH statistics. BRIEF A Total score was significantly correlated with sbsWMH progression volume, but not a significant covariate in the GLM. The reverse is true for HADS- A score, not significant with sbsWMH progression volume in correlation but significant in the GLM.

Baseline volume was a significant factor across correlation and GLM for all models investigating sbsWMH progression volume.

Table 5.2.5.1 GLM of factors against exercise intervention group, dependent variable natural log sbsWMH (corrected) volume progression.

	Model H1		Model H2		Model H3		Model H4		Model H5		Model H6		Model H7	
	F	Sig	F	Sig	F	Sig	F	Sig	F	Sig	F	Sig	F	Sig
Corrected model	10.662	<0.001	9.167	<0.001	9.368	<0.001	7.119	<0.001	9.156	<0.001	8.505	<0.001	4.584	<0.001
Age	0.428	0.515	0.776	0.381	0.528	0.469	0.560	0.456	0.502	0.48	0.387	0.535	0.922	0.322
Sex	0.141	0.708	0.057	0.811	0.036	0.850	0.099	0.753	0.419	0.519	0.157	0.693	0.296	0.588
Baseline WMH	35.408	<0.001	38.176	<0.001	37.784	<0.001	29.137	<0.001	34.121	<0.001	35.135	<0.001	30.443	<0.001
Number VRF	-	-	2.498	0.117	-	-	-	-	-	-	-	-	0.992	0.322
ApoE	-	-	-	-	3.19	0.077	-	-	-	-	-	-	0.861	0.356
PET Amyloid	-	-	-	-	-	-	0.160	0.690	-	-	-	-	0.000	0.322
Education	-	-	-	-	-	-	-	-	2.46	0.12	-	-	2.641	0.108
SMC/MCI	-	-	-	-	-	-	-	-	-	-	0.232	0.631	0.675	0.414
Exercise treatment	0.804	0.372	1.059	0.306	1.053	0.308	0.595	0.443	0.91	0.343	0.854	0.358	0.967	0.328
Other VRF effects?	No		No		No		No		No		No		No	

Table 5.2.5.2 GLM of Age, Sex and Systolic Blood Pressure (SBP), Dependent variable natural log sbsWMH baseline volume

	Model I1		Model I2	
	F	Sig	F	Sig
Corrected model	4.890	0.01	5.5	0.002
Age	9.024	0.003*	5.857	0.017*
Sex	1.526	0.220	1.587	0.211
SBP	-	-	6.184	0.015*
Age*Sex interaction?	No		No	
SBP* Age interaction?	-		No	
SBP*Sex interaction?	-		No	

Table 5.2.5.3 GLM of SBP effect of sbsWMH progression taking into account SBP and Baseline sbsWMH interaction

	Model J1	
	F	Sig
Corrected model	9.284	<0.001
Age	0.432	0.513
Sex	0.177	0.675
Baseline WMH	38.082	<0.001
SBP * baseline WMH	3.534	0.063
SBP	3.711	0.057
Age*Sex interaction?	No	
SBP* Age interaction?	No	
SBP*Sex interaction?	No	

Table 5.2.5.4 GLM of factors against ApoE ε4 status, dependent variable natural log sbsWMH (corrected) volume progression.

	Model K1		Model K2		Model K3		Model K4		Model K5		Model K6	
	F	Sig	F	Sig	F	Sig	F	Sig	F	Sig	F	Sig
Corrected model	11.441	<0.001	9.67	<0.001	7.245	<0.001	9.7	<0.001	9.063	<0.001	5.038	<0.001
Age	0.312	0.578	0.556	0.458	0.555	0.458	0.359	0.551	0.292	0.59	0.785	0.378
Sex	0.029	0.865	0.003	0.96	0.06	0.807	0.186	0.667	0.032	0.858	0.295	0.589
Baseline WMH	37.853	<0.001	40.193	<0.001	30.308	<0.001	36.435	<0.001	37.44	<0.001	30.396	<0.001
Number VRF	-	-	2.065	0.154	-	-	-	-	-	-	0.828	0.365
Abeta	-	-	-	-	0.001	0.976	-	-	-	-	0.006	0.94
Education	-	-	-	-	-	-	2.165	0.145	-	-	2.499	0.118
SMC/MCI	-	-	-	-	-	-	-	-	0.031	0.861	0.596	0.442
ApoE status	2.959	0.089	2.76	0.100	1.041	0.311	2.747	0.101	2.780	0.099	0.857	0.357
Other VRF effects?	No		No		No		No		No		No	

Table 5.2.5.5 GLM of factors against PET amyloid status, dependent variable natural log sbsWMH (corrected) volume progression

	Model L1		Model L2		Model L3		Model L4		Model L5	
	F	Sig	F	Sig	F	Sig	F	Sig	F	Sig
Corrected model	8.792	<0.001	7.237	<0.001	7.584	<0.001	7.078	<0.001	5.645	<0.001
Age	0.45	0.504	0.621	0.433	0.527	0.470	0.432	0.513	0.673	0.414
Sex	0.102	0.75	0.047	0.828	0.351	0.555	0.16	0.69	0.389	0.535
Baseline WMH	29.357	<0.001	30.361	<0.001	28.561	<0.001	29.453	<0.001	29.674	<0.001
Number VRF	-	-	1.010	0.318	-	-	-	-	0.865	0.355
Education	-	-	-	-	2.238	0.138	-	-	2.494	0.118
SMC/MCI	-	-	-	-	-	-	0.449	0.505	0.822	0.367
PET Amyloid status	0.106	0.746	0.092	0.763	0.063	0.803	0.087	0.768	0.034	0.854
Other VRF effects?	No		No		No		No		No	

Table 5.2.5.6a GLM of factors against baseline functional fitness assessment, dependent variable natural log sbsWMH (corrected) volume progression

	Model M1		Model M2		Model M3		Model M4		Model M5		Model M6	
	F	Sig	F	Sig	F	Sig	F	Sig	F	Sig	F	Sig
Corrected model	10.69	<0.001	10.434	<0.001	10.965	<0.001	11.039	<0.001	10.385	<0.001	10.441	<0.001
Age	0.014	0.905	0.079	0.779	1.066	0.305	1.073	0.303	0.291	0.591	0.379	0.54
Sex	0.026	0.872	0.059	0.809	1.741	0.19	1.72	0.193	0.141	0.708	0.181	0.671
Baseline WMH	35.593	<0.001	35.34	<0.001	35.183	<0.001	35.635	<0.001	35.255	<0.001	35.478	<0.001
Step test (number of steps)	0.881	0.350	-	-	-	-	-	-	-	-	-	-
TUG (natural log) (s)	-	-	0.173	0.678	-	-	-	-	-	-	-	-
Grip Dom (kg)	-	-	-	-	1.966	0.164	-	-	-	-	-	-
Grip non Dom (kg)	-	-	-	-	-	-	1.846	0.178	-	-	-	-
SitS (natural log) (s)	-	-	-	-	-	-	-	-	0.037	0.847	-	-
6 min walk test (m)	-	-	-	-	-	-	-	-	-	-	0.193	0.661
Other effects?*	No		No		No		No		No		No	

* Other effects investigated include exercise group, ApoE ε4 status, PET amyloid status, number of VRF and all other individual VRF

Table 5.2.5.6b GLM of factors against baseline weekly exercise measurements, dependent variable natural log sbsWMH (corrected) volume progression

	Model M7		Model M8		Model M9	
	F	Sig	F	Sig	F	Sig
Corrected model	10.373	<0.001	10.427	<0.001	10.404	<0.001
Age	0.258	0.613	0.286	0.594	0.252	0.617
Sex	0.116	0.735	0.071	0.791	0.153	0.697
Baseline WMH	35.010	<0.001	33.849	<0.001	35.355	<0.001
Min/week exercise (natural log)	0.005	0.946	-	-	-	-
Frequency/week exercise (natural log)	-	-	0.156	0.694	-	-
Weekly Kcal expenditure	-	-	-	-	0.090	0.765
Other effects?*	No		No		No	

* Other effects investigated include exercise group, ApoE ε4 status, PET amyloid status, number of VRF and all other VRF.

Table 5.2.5.7 GLM of factors against baseline functional fitness assessment, dependent variable natural log sbsWMH (corrected) volume progression

	Model N1		Model N2		Model N3		Model N4		Model N5		Model N6	
	F	Sig	F	Sig	F	Sig	F	Sig	F	Sig	F	Sig
Corrected model	10.56	<0.001	10.057	<0.001	0.9456	<0.001	9.973	<0.001	12.019	<0.001	10.911	<0.001
Age	0.339	0.562	0.258	0.613	0.321	0.575	0.284	0.595	0.035	0.851	0.294	0.589
Sex	0.13	0.719	0.003	0.953	0.14	0.709	0.089	0.766	0.028	0.868	0.055	0.816
Baseline WMH ADAS Cog	33.795	<0.001	30.164	<0.001	30.614	<0.001	30.165	<0.001	36.159	<0.001	36.25	<0.001
11 score BRIEF A BRI	0.522	0.472	-	-	-	-	-	-	-	-	-	-
raw score** BRIEF A MI	-	-	3.870	0.052	-	-	-	-	-	-	-	-
raw score** BRIEF A total	-	-	-	-	2.157	0.146	-	-	-	-	-	-
raw score** HADS A	-	-	-	-	-	-	3.63	0.060	-	-	-	-
score	-	-	-	-	-	-	-	-	4.559	0.035*	-	-
MAC Q score	-	-	-	-	-	-	-	-	-	-	1.492	0.225
Other effects?*	No		No		No		No		No		No	

* = Other effects investigated include exercise group, years of education, ApoE ε4 status, PET amyloid status, number of VRF and all other individual VRF

** = Patients rejected if they fail inconsistency of answering, infrequency score or negativity scoring positive (7 patients rejected as a result)

CHAPTER 6 COMPARISON OF WHITE MATTER HYPERINTENSITY SEGMENTATION METHODS

6.1 Introduction

The two white matter hyperintensity segmentation methods were compared in multiple ways. The distributions of baseline and progression volumes were investigated, with subsequent analysis of how both segmentation methods correlate to all the covariates tested above.

6.2 Results

6.2.1 Baseline volume comparison

6.2.1.1 Baseline volume distribution comparison

For ease of comparison, baseline volumes (with and without log transformation) are reproduced below in Figure 6.2.1.1. Statistics are given in Table 6.2.1.1.
From Figure 6.2.1.1, it can be seen that both baseline volumes are naturally skewed and that normalizing them yields similar distributions. Further analyses of the statistics (the log transformed values, Table 6.2.1.1) demonstrate similar mean (but slightly higher in the sbsWMH volume), standard deviation and minimum values. Both have the same maximal values. Both sets also have a similar degree of kurtosis and even closer values for skew.

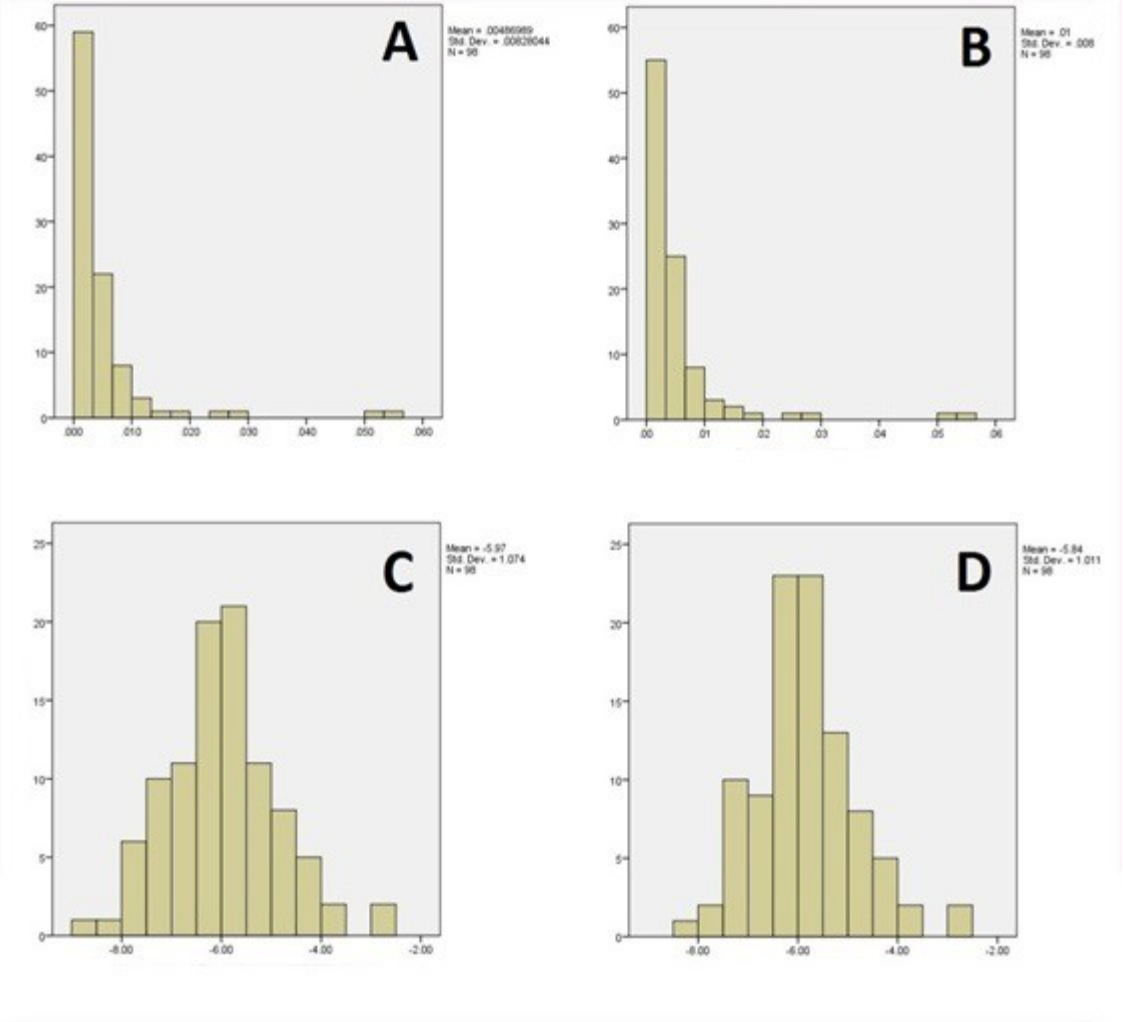

Figure 6.2.1.1 Baseline volume comparison:
A: cmsWMH (ICV corrected only) - From Fig 4.2.1.1
B: sbsWMH (ICV corrected only) - From Fig 5.2.1.1
C: cmsWMH (natural log, ICV corrected) - From Fig 4.2.1.2
D: sbsWMH (natural log, ICV corrected) - From Fig 5.2.1.2

Table 6.2.1.1 Statistical parameters for cmsWMH and sbsWMH baseline volumes.

	Log baseline volume	
Statistic tested	cmsWMH	sbsWMH
Mean	-5.97	-5.84
Standard deviation	1.07	1.01
Skew Kurtosis	0.326	0.347
Minimum value	0.467	0.68
Maximum value	-8.52	-8.46
Normal distribution?	-2.92	-2.92
	Yes	Yes

6.2.1.2 Clinical outcomes at baseline comparison

Table 6.2.1.2 compares the clinical outcomes between cmsWMH and sbsWMH at baseline, for both correlation and general linear modelling. It can be seen that the correlations are identical for both cmsWMH and sbsWMH. The significance of age holds for age in both segmentation methods in GLM models B1/B2 for cmsWMH (p=0.005 and p=0.023) and I1/I2 for sbsWMH (p=0.003 and p=0.017). It can also be seen that the same individual VRF are significant in both correlation (SBP, DBP) and GLM results (SBP). There are no interactions for any of the GLM for either segmentation method. Overall there is no difference between cmsWMH and sbsWMH baseline volume relationship to all other covariates.

Table 6.2.1.2 Clinical outcome differences between baseline manual segmentation methods

Baseline WMH Volumes	Significant correlation results?		Significant GLM results?	
Factors compared	cmsWMH	sbsWMH	cmsWMH	sbsWMH
Age	Yes	Yes	Yes	Yes
Gender	No	No	No	No
Treatment (Exercise)	No	No	No	No
Baseline PA measures	No	No	No	No
ApoE ε4 status	No	No	No	No
PET Amyloid status	No	No	No	No
Education years	No	No	No	No
SMC/MCI group	No	No	No	No
Number of VRF	No	No	No	No
Individual VRF	Yes (SBP, DBP)	Yes (SBP,DBP)	Yes(SBP)	Yes (SBP)
Neurocognitive assessments	No	No	No	No

6.2.2 Progression volume comparison

6.2.2.1 Progression volume distribution comparison

The distributions of progression volume can be seen in Figure 6.2.2.1 below. The same scale is used for both cmsWMH and sbsWMH distributions to allow easier comparison. The unmodified distributions show that sbsWMH progression volumes are more skewed, with a larger number of participants having very little change (per year, adjusted). Despite the larger numbers with lower changes, both have an identical positive skew of 2.3. Both log transformed volumes have a similar appearance of mean and shape (skew), however natural log sbsWMH progression volume appears to have a slightly larger spread. These observations are reflected in the values presented in table 6.2.2.1, with mean and skew values close (but slightly more skewed In D). The larger spread in D is reflected as a higher standard deviation, and the kurtosis reflects the shape of D with the left tail of the curve extending to lower values (which is also seen in the lower minimum value of D). This pattern reflects a larger number of cases with smaller changes in the side by side method of manual segmentation.

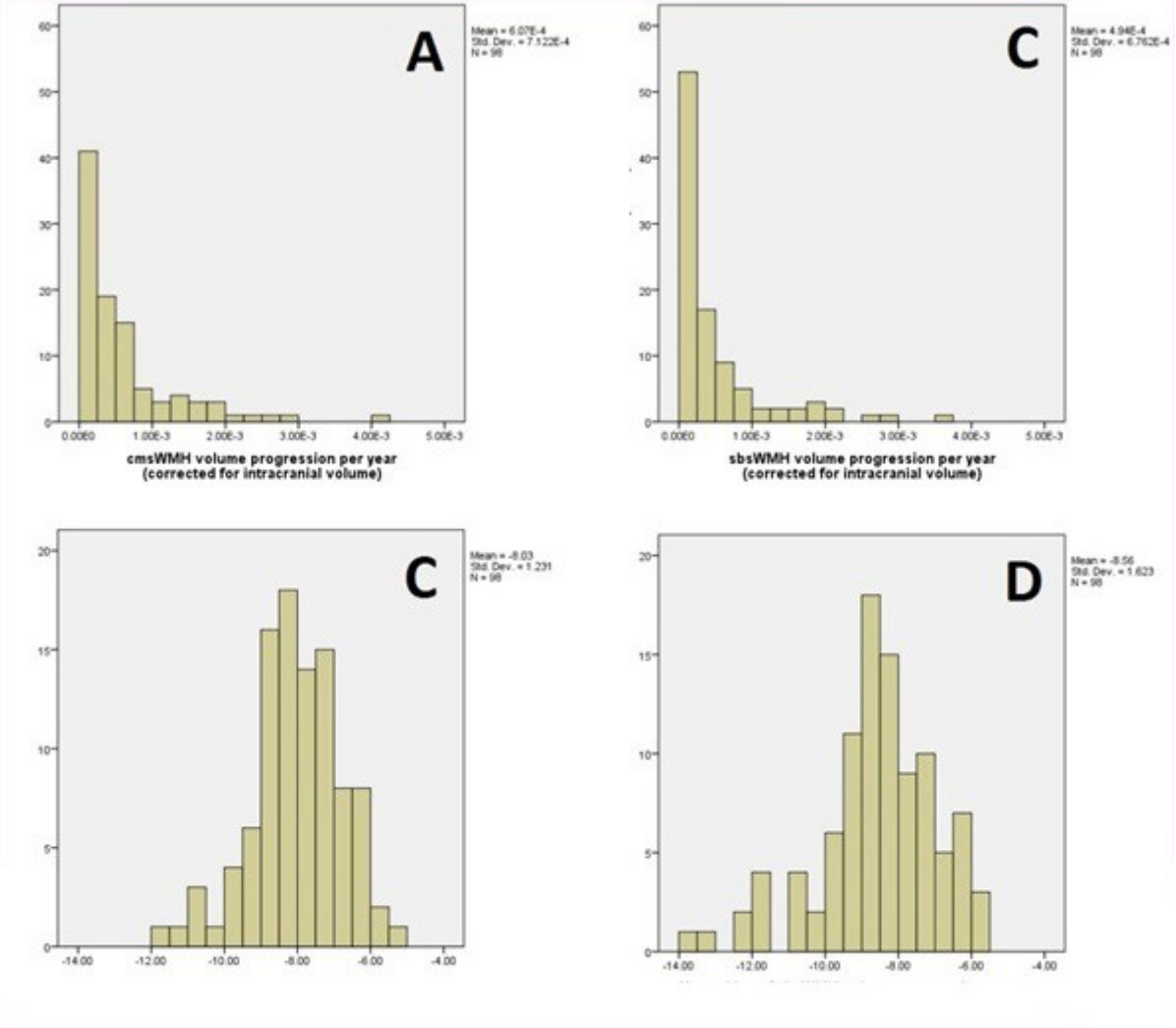

Figure 6.2.2.1 Yearly volume progression comparison:
A: cmsWMH (ICV corrected only) - From Fig 4.2.1.3
B: sbsWMH (ICV corrected only) - From Fig 5.2.1.3
C: cmsWMH (natural log, ICV corrected) - From Fig 4.2.1.4
D: sbsWMH (natural log, ICV corrected) - From Fig 5.2.1.4

Table 6.2.2.1 Statistical parameters for cmsWMH and sbsWMH progression volumes

	Log progression volume	
Statistic tested	cmsWMH	sbsWMH
Mean	-8.03	-8.55
Standard deviation	1.23	1.62
Skew Kurtosis	-0.482	-0.854
Minimum value	0.339	1.117
Maximum value	-11.58	-14
Normal distribution?	-5.49	-5.65
	Yes	No

6.2.2.2 Comparison of correlation clinical outcomes and progression volumes

The differences between cmsWMH and sbsWMH progression volume relationships to all factors in both correlations and GLM are presented in table 6.2.2.2. Age is significantly correlated against both cmsWMH and sbsWMH, but not for any of the GLM models. It can also be seen that gender is not significant for any statistical test.

Baseline cmsWMH and sbsWMH volumes are strongly significant in every correlation and GLM tested. Treatment group, ApoE ε4, PET amyloid status, years of education, cognition (SMC/MCI group) and number of VRF all show no significance. Of the remaining correlations, that differ between cmsWMH and sbsWMH volume include the individual vascular risk factors of hypertension, stroke history and BMI while the neurocognitive assessment correlations differ for which BRIEF A assessment is significant.

An elevated BMI versus normal BMI is significant in the cmsWMH progression group (p=0.021) but non-significant in the sbsWMH group (p=0.09), but the cmsWMH significance has already shown to be artefact above. The Hypertension combined score is non-significant for cmsWMH progression volumes (p=0.10), and is significant for sbsWMH volume (p=0.040). Of the constituent values, Systolic blood pressure is significant for both (p=0.004 for cmsWMH and p=0.001 for sbsWMH), while other values are statistically non-significant. Of interest also are the comparisons of the remaining values (although non-significant). History of hypertension is closer to significance in sbsWMH (p=0.32) than cmsWMH (p=0.71). The same is true for diastolic blood pressure (p=0.21 for sbsWMH versus p=0.43 for cmsWMH). The converse is true however, with cmsWMH being (p=0.69) being closer to significance than sbsWMH (p=0.97).

Stroke history is not statistically significant in the cmsWMH group (p=0.08) while significant in the sbsWMH group (p=0.005). This represents the difference in the mean averages of the two stroke patients versus the mean of the study participants with no history of stroke.

Of the neurocognitive assessment correlations, BRIEF A BRI T score is significant for cmsWMH (p=0.031) but just failing to reach significance for sbsWMH (p=0.050). For the BRIEF A Total T score, the converse applies. This score just fails to reach significance for cmsWMH (p=0.050) and is significant for sbsWMH (p=0.048).

Of the general linear models, all results agree apart from individual VRF. For both cmsWMH and sbsWMH, there are significant results for baseline WMH volume and the HADS-A neurocognitive assessments. All remaining results agree in lack of significance aside from SBP. While being negative in the majority of models, SBP is significant in model C1 that examines the effect of SBP on cmsWMH progression once the SBP and baseline WMH interaction is taken into account (p=0.046). The corresponding model J1 for sbsWMH is not significant for SBP (p=0.057).

Table 6.2.2.2 Clinical difference between cmsWMH and sbsWMH progression volumes in correlations and general linear models. *=BMI result is artefact, see above.

Progression WMH Volumes	Significant correlation results?		Significant GLM results?	
Factors compared	cmsWMH	sbsWMH	cmsWMH	sbsWMH
Age	Yes	Yes	No	No
Gender	No	No	No	No
Baseline WMH Volumes	Yes	Yes	Yes	Yes
Treatment (Exercise)	No	No	No	No
Baseline PA measures	No	No	No	No
ApoE ε4 status	No	No	No	No
PET Amyloid	No	No	No	No
Education years	No	No	No	No
SMC/MCI group	No	No	No	No
Number of VRF	No	No	No	No
Individual VRF	Yes (SBP, BMI*)	Yes (SBP, HTN combined and history of stroke)	Yes (SBP)	No
Neurocognitive assessments	Yes (BRIEF A BRI)	Yes (BRIEF-A Total)	Yes (HADS-A)	Yes (HADS-A)

Chapter 7 discussion

7.1 Introduction

The discussion will firstly consider the baseline patient demographics and how each variable lies with respect to the literature. This will be followed by consideration of results that are identical to cmsWMH and sbsWMH, addressing similarities and differences. This will be concluded by an analysis to why this may be the case.

7.2 Baseline population demographics

As the allocation to either treatment arm split between each and in blocks of 8 (4 in each arm), there were originally supposed to be 48 in one group and 52 in the other. As 2 patients dropped out (from the 52 that were due to be in the exercise group), there were 48 patients in the control group and 50 in the exercise group. As this allocation was random, there may be some uneven allocations that occur by chance so need to be investigated to ensure final results are not influenced by a-priori biases in group makeup.

The main determinants that may have influenced results would be the distribution of age across groups (which may influence white matter hyperintensity progression), gender (which may influence vascular risk factor and physical activity performances) and years of education (which may influence cognitive reserve, performance on neuropsychological tests). Luckily these main factors are equally spread across both groups as expected from a random allocation. Average age at baseline and follow up scan was investigated as this may have changed with some patients getting scanned before 24 months and some getting a scan after 24 months. With both scan dates there was no difference between age across groups. There was also no difference in terms of ApoE ε4 and PET Amyloid imaging result, a factor which may have also created an uneven progression between groups. This occurred because despite the lower numbers in the ApoE ε4 gene and PET amyloid positive groups having lower numbers, this occurred evenly across both groups. A similar situation is seen with the cognitive classification of patients in SMC and MCI groups, with approximately one third of patients in the MCI group with two thirds in the SMC group, a pattern that is upheld across each treatment arm.

Interestingly, all of the vascular risk factors were spread evenly across groups, despite there being much lower numbers in some of the groups. The combined values became positive if any of the constituent values were positive. From the data it can be seen that some values influence the combined positive values more than others.

The majority of participants were obese (obesity combined having 82 positive versus 16 negative, making nearly 84% of participants obese). This was similarly reflected in its constituent values of high waist measurement and BMI. This is an interesting phenomenon, as although 63% of Australian adults are obese, only 28% are obese in the general population (Australian Bureau of statistics 2011). This may be due to the inclusion criteria mandating at least one vascular risk factor (including obesity, hypertension, diabetes and heart disease, all of which are associated with obesity). An analysis of the distribution of obesity by gender was undertaken and is displayed in table 3.2.2.1b. Although there were high numbers of obese overall in our population, there was a slightly higher amount in males (86.05%) versus females (81.15%), this is in line with current obesity statistics in Australia (The Boden Institute of Obesity, Nutrition, Exercise and Eating Disorders & Eating Disorders and the Menzies Centre for Health Policy 2014). This did not result in any difference among genders when investigating obesity trends in control and exercise groups.

More participants in our cohort had positive combined hypertension as a risk factor than not (71.4% positive versus 28.6% negative, table 3.2.2.2). This was higher than a study of Australians in 2011-12 where 31.6% had hypertension, (21.5% with high blood pressure of 10.1% on anti-hypertensive medications). These values were defined as hypertension being raised systolic BP, diastolic BP or the use of blood pressure lowering agents (Australian Bureau of Statistics, 2012). Our data is slightly different in that it also includes a measure for hypertensive history, however a quick review of our data also reveals that patients with a history of hypertension all satisfy at least one other hypertensive criteria. This means that there are no participants with only a history of hypertension that may account for the increased hypertensive prevalence in this cohort; there must be a reason for this. Again, one could imagine that the greater number of obese patients may result in an increase in hypertension as obesity as associated with high blood pressure, as would the fact that our cohort is comprise of older adults. Again, no differences were seen across treatment arms.

Our cohort is comprised of 50% of participants who are positive and 50% who are negative for dyslipidaemia (table 3.2.2.3). Our combined value of dyslipidaemia definition match that of medical classification of dyslipidaemia (if on lipid lowering medication, Total Cholesterol >5.5mmol/L, HDL cholesterol <1.0mmol/L for men and <1.3mmol/L for women, LDL>3.5mmol/L and Triglycerides above or equal to 2.0mmol/L, Australian Bureau of Statistics 2013). In the Australian Health Survey in 2022-12, 63.2% of Australians over 18 had dyslipidaemia (Australian Bureau of Statistics 2013) which was higher than our value of 50%. In our cohort, a larger proportion of our participants were on lipid lowering medications (41.8%) versus the population in the Australian Health Survey (18%). The trend was also reversed in that 5.1% percent of participants had high triglycerides and 11.2% raised cholesterol, compared to 49.4% of the survey having elevated cholesterol of triglycerides but not on medications.

This reversal in values can be explained by the fact that our cohort are more elderly, so more likely to be seeing a family practitioner for either general check-ups or some ongoing ailments. This result in more of our participant's dyslipidaemias being identified and the patients put onto lipid lowering medications. The reason why our cohort has a slower dyslipidaemia value than the general population remains unclear. The values were obtained at baseline so any healthy living information given to participants is not reflected in these results. It may seem likely that because our cohort are older and less likely to indulge in processed and unhealthy food, (which may occur in the younger segment of the general population), that this results in this difference. A detailed examination of this reveals this not to be the case, with dyslipidaemia in 44.3% of 18-34 years olds compared to 81% in 65-74 year olds and 77.7% in 75+ year olds (Australian Bureau of statistics 2013). Being less overweight is not a cause of lowered cholesterol in our population as we know we have a higher proportion of obese study participants. The remaining reasons why our group's cholesterol is lower may be due to them doing more exercise than the general population, eating better diets or having less genetic susceptibility. It also must be remembered that our population are a group at risk of Alzheimer's so that their health profile will not exactly match that of the general population, and that some of the values may vary due to our cohort having a smaller sampling size (98 in our cohort and 11,000 in the AHS survey, Australian Bureau of Statistics 2013).

In our cohort, 8.2% of patients had Diabetes (Combined), with the same number of people having a history of diabetes, and 5% of the population on diabetic medication (Table 3.2.2.4). This is somewhat more than the reported values in the general population of 4.6% (Australian Bureau of Statistics 2013), but investigating the general population numbers more deeply, there are 16.6%, 17.0% and 11.8% of people with diabetes (both types) in the 65-74, 75-84 and 85+ groups respectively. Our population having lower diabetes prevalence than the general population may be due to a few factors, it may be due to a sampling bias (perhaps diabetic patients are too unwell or unwilling to volunteer due to their chronic disease). In addition, perhaps our recruitment area has a slightly lower prevalence of diabetes to the general population. Once again, the variability could be due to our reduced sample size in comparison to the AHS Survey.

36.7% of our population were either a current or ex-smoker, with 4.1% of our population still smoking (Table 3.2.2.5). The values for having smoked ever and smoking combined being the same due to "smoking ever" would include ex and current smokers. This value was slightly lower than the Australian population in 2011 (Australian Bureau of Statistics 2013) in both the 65-74 age groups (43.5% ex-smoker and 9.3% current smoker) and the 75+ age group (44.2% ex-smoker and 3.9% current smoker). It is interesting to note that while there are slightly higher values of ex-smokers in the general population, our current smoking numbers fall between the two values in the general population. As smoking is a voluntary process, the cause to as why people smoke is highly variable and difficult to interpret, placing it outside the scope of this study.

The presence of atherosclerotic disease in this study is made up of both heart and cerebrovascular disease (Table 3.2.2.6). Our cohort had low numbers of both, with 8 (8.2%) participants having a positive heart disease history (as per questionnaire) and 2 (2%) having a positive stroke history. This was slightly different from the AHS values which had 7.9% of patients with heart disease and 5.35% of patients with stroke and other cerebrovascular disease (Australian Bureau of Statistics 2013) in the group 65 to 84. There is good agreeance between our data for heart attacks, but a slightly lower history of stroke in our data. This may be due to the AHS values (Australian Bureau of Statistics 2013) including "other cerebrovascular disease" along with stroke in their data (i.e. transient ischaemic attack), no further data is available.

Although there are studies that examine the number of vascular risk factors against conditions such as vascular disease and dementia, there are no large epidemiological studies that count the number of vascular risk factors in a general population. The data is presented anyway (Table 3.2.2.6), with no statistical difference between distributions at baseline. The number of vascular risk factors against WMH progression can be compared in later chapters.

In summary, there is no statistical difference between allocations in demographics, ApoE ε4/Abeta, cognition group, Age and VRF at baseline, physical activity and cognition. This stipulates that any differences between groups are due to other factors other than differences due to baseline allocation. Differences between our cohort and the general population are discussed above, while there is some variation between the two, it must be remembered that our population are those at risk of Alzheimer's disease, are subject to inclusion and exclusion criteria to be part of the study and recruited from one region in Australia. Having said this, our baseline characteristics are quite similar to the general population.

7.3 Discussion: Results identical for cmsWMH and sbsWMH

7.3.1 Introduction

The majority of results are identical for both cmsWMH and sbsWMH, with the exception of individual VRF and cognitive risk factors (see Table 6.2.2.1 and Table 6.2.2.2). As this is the case, cmsWMH and sbsWMH will be referred to as a grouped result in this section (as WMH, or "our results"). In the following two sections, cmsWMH and sbsWMH will be referred to individually as the results differ between the two.

As such, all the results will be discussed here with the exception of the statistical parameters of cmsWMH and sbsWMH, individual VRF and neurocognitive tests, which will be discussed in the next section.

The main study outcome of effect of physical activity on WMH volumes will be discussed first, followed by the sub hypotheses of ApoE ε4 and PET amyloid status affecting WMH. Age and gender will be considered next, with education to follow. Cognitive group diagnosis (SMC/MCI status) and number of VRF will also be discussed here as the outcomes are the same for both cmsWMH and sbsWMH.

With review of Table 6.2.2.1 and 6.2.2.2, it is interesting to note a few facts. The first is that with the exception of age and baseline WMH volume (tested against WMH progression in table 6.2.2.2), individual VRF and neurocognitive tests, there is no difference between statistical correlations and GLM, for both cmsWMH and sbsWMH, for both baseline WMH volumes and WMH progression volumes. That is, none of the tested factors were statistically significant at all despite being tested against baseline WMH volume and progression WMH volumes. It would be expected that the use of longitudinal data would be more sensitive to any change, but this is not the case for almost all of the data tested. The exception to this is the neurocognitive results which will be discussed in the next section, which is not significant with baseline WMH volume and shows statistical significance with WMH progression volumes. It is discussed further in the next section as there is also variability in outcome between cmsWMH and sbsWMH. Age has the opposite pattern (significant with baseline WMH volumes but not progression WMH volume GLM) but will be discussed later.

7.3.2 Physical activity

Whilst it is encouraging to see cross-sectional studies emerging that demonstrate a correlation between white matter hyperintensities and physical activity in normal participants (Gow et al. 2012, Saczynski et al. 2008, Sen et al. 2002 and Wirth et al. 2014), there are a number of studies that have also failed to show any correlation (Burzynska et al. 2014, Carmelli et al. 1999, Fleischman et al. 2015, Frederiksen et al. 2015, Frederiksen et al. 2015, Frederiksen et al. 2015, Ho et al. 2011, Rosano et al. 2010, Tian et al. 2014, Tseng et al. 2013a, Willey et al. 2011). A study by Rovio et al. 2010 examined normal, MCI and demented patients and failed to find an association between physical activity questionnaire results from mid-life and WMH volume. The non-significant studies were not any more underpowered than the significant results (For example, 1238 participants in a non-significant result, Wiley et al) and both utilised various types of WMH measurement type (both significant and non-significant studies have employed volumetry and visual rating scales) and physical activity assessments (questionnaire, VO_2 max readings).

The majority of studies assessed physical function in terms of a questionnaire, while two employed a fitness test measuring VO_2 max (Burzynska et al. 2014 being insignificant and Sen et al. showing an associated decrease in WMH volume). Although these studies were cross sectional in terms of MRI imaging, there was a variation between study designs. 11 of the studies employed a design of physical fitness before MRI assessment, while two assessed the participants with MRI before the physical fitness assessment which was done via questionnaire for both (Frederiksen et al. 2015, Tian et al. 2014). The interval between is also quite variable, with Gow et al. 2012 measuring physical activity 3.2 years before the MRI (with significant outcomes) to Tian et al. 2014 performing the MRI 8-11 years before the physical activity assessment (with no significance).

The majority of the studies examined physical activity per questionnaire, using this to calculate either activity scales or energy expenditure per week. We also investigated baseline functional fitness assessments. The majority of our assessments are indicators of fitness rather than a direct cardiovascular fitness measurement, with the exception of the 6 minute walk test. A number of the cross-sectional WMH physical activity studies also used VO_2 max as a marker of physical fitness and capability. The 6 minute walk test has shown to correlate with the standard of cardiovascular fitness VO_2 max (Cataneo et al 2010) and has good re-test reliability (Steffen et al 2002), so it is an analogous measurement to VO_2 max. Unlike the cross-sectional studies that have shown a significant relationship between "questionnaire calculated" weekly activity, energy expenditure or VO_2 max measurements, we did not have any relationship between any of our measurements and our baseline WM volume.

From studies that only make correlations, it is not clear if physical activity is resulting in lower WMH volumes, or that the WMH are causing participants to become less active. In fact, one study has shown that corrected for baseline fitness, WMH volumes are an independent predictor for physical decline in community dwelling older adults (Zheng et al. 2012). While longitudinal studies require less participants to see a statistically significant result from participants being their own control which removes a degree of variability which would normally be present in cross-sectional studies, the order of cause and effect cannot be proven, although it can be implied from mechanism based logic and increasing literature consensus on the topic.

While a few of the studies used imaging at a single point in time and are therefore a cross-sectional examination of WMH volumes, their overall study design means that they can be considered a longitudinal change study due to imaging occurring after physical activity (Gow et al. 2012, Carmelli et al. 1999, Wiley et al. 2011). This study design increases the strength of conclusions, however only one (Gow et al. 2012) was significant. One study with a true longitudinal design is Podewils et al. 2007, which examined the association between physical activity as calculated and WMH progression. This study found an association between energy expenditure per week and normal participants, but not MCI or AD patients.

As there has shown to be an association with physical activity with WMH volume in normal patients but not AD/Dementia patients, it could be equally justifiable to predict either an effect or no effect of physical activity. It is likely however that SMC/MCI patient may still be affected by physical activity, but it may be below a detectable threshold. In our cohort, our participant's WMH may have been too damaged already to see an effect as is the case with Rosano et al. 2010 and Podewils et al. 2007. Our lack of correlation with baseline measures/fitness and WMH volume share the same results as Rosano et al. 2010, and our baseline fitness measures not being associated with WMH progression share the same conclusion as Podewils et al 2007.

With our cohort, we have consistently shown the significance of baseline WMH volume on progression. This is reported in additional MRI WMH progression studies also (Tosto et al. 2014) and has been demonstrated to be a significant predictor of further progression in dementia patients (Burton et al 2006). It is therefore possible that patients already exhibiting cognitive decline are too far along in the WMH pathogenesis cascade (which still requires full elucidation) to see an impact of exercise.

Having said this, there are a number of reasons to why our study may have failed to detect an effect of physical activity on WMH progression which may still be possible in SMC/MCI patients. The inclusion criteria requiring presence of VRF, our cohort being motivated, dishonest participant use of physical activity logbooks and our reduced numbers may have masked a potential modifying effect of physical activity.

With our participants being selected only if they have vascular risk factors (and SMC/MCI) cognitive status, it may be possible that their white matter integrity is more damaged than normal older individuals. While this is part of the study design, in that selecting those with VRF may have resulted in higher overall rated of WMH progression and more likely to see an effect of VRF modification, it may have also resulted in selection of participants with WMH relatively robust to modification by exercise at this point. This is reflected by Smith et al. 2009 who found no association of physical activity and WMH in community dwelling adults with essential hypertension diagnosed before 60. In addition, with each participant being prescribed personalised physical activity, this would vary the groups of muscles used (for example, jogging, swimming, running), and also the level of vascular risk factor modification. At current we are limited by only examining the dichotomous nature of exercise and control groups, which may have contributed to our lack of significance.

The second reason is that our study cohort is full of arguably very motivated individuals. This is the second trial they have all been involved in (first the AIBL trial and next the AIBL Active trial). A motivated control group may have also been more receptive to media that encourages older adults to stay active and may have been more active than they usually have been. This would have an effect of reducing the difference between both treatment arms, resulting in our lack significance of main trial outcome.

While there is no particular imperative for participants in the control group to fabricate results, there is a pressure for the exercise study arm to perhaps state they perform their prescribed exercise when in fact they may not have. This would be mitigated in part by the compliance measures of phone calls, healthy handouts and pedometer wearing, this cannot absolutely be discounted. The associated stigma and shame of being inactive may have also resulted in participants falsely reporting how inactive they have been, resulting in false questionnaire results. This is one of the drawbacks to performing a community based study. Performing this amount and duration of exercise in all individuals in a controlled physiology lab or the like would become prohibitively expensive, logistically very complicated (read: near impossible) and the conclusions are not as valid to the general populous as a home based study of community dwelling participants would be.

Finally, with the reduced number of participants in our study, we may have missed out on results due to being statistically underpowered. The cross-sectional studies who showed statistically significant results had larger numbers; 1781 (Sazcynski et al 2008), 715 (Sen et al. 2012). Tseng et al. 2013b showed a significant difference with only 20 patients, however the physical activity difference between groups was immense, comparing masters athletes with over 15 years of endurance training to sedentary older adults not participating in moderate or high intensity exercise for no more than 150 minutes per week over two years. Gow et al 2012 and Podewils et al. 2007 also recruited larger numbers to longitudinal studies of physical activity (691 and 179 participants respectively). Having said this, several studies with greater numbers than AIBL Active failed to show any effect. Smith et al. 2009 recruited 777 participants but showed no effect, this may have been due to VRF inclusion as mentioned above. Zheng et al. 2012 recruited 287 participants, however the study design scanned patients at the commencement of the study (and repeated physical activity measurements rather than repeat imaging). Without a second MRI scan it is not surprising there are no effects. Willey et al 2011 studied 1238 participants, 63% of which are Hispanic. It is not clear whether this resulted in the lack of significance.

In future, after processing of pedometer and compliance data, the exact exercises and amount performed over the 24 months will become available. With continuous measures of activity across the whole cohort (not just those in the exercise group), there may still be an association of physical activity and WMH progression but this information is not yet processed. From the data analysed here, there is no effect of physical activity or exercise intervention on WMH progression.

Studies have demonstrated additional effects to WMH (total volume). Benedict et al. 2013 and Gow et al. 2012 have both demonstrated a significant positive relationship between physical activity (questionnaire results) and global white matter volume in cross-sectional studies. Changes have been detected in localised areas of white matter also. Erickson et al. 2007 demonstrated associations between fitness test results and frontal and corpus callosum volumes (in post-menopausal women). Ho et al. 2011 have shown associations between physical activity questionnaire results and the corona radiata and parietal occipital white matter volumes. Tseng et al. 2013b showed a relationship between questionnaire data and the temporal, parietal and occipital white matter volumes, however this was in masters' athletes versus sedentary older individuals. Interestingly, Colcombe et al. 2006 demonstrated preservation of white matter volume in older adults in a 6 month physical activity intervention, but interestingly no change in the younger adults tested in their cohort. In addition to the significant global WMH volume results as previously discussed, there are also studies that have shown promise in examining localised areas of WMH. Tseng et al. 2013a have shown a significant cross-sectional association between AP questionnaire and deep WMH lesions. In addition, Podewils et al. 2007 have shown longitudinal changes in deep and peripheral WMH volumes and PA questionnaire assessment, with 5 years elapsed between first and second scans.

Within the literature, a few areas of interest are emerging. The first is that global volumes of WMH, even if measured very accurately with manual segmentation, may be missing local effects of physical activity. It is also apparent that changes in addition to WMH are likely to be evolving which FLAIR imaging does not detect. While some neuropathological studies have shown correlations between FLAIR WMH and histopathological changes (Shim et al. 2014), others have suggested that WMH lesions overestimate irreversibly injured areas (Haller et al. 2013), this is an ongoing debate. This is interesting as other forms of imaging are detecting changes in the white matter surrounding WMH, the so called "normally appearing white matter" (NAWM). This is being increasingly labelled as the "penumbra", the normal region that is at risk of further damage. This is evident on both diffusion tensor imaging (Maillard et al. 2011, Maillard et al. 2014) and measurements of cerebral blood flow on arterial spin labelling (Promjunyakul et al. 2015).

In addition to the changes seen in white matter (volume, WMH, neuropathological and diffusion measures), changes to grey matter is gaining Importance. As the brain naturally atrophies over time, a distinction between "accelerated aging" and "successful aging" is emerging (Thielke et al 2012). This is changing the field of neurological research, and providing a number of avenues to possibly change what has traditionally been accepted as "normal" age related decline. Of relevance to our data, physical activity is showing the ability to slow the rate of grey matter atrophy in older adults. Cross sectional studies have shown an association between fitness and whole brain volume (Burns et al. 2008, Ho et al. 2011 but effect disappeared when correcting for BMI in the model), total grey matter volume (Alosco et al. 2013, Erickson et al. 2010, Gordon et al. 2008, Rovio et al. 2010), cortical grey matter volume (Colcombe and Kramer 2003, Erickson et al 2007 in postmenopausal women), frontal volume (Bugg and Head 2011, Floel et al. 2010), temporal and parietal volume (Honea et al. 2009) and hippocampal volume (Bugg et al. 2012, Erickson and Kramer 2009, Head et al. 2012, Szabo et al. 2011).

Additional studies have shown increased fitness to be associated with increased volume in the striatum (Verstynen et al. 2012) and the dorsolateral prefrontal cortex (Weinstein et al. 2012). 2 studies failed to show an effect on grey matter volumes, but did show an association between physical activity and changes on fMRI imaging (Rosano et al. 2010 and Smith et al. 2011). These many results in cross-section are further backed up by the existence of longitudinal studies. Gow et al. 2012 demonstrated that increased physical activity was associated with decreased atrophy, and increased grey and white matter volume. Erickson et al. 2011 and Ruscheweyh et al. 2011 examined the effect of physical activity in randomised controlled trials with promising results. Erickson et al. 2011 demonstrated an increase in hippocampal volume in the treatment arm while Ruscheweyh et al. 2011 showed an increase in grey matter volume along with BDNF levels and memory performance. More interesting still was that Ruscheweyh et al. 2011 showed this effect in all levels of activity, which implies a positive effect of even low levels of physical activity in older patients.

Despite all of this and despite our negative result, it is still very likely our exercise treatment arm have benefited from their intervention. It is increasingly likely that the effect of physical activity is multidimensional and multi-modal imaging and sub-region analysis is required to fully elucidate its impact. With further studies too, the length and intensity of exercise program required to see an effect can be better stipulated.

With regard to additional covariates, there are a number of factors that we expected to be significant but were not. It was expected that age was associated with a more rapid accumulation of WMH in most models. Additionally, we expected that ApoE ε4 and PET amyloid beta negative status would have slowed progression of WMH but we did not see this. It was also expected that there would be more impact of the vascular risk factors and we were hoping to see all of this reflected in cognitive status. Each of these will be discussed in turn.

7.3.3 Age

It has been known for some time that WMH are associated with advanced age (Kertesz et al. 1988). What is less clear is whether WMH are purely accumulating due to age or due to concomitant medical conditions that cause damage over time. The heterogeneity of neuropathological correlate studies suggest that although appearing similar on T2 weighted imaging such as FLAIR sequences, that the underlying pathology may be variable (Fazekas et al. 1988, Braffman et al. 1988). In addition to this, other imaging modalities such as Magnetisation Transfer Imaging (MTI) are demonstrating differences between DWMH and PVWMH (Spilt et al. 2006). While some of this may be due to fluid differing fluid dynamics between the deep and periventricular white matter as suggested by Spilt et al. (that particularly in older individuals, ventricular ependymal breakdown results in more PVWMH interstitial cell fluid), the differences in neuropathological correlation studies give more weight to their being actual differences in pathogenesis. An interesting study by King et al 2014 demonstrated that while age is associated with accumulation of WMH, it is even more strongly associated with the presence of vascular risk factors of hypertension, obesity and diabetes.

With this heterogeneity, we would expect to see different effects with the addition of VRF. In our data, we showed a correlation between age and baseline cmsWMH and cmsWMH progression. We also demonstrated significance in all GLM models that include baseline cmsWMH volume as the dependent variable, revealing baseline cmsWMH to be a statistically dominant factor. Age was not significant in the majority of GLM combinations, but it did become significant when we included the interaction between baseline cmsWMH and systolic blood pressure (model C1). This agrees with the results of King et al 2014 in that VRF are associated with a stronger age correlation for SBP, but does not agree with this effect being present with other VRF or age associated in the remaining models. This difference may be explained by the difference in their population and numbers recruited (2077). Their comorbid group had a higher proportion of African Americans, fewer whites and fewer females, and they also corrected for ethnicity whereas we did not. Ethnic minorities have been shown to have more variable WMH loads (Stavitsky et al 2010), and have been particularly shown to be more prevalent in African Americans (Nyquist et al. 2010).

7.3.4 Gender

Differences may have also been to a difference gender percentage between our study and King et al 2014. This was also shown in the Rotterdam Scan Study, where age and baseline load influences the associations with blood pressure (Van Dijk et al. 2008), but in this case older patients (over 90) no longer had significant associations between blood pressure and WMH lesion severity. While King and Van Dijk have somewhat contradictory results, they are looking at different populations, and comparing the groups in different ways (<50, >50 for King et al 2014, 60-69, 70-79, 80-90 for Van Dijk et al).

Several studies have demonstrated a difference in WMH between genders. Longstreth et al. 1996 and De Leeuw et al. 2001 both showed cross-sectional gender difference, with more WMH volume in women than men. This is contradictory to our baseline results, which show no gender difference with baseline cmsWMH volumes. One might predict that this could be due to our inclusion criteria requiring the presence of VRF, but the population of Longstreth et al's (1996) is quite similar to ours, community dwelling adults over the age of 65. While not requiring the presence of VRF, it is prevalent in their population also; however, the high percentage of cardiovascular disease (being part of the cardiovascular study, 3301 participants recruited, 23% with cardiovascular disease and 13% with ischaemic heart disease) and higher rates of hypertension (43% versus our cohort having 20.4%) means that their significance could be due to their risk factor profile.

On the other hand, De Leeuw et al. 2001 recruited from both healthy older subjects (The Rotterdam Study, 1077 recruited) and a study of chronic diseases (The Zoetermeer study, 514 recruited). Although exact patient risk factors are not available, 8% of their cohort was free of DWMH, 20% free of PVWMH and 5% without WMH suggesting a relatively healthy cohort. Taken together, two cohorts, one more healthy (inclusion of some disease free participants) and one more diseased than ours (higher VRF load), both showed a cross-sectional difference between genders. However, this may be due to their larger statistical power (1691 and 3301 versus our 98 participants).

The lack of gender difference may also be due to our patients being cognitively at risk of AD (SCM/MCI status). As there are accepted gender (and age) differences, these values are usually corrected for when examining other factors, so the current field of research is more focusing on other areas affecting WMH. Although aimed at studying the progression to AD and cognitive effects, Kim et al 2015 published their baseline data on differences of baseline characteristics of 294 Korean MCI patients. They found a difference between PVWMH (more in females, p=0.014) but not for DWMH lesions (p=0.685), they did not however publish the overall volume difference and excluded patients with lesions under 10mm and with severe WMH. A study by Sachdev et al. 2009 found a similar pattern, in that cross-sectional study of normal participants there are more PWMH but not DWMH in females, and in the total volume (significant with both automated segmentation and visual rating scales). While this is interesting, other studies have shown no difference between genders (Raz et al. 2012).

With regards to age effect on WMH progression, the results are also mixed. Some studies found a higher rate of progression in women (Sachdev et al. 2007) while other studies did not (Gouw et al. 2008b). As Sachdev (in Sachdev et al. 2009) conclude, up to 80% of the variation in WMH is still unexplained, and we should move beyond cerebrovascular causes (and the different cerebrovascular profile seen between genders as a possible cause for WMH). While it is interesting to note the potential differences emerging between DWMH and PWMH in a number of areas (age, gender, neuropathological correlates), it is likely that genetic and other unexplained factors play a more important role than gender in WMH progression, and even more detailed variability patterns exist than purely DWMH and PVWMH.

7.3.5 ApoE ε4 status

Whilst some studies examined the effect of homozygous ApoE ε4 (ε4/ ε4) differently to heterozygous (ε4/other allele), we did not have the power to do so as we had only two homozygous patients. Instead both homozygous and heterozygous were grouped together as ApoE ε4 positive, which consists of 2 homozygous and 26 heterozygous ApoE ε4 patients. The remainder consisted of 70 patients without any ε4 alleles (therefore being homozygous ε2, ε3 or heterogeneous ε2/3). No analysis of ε2 or ε3 homozygous/heterozygous status was performed due to hypothesis focusing solely on the effect of ε4.

Our ApoE ε4 cohort can then be considered grossly analogous to studies examining heterozygous ε4, even though there are two homozygous cases included. It had been expected that the presence of ApoE ε4 allele would have been associated with higher baseline WMH load and additionally with more WMH progression over the two year time period, which was predicted because previous studies that have shown associations between ApoE ε4 allele and AD (Corder et al. 1993 and Farrer et al 1997), particularly late onset AD (Saunders et al. 1993, Poirier et al. 1993) and cardiovascular disease (Stengard et al. 1998). This was not the case with our data. Further examination failed to show any modification of this with the addition of other VRF.

The literature surrounding ApoE allele studies varies owing to the difference combinations of alleles tested. Some studies only examined homozygous ε4 alleles (ε4/ ε4), while others compared heterozygous ε4 against a specific other allele (for example ε3/ε3). Further yet studies examined the protective effects of ε2. For the studies to be compared to our data, only the studies involving ε4 positive (homozygous and heterozygous) and heterozygous ε4 against non ε4 (i.e. any combination of ε2 and ε3) were included. This ensures comparisons are possible between our results and the literature.

With the ApoE ε4 being associated with higher WMH volumes in some studies examining both normal patients (Hafsteinsdottir et al. 2012, with 4303 participants cross-sectionally, Høgh et al 2007) and AD patients (Lunetta et al 2007), it seems logical that this would be the case for our cohort that sits cognitively between the two. However, a number of studies have failed to show any association which suggests that the involvement of ApoE and other genetic factors is a lot more complex than this. It would at least suggest that the pathway between ApoE allele expression and WMH outcome may be less direct and influenced by multiple other factors.

As Lunetta et al. 2007 explored, with cases of AD and their siblings, a large amount of the genetic cause for WMH are yet to be explained. In fact, a study by Morgen et al. 2015 has revealed that WMH volumes were more pronounced in ApoE ε4 non carriers, and suggested that this may be due to a higher sensitivity to other vascular risk factors in this group. With our cohort all having at least one VRF, It is therefore not surprising that our data was unable to show an effect of ApoE ε4 allele. This was reflected in a number of other studies that also didn't show any association with ApoE ε4 allele in both normal (Sachdev et al. 2009, Raz et al. 2012) and AD patients (Hirono et al. 2000, Sawada et al. 2000 and Grimmer et al. 2012).

7.3.6 PET amyloid status

PET amyloid imaging in older adults with normal cognition (or SMC/MCI/AD) shows a great deal of variability. In cognitively normal elderly, the prevalence of PET amyloid positive status ranges from 0% (Okello et al. 2009) through to 47% for PIB imaging (Jagust et al. 2009), and 7% (Vandenberghe et al. 2010) through 28% for Florbetapir (Fleisher et al. 2011). It is generally accepted that the prevalence is closer to 10-33% in cognitively normal elderly (Pike et al. 2007). MCI is higher in prevalence with values between 40 % and 72% for PIB and between 47% and 60% reported for Florbetapir (Villemagne et al. 2011, Lowe et al. 2009). This rises in AD to 90% (Mormino et al. 2009) to 100% for PIB (Jack et al. 2008 and Lowe et al. 2009) and 81-85% (Fleisher et al. 2011) to 97% for Florbetapir (Villemagne et al. 2011). From this it can be seen that the percentage of PET amyloid positive scans increases with progression from normal cognition through to AD.

With our study cohort being comprised of SMC/MCI patients, it would be expected that the prevalence of Amyloid in our population would be between cognitively normal elderly and MCI participants. With an overall proportion of 13.3% positive in our cohort of 90 who were imaged with 16.8% (4 out of 25 MCI patients PET amyloid positive), this would seem low compared to the literature. In terms of amyloid load, the difference between cognitively normal and SMC status is not always clear. An investigated by Chetalat et al. (2010) found no difference in amyloid load between cognitively normal elderly and those with SMC.

If our SMC participants are considered analogous to cognitively normal with regards to amyloid positivity, and the proportion of MCI positive patients possibly low due to statistical aberration from a low sample size, then our data is still close to proportions reported in the literature. It may also be possible that as a number of our participants were recruited from AIBL, that the PET amyloid positive patients had cognitively declined and therefore were not able to be recruited to the AIBL Active study, lowering the proportion of positive participants.

In this study, PET amyloid status was not significantly associated with baseline WMH volumes or WMH accumulation in any of the statistical models. This is in contradiction to a study which had found associations between WMH and PET amyloid status (Grimmer et al. 2012), however this study used voxel based methods and 22 patients only. While the lack of association may seem likely due to our use of multiple radio-ligands, the results from different markers were standardised (Villemagne et al. 2014) and it has also previously been shown that there is good concordance between separate radio ligands (Villemagne et al. 2012 and Vandenberghe et al. 2010). It is hence more likely that the lack of relationship with WMH is a true occurrence in the AIBL Active data. This is in agreeance with an emerging number of studies that are finding that although PET amyloid load and WMH are often co-existing, they likely represent different aetiologies and is therefore not likely to be related. This is based on distinctly different cognitive profiles observed in WMH and amyloid disease (Hedden et al. 2012), and that the presence of either WMH or amyloid does not predict the presence of the other (Vemuri et al. 2015). It is therefore plausible that our results demonstrate the separate nature of WMH load and PET amyloid status, and also are not related due to coincidence.

7.3.7 Education

Some studies it has been shown that age and education can account for up to 22% of variation in neurocognitive assessment results (Ganguli et al. 2010). Age and education have also shown to be more potent modifiers of neurocognitive outcomes than gender and race (Snitz et al 2010). It is therefore vital that all of our neurocognitive tests have been corrected for age and education, which has been the case in our data.

In addition to education being a corrective factor, it was tested against WMH baseline volume and WMH progression volume. In all models tested, across both cmsWMH and sbsWMH, in correlation and GLM, and using baseline and progression WMH volumes, education was not significantly associated. This is consistent with the cross-sectional study by Dufouil et al. 2003 that found no association between mean education years and WMH load in a sample of 845 elderly subjects; however WMH load was determined with a visual rating scale only and not segmented to give a continuous volume. Another study by Mortamais et al. 2014 studied the longitudinal cognitive outcome of a cross-sectional WMH load and examined the interaction with education. A significant interaction between semi-automated WMH segmentation and education level was found, however this study defined "education level" as low if it was below 8 years (primary school and early high school) and high if above 8 years (likely high school completion of further). This differs from our data as education was tested as a continuous variable, and our participants have achieved a higher average education level. The average mean education in the AIBL Active cohort is 14.2 years, with 2 participants with 8 years of education and all others with more years of education. As Mortamais had suggested, perhaps education is only protective up to a certain level.

It may be imagined that increasing education is associated with a change of average occupation area, from "blue collar" jobs into more analytical or "white collar" office type jobs, and that this too may influence WMH volumes, however an analysis of occupation by Dufouil et al. 2003 failed to also see an impact of occupation of WMH volume.

7.3.8 Cognitive (SMC/MCI) group

It is now well recognised that increasing severity of diagnosis from normal cognition, through at risk of AD (SMC and MCI) and onto AD is associated with increasing burden of WMH (Yoshita et al. 2006). It is less clear to differentiate between the WMH load between SMC and MCI. A diagnosis of subjective memory complaints is limited to complaints regarding memory, and has been more strongly linked to a history of depression and anxiety than vascular disease (Paradise et al. 2011). Having said this, a study by Stewart et al. 2011 did successfully link SMC to WMH volume; however this was present only for subcortical WMH and not for total WMH volume. It was also interesting that SMC is more strongly linked to previous WMH change than future WMH in the same study, which measured cognition at the entry and exit of the study.

It is therefore still plausible that cognitive classification is linked to WMH volume but in cognitive classification at the conclusion of AIBL Active which is not yet available. As a diagnosis, MCI is increasingly being divided up into amnesic and non-amnesic MCI (Rapp et al. 2010, Clark et al. 2013), and also being classified into single or multiple cognitive domains (Lenzi et al. 2011). As a result of this heterogeneous subtype of a single diagnostic label, the prognostic value of a pure SMC or MCI diagnosis is losing favour and studies now prefer to examine particular cognitive domains and more targeted tests to examine specific deficits which may be missed in purely an SMC or MCI diagnosis. It is therefore not surprising that there is no association between SMC/MCI diagnosis and WMH in any of the results. This may also be due to the educational attainment of our cohort, which aligns with the results of both Dufoil et al. 2003 and Mortamais et al 2014 who found no association between cognitive diagnosis and WMH load in their higher educated groups. This was also mirrored in the study by Nebes et al. 2006 who demonstrated that cognitive processing speed was more strongly associated to WMH volume in the less-educated compared to more educated.

7.3.9 Number of VRF

While individual VRF, particularly hypertension, are associated with increased WMH volumes (Murray et al. 2005, Raz et al. 2012), the role of VRF number as a number score is less clear. As already mentioned, each VRF in isolation will be discussed in the next chapter.

Increasing VRF number has been associated with both neural vascular pathologies and cognitive dysfunction in numerous studies. VRF score has been linked to brain micro bleeds (Olazaran et al. 2014), stroke (Putaala et al. 2012) and cerebrovascular disease on post-mortem examination (Bangen et al. 2015), decreased cerebrovascular flow (Bangen et al. 2014), and cross-sectionally to decreased hippocampal and entorhinal cortex volume (Qiu et al. 2012). VRF score has also been implicated in worse cognition within an MCI diagnosis (Tay et al. 2013). It is also correlated with worse executive function within the amnesic subtype of MCI (Villeneuve et al. 2009), and that within that group, higher numbers of VRF was associated with multiple cognitively domains being affected. It has also been associated with a higher risk of AD (Luchsinger et al. 2005).

The association between VRF and AD is hotly debated at the level of review articles (Chui et al. 2012, Davey et al. 2012); it is still unclear whether vascular risk factors promote AD pathology or whether their presence results in cognitive dysfunction that results in an earlier AD diagnosis as VRF and AD often co-exist in the same patients. An examination of VRF number and these factors can actually give some insight into this conundrum.

It is likely that VRF and AD co-exist only, and that vascular disease results in a higher chance of AD diagnosis. Whitmer et al. (2005) revealed an increasing association of AD diagnosis later in life with increasing number of mid-life VRF. This was further backed up by the study of Bangen et al. (2015) who showed an increase of post-mortem cerebrovascular disease within only patients with a diagnosis of AD and with ante-mortem multiple VRF, and that increased VRF is not associated with increased PET amyloid load (Lo et al. 2012). This would also explain why there are no cognitive associations with number of VRF in our data.

While VRF are associated with WMH, so are surrogates of AD, with plasma beta-amyloid being independently associated with WMH (Gurol et al. 2006). Yoshita et al. 2006 not only correlated WMH with VRF, but also demonstrated different patterns between cognitively normal, MCI and AD. This suggests that WMH are not purely vascular and can be modulated by other brain pathologies, despite the fact that vascular disease promotion has shown to be separate from AD disease. Despite this, it was still expected that increasing VRF would be associated with higher WMH volumes.

There are a number of reasons why this may be the case:

The first reason our data may have not been significant is the fact that we examined the number of VRF continuously. Of the previously mentioned studies, all the studies grouped their VRF numbers to a differing extent. Qiu et al (2012) grouped their VRF numbers into 0, 1 or multiple VRF. Olazaran et al. (2014) just presented the association that their participants with a high number of micro bleeds have a high number of VRF. Tay et al. (2013) classified groups into MCI plus VRF with 0-1 VRF, MCI plus VRF with 2-4 VRF and MCI plus infarct groups. Luchsinger et al. (2005) grouped participants with 3 or 4 VRF together, giving number of VRF as 0, 1, 2, and 3/4. Putaala et al (2012) who stratified results depending on number of VRF into 0, 1, 2, 3 and 4 and above, however they examined a much larger number of VRF (13 well documented stroke VRF and 12 less well documented factors). With our data, grouping the number of VRF into different group sizes as used above had no effect on the statistical outcome.

Also, a limitation of all the studies thus far and the data in our study is that they are the VRF profile at a single time point. Being positive for any particular VRF is a binary outcome only. There is no weighting given to any of the scores depending on how long they have been present, how severe they are (for example, number of cigarettes smoked, how elevated the systolic/diastolic BP is) or how the vascular risk factors interact. Possible synergistic effects of multiple factors were not accounted for in our score, nor were any proportionality effects, with some factors possibly having a larger influence than others. It is also possible that that VRF have the majority of their influence in mid-life and don't influence WMH progression much in later life (Debette et al. 2011).

Finally, it is also possible that potential participants who are more affected by the manifestation of a particular VRF were excluded from the study. This may be due to them being too unwell to be involved in the study (for example, severe hypertension, multiple heart attacks, and disabling strokes). Additionally, possible study recruitments with a larger effect of 1 or more VRF (perhaps having a more severe/uncontrolled form of disease or having it for longer) may have resulted in diagnosis of dementia/reduced MMSE (including perhaps vascular dementia).

7.4 Discussion: Results that differ between cmsWMH and sbsWMH

7.4.1 Introduction

The data characteristics will be discussed, along with individual VRF and neurocognitive assessments, both of which vary between the two segmentation types.

7.4.2 Data characteristics

Of the individual VRF, most results for cmsWMH and sbsWMH are similar while only a few differ. Both have identical significant results for their respective correlation (SBP and DBP) and GLM (SBP only) for baseline volumes. The differences between cms/sbs methods arise with the WMH progression, for both correlation and GLM. Individual VRF that are significant are SBP (both correlation, cmsWMH GLM), HTN combined (sbsWMH correlation only), stroke (sbsWMH correlation only) and BMI (cmsWMH correlation only). All the remaining VRF were not significant in all models.

7.4.3 Individual VRF

Despite there being no association with number of vascular risk factors and other factors (age, ApoE and PET amyloid, gender etc.), it is probable that these interact together to at least some degree but was not detectable. With this in mind it must be remembered that the influence on each individual's WMH load is multi-factorial, and therefore not caused by any single factor alone. While this cannot be proven, it is still worth keeping in mind to view the following interactions in a multi-factorial context.

With regards to WMH and blood pressure, this is also the case as it is comprised of multiple constituents. The components of hypertension are peripherally measured variables (SBP and DBP), along with medical history components (Medication use or positive history of hypertension). Hypertension as a collective term has been previously associated with WMH (Dufouil et al. 2001, Van Dijk et al. 2004 and Maillard et al. 2012). Although hypertension is increased blood pressure, a number of studies have found decreased cerebral blood flow in the region of WMH (Brickman et al. 2009, Ten Dam et al. 2007 and Markus et al. 2000). This then suggests that hypertension may cause damage to cerebral blood vessels, wall thickening and therefore decreased flow. This has been postulated by Aribisala et al. 2012 in a study investigating the effect of internal carotid artery flow changes on WMH. It must also be mentioned that a number of studies don't make the distinction between the individual components of hypertension (SBP, DBP, positive history or anti-hypertensive use).

While our data demonstrated an association mostly strongly with SBP (and to a lesser extent DBP and hypertension combined), it is our hypertension combined factor that is most analogous to "hypertension" as described in the literature. As we are investigating individual; components of hypertension, we can infer that the effect seen in hypertension is most likely due to SBP (but again we are not investigating intra-cerebral parameters so cannot comment fully on the overall strongest component of blood supply to the brain tissue which may cause WMH). Of the peripherally measured components of blood pressure, SBP specifically is being increasingly identified as the driving force behind the deleterious effect of WMH (Gottesman et al. 2010, Liu et al. 2016 and Rosano et al. 2015), but also recognises that SBP variability as an aggravating factor for WMH accumulation.

Cerebral blood flow is not only influenced by extra-cranial pressure as discussed above, but also under its own autoregulation, keeping the flow of blood to the brain relatively even despite the varying blood pressures supplied to it (Fujishima et al. 1995, Paulson et al. 1990). In addition to SBP and DBP, decreased cerebral blood flow is seen in patients with low nocturnal blood pressure (Reinprecht et al 2008).

The case of pulse pressure can also be thought of DBP effect on WMH presents a paradox. Studies have shown that low DBP is ironically associated with WMH accumulation when paired with a normal or high SBP (resulting in increased pulse pressure), as seen in studies by Aribisala et al. (2012), but also associated with WMH when DBP is elevated (Marcus et al. 2011). This may explain why perhaps the association with DBP is limited. The effect of DBP together with SBP need to be considered together, along with the unexamined metric of cerebral blood flow (as a result of autoregulation) to gain a more complete picture of damage occurring to the brain which may cause WMH to accumulate.

Overall, the effect of blood supply to the brain is complex but interesting to consider the associations seen with not only SBP and DBP but also positive hypertensive history and use of anti-hypertensive medication (all of which contribute to the hypertension combined score).

Hypertension history is a variable term. It can mean a history of hypertension for 1 year, 10 years or many decades. It is therefore not surprising that there was no association with this term in our data. There are a number of studies that have examined effects of mid-life hypertension on later outcomes, and despite the interesting findings of mid-life hypertension being associated with dementia diagnosis after a 40 year follow-up (Ronnemaa et al. 2011), these were not correlated with WMH load. As hypertension has also been associated with grey matter atrophy (Glodzik et al. 2012), it is unclear by which mechanism elevated blood pressure in mid-life causes the cognitive decline (either by atrophy or white matter disease progression). This is another reason why a positive history of hypertension may not be directly causing WMH progression, this also suggests that positive history may not influence the hypertension combined factor. Late life hypertension is also a relatively contentious area, with conflicting studies.

Several studies have found an association between later life hypertension and cognitive decline (Tzourio et al. 1999, Elias et al 2003). Studies have also concluded no effect of hypertension on cognition (Herbert et al. 2004, Tervo et al. 2004). A comparison of both mid-life and later life hypertension upon cognitive decline, while finding an effect of mid-life hypertension, found no effect of later life hypertension (Gottesman et al. 2014). This study also rejected the idea of a "J curve" or "U curve" proposed in some literature (Taylor et al. 2013) with regard to mid and later life hypertension affecting cognition, that there is an increased risk of decline with lower than normal blood pressure as well as elevated blood pressure. It is interesting to note however, that not only pure hypotension, but hypotension as a result of neurocardiovascular instability (with associated possible episodes of syncope and falls) has been shown to affect cognitive decline by Kenny et al. 2002. Despite this, the effect of low blood pressure is hard to conclude with studies that examine purely cognitive decline and not WMH damage.

While these studies are interesting to compare later life hypertension to midlife hypertension, they again suffer from the same weakness of conclusion. We cannot conclude that a history hypertension results in purely white matter damage based on these studies. It is also not clear if it is the same pathway acting over decades or whether there is a different form of damage occurring early on. As patients with current hypertension will probably be positive for history of hypertension and with variable length of the condition, it is difficult to dissect the effect of hypertension history from current ongoing hypertensive damage. Despite this, one study by Vuorinen et al (2011) demonstrated a reduction in WMH volumes in those with controlling of mid-life vascular risk factors including hypertension. Another study also showed an association between mid-life hypertension and increased WMH (Swan et al. 1999). Together, these suggest that elevated blood pressure is an important risk factor for later life WMH changes and cognitive decline based on the cognitive correlations with hypertension described above. This is starting to emerge as a hypothesis in which mid-life hypertension is also damaging to white matter resulting in WMH. Despite this, hypertensive effect on cognitive decline is less well defined as grey matter atrophy has been shown to continue in previously hypertensive patients who have had their blood pressure controlled (Jennings et al. 2012).

As discussed above, hypertension is a risk factor for WMH progression. In terms of the main outcome of WMH progression, it has been shown that uncontrolled hypertension leads to higher progression than controlled pressure (Verhaaren et al. 2013). While this and other studies that demonstrate associations between anti-hypertensive use and WMH volume add weight to the vascular cause of WMH, consideration of the effect of anti-hypertensives on cognition allows a deeper consideration of effects.

In the Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS) (Tzourio et al. 2003), a double blind randomised placebo controlled trial of 6105 participants with previous stroke or TIA showed a reduction in subsequent stroke and major vascular events in those taking the antihypertensive perindopril (4mg) +/- the antidiuretic indapamide (2.5mg in most centres, 2mg in Japan). This study also showed a reduction of cognitive decline in these patients.

Other studies shown also preservation with the use of an angiotensin receptor blocker Eprosartan (Hanon et al. 2008), while additional studies failed to show cognitive preservation with the ACE (angiotensin converting enzyme) inhibitor Ramipril and angiotensin-receptor blocker Telmisartan (Anderson et al. 2011), this is despite these studies using the same cognitive test (Mini Mental State Examination). Wafta et al. 2010 shower that the use of a calcium channel blocker resulted in preservation of cognition. A meta-analysis examining the effect of antihypertensive effect upon cognition, found relationship with overall antihypertensive use, but also showed an isolated reduction in cognitive decline with calcium-channel blocker use (Staessen et al. 2011).

While only testing cognition, the studies above indicate a heterogeneous effect of antihypertensives. These studies also back up why there was no interaction seen with hypertensive medication use and neurocognitive outcomes when assessing cms/sbsWMH progression as the dependent variable. In fact, Salat et al. 2012 have demonstrated an effect of hypertension in Diffusion Tensor Imaging (DTI) on the "normal appearing" white matter skeleton when controlling for white matter hyperintensities. Additional DTI studies have shown not only untreated hypertensives performing poorly cognitively, but treated hypertensives performing worse than normotensive patients on cognitive tests (Hannesdottir et al. 2009).

The caveat in anti-hypertensive use is the potential for hypotension, which is a potential WMH promoting risk factor. While the effect of anti-hypertensives is promising, the different mechanisms by which different medications act may account for the mixed results. In our cohort, the use of multiple different anti-hypertensive agents may have been responsible for a lack of effect, along with unknown compliance and variable time of use. It is therefore not surprising that there is no effect of blood pressure medication in our cohort, as only 42 patients were on the medication and a variety of medication was used. Finally, as our study was concerned with exercise and not properly examining medication, we do not have any compliance data regarding use, with some medicated patients in our cohort also suffering from hypertension.

Despite the low number of patients with a history of stroke, it is interesting to consider why the mean values are so much higher than the rest of the study cohort. As WMH are considered a form of microvascular damage, and lacunar infarcts and stroke are also a form of microvascular to vascular pathology, it is likely that these all lie on the same continuum. However, it can also be argued that WMH and stroke are parallel occurrences, being affected by the same risk factors. It has been shown that patients with high WMH load are at increased risk of stroke (Bokura et al. 2006, yamauchi et al. 2002, Fu et al. 2005), as are patients with silent brain infarcts and cerebral micro-infarcts (being at risk of stroke) (Kobayashi et al. 1997, Vermeer et al. 2003, Naka et al. 2006). Healthy patients with a profile at risk of stroke were also shown to have more WMH progression (Jeerak et al. 2004). It has also been shown that lowering blood pressure in patients with a history of stroke can prevent WMH accumulation (Dofouil et al. 2005). In addition, even patients with a family history of stroke even have higher rates of WMH accumulation (Reed et al. 2000). Of the two patients with a history of stroke, there were no appreciable pattern in their other risk factors, aside from both being obese and having lipid disorders. Only one smoked, one had diabetes, one had high blood pressure. With only two patients, further interpretation is not possible. It is actually surprising that our cohort has only 2 patients with a history of stroke considering that our population can be considered more "at risk" than the general population due to the inclusion criteria requiring at least one vascular risk factor.

Although lacunes are a form of microvascular pathology, their presence has also been associated with a higher degree of WMH accumulation (Cavallari et al. 2014), and have been particularly associated with increased cognitive impairment (Warren et al. 2015, Benjamin et al. 2014). Of the two stroke patients, one has 3 lacunes at baseline and the other has none. Paradoxically the patient with lacunes has less accumulation of WMH (25% accumulation of cmsWMH) than the patient with none (85% accumulation of cmsWMH). It is therefore cannot be concluded that lacunes are responsible for this significance seen in these two stroke patients.

7.4.4 Neurocognitive assessments

While studies exist that demonstrates an association between WMH volume and global cognition, they analysed decline over a number of years and all used the MMSE as main outcome (Kuller et al. 1998, decline over 3 years, Appleros et al. 2005, 5 years, Dufoil et al. 2009, 4 years, Jokinen et al. 2009, 3 years, and Debette et al. 3.8 +- 1.6 years). Another study by Van der Flier et al. 2008 examined WMH and cognitive decline over 1.8 years an instead used another test, the CAMCOG. While it has been shown that the CAMCOG, MMSE and ADAS-Cog can be used interchangeably for demonstrating cognitive decline (Wouters et al 2010), our cognitive data is from the baseline assessments only and it is therefore not surprising that there is not an association between global cognition and both baseline WMH volume and WMH progression volumes. While other studies had shown an increased conversion from normal to MCI and MCI to dementia with increasing WMH load (Smith et al. 2008, Silbert et al. 2009), at time of writing, the subsequent cognitive data is not yet available so comment on participant cognitive progression is not possible.

Additional studies found no association with global cognition, indicating that the drive behind the above studies may be due to components of WMH and cognition (Firbank et al. 2007, smith et al. 2004 and Mungas et al. 2002). A final component may be the ADAS COG itself, although a common research based cognitive assessment, an emerging number of studies have questioned the validity of the ADAS COG and offered modified versions, citing that it may be too insensitive for detecting smaller changes in cognition, particularly in SMC/MCI patients as the ADAS COG is designed for cognition changes in AD (Ylikoski et al. 2007, Skinner et al 2013). This would also explain our lack of correlation with cross-sectional cognitive assessment and WMH volume.

Our positive association of WMH volume with executive function (from BRIEF A score) rather than memory deficits (in the form of MAC Q score) mirrors other studies which have shown executive function to be the cognitive component most strongly associated with WMH (Jokinen et al. 2009, Mungas et al. 2005, Debette et al. 2007, Van Heuvel et al. 2006). The studies by Debette et al. 2007 and Van Heuvel et al. 2006 were significant for periventricular WMH only, which indicates that subregions of WMH drive the cognitive decline, and specifically the executive dysfunction. Our use of whole brain WMH and not subregions may explain why the executive dysfunction seen in our data disappears in our GLM testing. Additionally, further studies utilising DTI suggest that white matter integrity is compromised in larger areas than indicated by WMH seen on T2 weighted MRI (Leritz et al. 2014, Mailard et al. 2011, Mailard et al. 2014 and O'Sullivan et al. 2002) and that the white matter as a whole changes in those with more WMH (Munoz et al. 2009). Yet further studies are demonstrating that there are regional differences in MTR (Magnetization Transfer Ratio) of WMH, with frontal periventricular WMH having lower values that occipital periventricular WMH (Spilt et al. 2006). This further divides periventricular WMH (which is already associated with executive dysfunction) into functional subregions, and suggests that the drive for executive dysfunction is from frontal periventricular WMH. These factors together may explain why there isn't a stronger relationship between our global measured WMH volume and cognitive dysfunction.

The lack of memory deficit can be explained by a number of findings which have shown memory dysfunction to be more strongly associated with hippocampal atrophy rather than WMH volume, which has been shown in normal aging patients, MCI patients and particularly patients with AD in whom hippocampal atrophy is more prominent (Godin et al. 2010, Kramer et al. 2007, Jack et al. 2000, Wolf et al. 2004). This difference in cognitive influence between AD and WMH is often artificial as both conditions often co-exist, but the differential effects are seen in correlations of each with different memory components as outlined above. WMH and AD have also been shown to be functionally discrete in their effect on brain glucose metabolism in an important FDG PET study by Haight et al. 2013. Whether WMH and AD interact together in vivo remains to be seen, both have been associated with damage and accumulation over many decades, often from mid-life (Debette et al. 2011 and Tolppanen et al. 2012).

Dissecting the contributions of two chronic and insidious pathologies to cognition is difficult and making links between the two without solid neuropathological correlation data is not possible. As the majority of investigation into WMH is image based, caution is needed in extrapolating the findings beyond correlations. The expansion of DTI and functional image will hopefully enable more detailed understanding of the relationships between WMH damage and outcome (not just the damage visible as T2 hyperintensity), but interactions between WMH and AD at the cellular and molecular level are unfortunately still unknown. WMH may provide the second insult to exacerbate underlying AD effects on cognition (but be unrelated), WMH and AD may influence each other by middle (but yet unidentified) risk factor or they may be mutually exclusive. Further work is needed to clarify this.

The GLM appearance of subclinical anxiety results being negatively correlated with WMH progression volume was not predicted. The association with HADS A which is negatively correlated with WMH progression volumes in GLM, for both cmsWMH and sbsWMH is particularly unexpected. That is, participants with higher WMH progression are actually less anxious. This has not yet been demonstrated in the literature. Anxiety has been demonstrated to be positively associated with WMH (Berlow et al. 2010 and Kim et al. 2011a). It has also been demonstrated in patients with mild anxiety symptoms (Bijanki et al. 2013). Causation is yet to be shown in these studies and it is not yet clear whether anxiety causes WMH accumulation or WMH damages anxiety control networks resulting in expression of anxiety. It is not fully apparent why our results contradict this and show a reduction of anxiety being associated with more WMH progression. Our negative correlation certainly suggests that anxiety symptoms, diagnosis and WMH volume is not necessarily linearly related and may follow another pattern, as anxiety has been shown to follow many different trajectories over its clinical course (Lee et al. 2016). A number of studies have also suggested that sub-threshold results indicate that more sensitive neurocognitive evaluations are often needed (Papassotiropoulos et al. 1999, Stillman et al. 2012). This is likely the case to better understand the subtle interactions between WMH and cognition. Additionally, sub-threshold anxiety may be a symptom of a different pathology to diagnosed anxiety, as anxiety is a heterogeneous cognitive disorder (Nandi et al. 2009) with many different causes and subtle differences in presentation (Vytal et al. 2013). All of these variables may account for the differences seen in our data with regard to anxiety.

Finally, as WMH are of presumed vascular aetiology and separate to AD, it can be presumed that modifying the VRF may influence WMH and therefore cognition. There was no relationship between any VRF and cognition in our data; however other studies have demonstrated a link with WMH, SBP and cognition (DeCarli et al. 1995). Our results were similar in that WMH is individually related to SBP and cognition, but just that there was no SBP and cognition interaction. This is complicated yet again by recent DTI results that suggest that SBP and WMH interact individually to affect cognition (Jacobs et al. 2013), which is entirely possible given that cognitive decline is associated with other brain structural changes in addition to WMH. Despite this, there is still credence to slow progression of WMH as they influence the overall cognitive status of patients who may already have AD accumulating over a number of decades. Although the effect of physical activity was not shown to be effective in this study, WMH remain a valid target for further study.

7.5 Comparison of segmentation methods

There are only two possible outcomes. The first is that both cmsWMH and sbsWMH agree (both have a statistically positive or negative outcome), or that the methods disagree (one statistically positive and one negative). Although there may be slight differences in correlation and GLM outcomes, we are more interested in comparing the cmsWMH and sbsWMH differences within each, as the correlations give an indication of underlying relationships but the GLM are the final outcome (due to inclusion of more factors, and being more logically "complete").

For manual segmentation at a single time point (baseline), it is interesting to observe that despite slight variations in p-values, there is no difference in statistical significance (clinical outcome) between cmsWMH and sbsWMH. This holds for both baseline correlation and baseline GLM results. It is worth noting that the correlation and GLM results are very similar as well (age and SBP significant, all other results not significant), apart from DBP no longer being significant in GLM results (for both cmsWMH and sbsWMH). This suggests that while sbsWMH manual segmentation does indeed modify the cmsWMH volumes, it does not do it to such a degree that result in difference of outcome.

Given this result it would therefore be expected that a similar result would apply to the follow up scan, and therefore the cmsWMH and sbsWMH progression values would also have a similar clinical outcome. This is indeed the case for the majority of correlations but with a few exceptions. Of the categorical correlations modelled, BMI high was significant in cmsWMH ($p=0.02$) but not sbsWMH ($p=0.09$). The opposite was true for HTN combined, with cmsWMH being non-significant ($p=0.10$) versus sbsWMH being significant ($p=0.04$). This was also the case with stroke, being significant in sbsWMH ($p=0.005$) and not in cmsWMH ($p=0.08$). With the BRIEF A scores, a reciprocal pattern present in both BRI and Total scores when comparing cmsWMH and sbsWMH volumes. BRI T-score (correlation) is significant with cmsWMH ($p=0.031$) but not with sbsWMH ($p=0.050$). BRIEF A total score is not significant for cmsWMH ($p=0.050$) and significant for sbsWMH ($p=0.048$).

Although cmsWMH and sbsWMH differ slightly as stated above, it can be seen that the non-significant values are close to significant. This is especially the case for the reciprocal pattern in BRIEF-A results. It must also be remembered that sbsWMH is not normally distributed, so that correlations for categorical factors are analysed with the Mann-U Whitney test (rather than independent sample t-test). The continuous correlations differ too, in that sbsWMH volume statistics use a Spearman correlation (while cmsWMH use a Pearson correlation). It is possible that this difference use of tests may explain the slight statistical variation observed. In the case of baseline functional fitness assessments, cmsWMH and sbsWMH are not as easily directly compared.

Baseline functional fitness assessments are partially correlated to cmsWMH and correcting for age and sex (Table 4.2.4.5) and also age, sex and baseline cmsWMH volume (Table 4.2.4.6), which is done to correct for gender and age differences which may affect physical performance. Due to statistical limitations, sbsWMH is only able to be (Spearman) correlated without correction for age and sex (Table 5.2.4.5). Despite the different tests used, both cmsWMH and sbsWMH are not affected by the baseline functional fitness assessments.

With regard to the general linear models, all results agree except one. The effect of systolic blood pressure on progression volume is significant for cmsWMH (Model C1, p=0.046) but not for sbsWMH (Model J1, p=0.057).

In the models that take into account the interaction between SBP and baseline WMH volume. All values for correlations and general linear models have the same correlation direction (positive or negatively). There is also no discernible pattern between cmsWMH or sbsWMH volumes with either baseline and progression volumes. Some p-values are lower for cmsWMH in some instances and lower for sbsWMH in others. This is true for both statistically significant and insignificant values.

When comparing the results for all the data, there are roughly three patterns across the data; (1) both cmsWMH and sbsWMH are statistically significant, (2) one significant and one not significant and finally (3) both not statistically significant. Of the correlations tested, 4 were different between segmentation types. Of the general linear models run (including all models plus a new model for each VRF, or "other" covariate tested), only one model was different between the two groups. This is also mirrored with both cms/sbs volumes being significantly correlated at both baseline ($p<0.001$, $r=0.992$) and in progression volumes ($p<0.001$, $r=0.919$). Of the values comparing differences between segmentation methods, it can also be seen that the non-significant values are also close to being significant. In the case of correlations with categorical factors and progression volumes (BMI, hypertension combined and stroke), the difference may also be due to the different statistical power of the tests employed (independent sample t-test versus Mann-U Whitney test).

When all the above are taken into consideration, there is very high agreement between cmsWMH and sbsWMH volumes, for both baseline and progression. The majority of clinical outcomes are identical for both methods in terms of statistical significance. Of the few results that statistically differed between groups, the corresponding value is not far off significant also (especially in the case of BRIEF A scores where the opposing score has a p-value of 0.50 twice). This suggests that these differences are more likely due to small statistical variations and slight methodological variations rather than a true result. Therefore, not only is there minimal difference when using side-by-side manual segmentation methods to image processing, but there is no significant outcome in terms of clinical significance. In addition, there is no discernible benefit in calculating the additional step of side-by-side manual segmentation.

These results apply only to this data set, and this particular reviewer and overviewing neuroradiologist. As the cmsWMH volumes are calculated first, it suggests that the additional step of side-by side review makes little difference. This also implies that with sufficient training and review, it is possible to manually segment volumes to a high level of accuracy. It may be the case that with other studies, another reviewer or clinical outcomes that there are differences between the two methods.

Radiologists are increasingly concerned with observing a change in disease and almost exclusively use visual rating scales rather than the labour intensive methods performed in this thesis. It would seem that conventional manual segmentation, which is often used to refine the coarse nature of visual scales, still remains the gold standard. It is reassuring that even though the field of radiology imaging heads towards fully automated and semi-automated methods, that manual segmentation remains robust to further modification.

After careful comparison of our two manual segmentation methods, and their relationship to other methods in the literature, we conclude that conventional manual segmentation remains the best method for obtaining the most accurate WMH volumes and no further work (in terms of side by side comparison) is required as long as the reader is well trained and expert neuroradiologist input is sought.

CHAPTER 8 LIMITATIONS AND SUMMARY

8.1 Introduction

A discussion of limitations will headline this chapter, followed by a discussion of implications. The implications will be discussed in terms of both the clinical results and the segmentation methods employed in this thesis. The chapter and also this thesis will conclude with some thoughts towards future directions which also will be helped by some of the data soon to be available from the AIBL Active study.

8.2 Limitations

The number of participants recruited resulted in an underpowered study for examining the effects of physical activity on white matter hyperintensity progression. It may be that with a larger study, we may see some effects of physical activity on progression and more significant results emerge from the vascular risk factor, cognitive and genetic data. Additionally, differences between the conventional and side-by-side methods of segmentation may have emerged. Our results did align well with other findings in the literature with larger numbers of participants however, and the number of 98 participants is relatively close to the required number of 122 (148 initially recruited with 15% dropout rate = 122).

A further limitation lies in the numbers included in the study. Although 98 patients is a large number for this type of study, we are still limited in the number of conclusions we can make. This is for a number of reasons: The first is that the number of covariates able to be included in a model is limited. The next reason is that due to this number, we are unable to perform subgroup analyses with much power (erg: an effect in the exercise group only, an effect in Amyloid beta positive group etc.). A larger group would enable examination of associations corrected for covariates, and thus an effect could be more strongly concluded to have come from just the one factor.

The two segmentation methods were completed by one person, which is an advantage, but without multiple people each doing both methods, comment on the reproducibility of both methods cannot be made.

Even though the same protocol was utilised and in spite of regular QA, a base-level software or hardware change may have resulted in slightly different image magnet gradients and image processing. This may have resulted in differing image contrasts and qualities which in turn may affect what volumes of white matter are segmented as hyperintensities.

The WMH were not manually segmented on another monitor and the contrast levels not adjusted. We also did not use a full diagnostic PACS monitor, which may have enabled visualised of further detail due to their high resolution and contrast levels. Studies comparing diagnostic and consumer monitors have demonstrated comparable results however (Kawasumi et al. 2008 and Ong et al. 2011). Whilst too time consuming for this study, reproduction of results on another monitor (either consumer grade or diagnostic PACS) and with different contrast levels would indicate that our results are robust to changes in equipment and may reinforce manual segmentation as an ongoing standard of measurement (or at least until automated methods catch up).

An additional limitation is a lack of cognitively normal individuals included in the study. As this is a novel study in terms of intervention and imaging technique, a comparison of normal individual's WMH progression, cognitive change and VRF risk factor profile with the literature would add validation to the results.

The use of an automated program (FREESURFER) may have resulted in slight errors due to computation, however all segmentations were checked visually. The process of registering both time point images to each other as part of the longitudinal stream may have created very slight distortions in voxel locations and therefore ETIV volume, however the methods used are currently recognised as best practice (Nordenskjöld et al 2013, Reuter et al. 2012) .

Manual segmentation of WMH only identifies the lesions with visual abnormality. DTI suggests that the area of WM abnormality may be larger than the outlined lesions. No examination of this was performed. We therefore cannot conclude whether a cognitive change is due to the WMH volume or the surrounding damaged NAWM penumbra, although associations with cognition are still of interest.

We also did not measure the location of WMH or indeed segregate lesions into deep and periventricular. Although it has been shown that there is not really deep and periventricular but rather a continuum of pathological change, spatial correlations may have been interesting. Consideration of rates of growth and directions of growth could have functional associations such as physical measures and cognition.

Another factor not taken into account is the "brightness" of WMH, with volumes only being calculated. Although MRI contrast changes with many factors and is quite variable, perhaps broad classes of brightness (maybe even once taking into account for overall image contrast) could be utilised. The rationale behind this would be that more "bright" (white) regions may represent further damage, possibly even differing aetiologies. A variation on this is how "blurred" the edge of a WMH is, with a gradual progression from NAWM to WMH having a possibility of being a distinct entity to WMH lesions with sharp edges.

There is also some slight subjective difference in manual segmentation of WMH lesions. In our data we were able to achieve a high inter-rater reliability but this therefore may not be generally applicable to other sites. Further studies are needed to replicate our findings.

As there is only data available from two points in time, we are limited in describing the relationship. We can only call a relationship significant or not, and comment on whether It is positively or negatively correlated. As a line drawn from 2 dots is always linear, this is the limit of inference we can make at current. With the collection of data at 3 of 4 (or more) points, we could start to see whether a relationship may be linear, exponential (or others), and the provision of data at multiple points would add strength to relationships found.

In addition to the ApoE ε4 allele that was investigated, a genome wide association study with WMH progression and other factors would have been great but is outside the scope of the study. As such, we are unable to draw further inference as to the cause of WMH lesions, we can only examine correlations correcting for other factors and hypothesise from this.

As this study was performed in a community setting, it has advantages and disadvantages. Advantages include results being applicable to a general population and are cheaper to obtain. Disadvantages include potentially unseen variables impacting upon the data and not being able to be controlled for. These include environmental factors such as pollution, dietary indiscretions (junk food), toxin exposure (cleaning products, makeup etc.) and lifestyle situations which may lead to stress. Another factor to be considered is the local environment, one participant may do 100 steps on a flat surface while another performs the same amount on an incline, resulting in further energy expenditure. An alternate participant may prefer to walk in a park or on the nature strip, increasing energy expenditure too slightly.

Although baseline cognition and previous education years are tallied, the day to day activities were not scrutinised. One member may do activities which involve much thinking and calculations, while the other watches movies or television. One may prefer crosswords and puzzles while another listens to classical music. This might vary each night. The extent of activities performed is definitely out of the scope of this study. Even with every detail known, drawing conclusions would remain difficult as not everyone does a single action repeatedly, and even in an evening multiple activities are possible. Also, we do not have data on whether a patient became depressed over the course of the study (even if progressing sub-clinically, due to only having baseline neurocognitive data). Knowing this may help to exclude some participants or at least analyse them separately.

Another concept that has not been assessed is cognitive reserve. Although we are measuring cognitive change which is the difference that cognitive reserve cannot compensate for, there is still a potential amount of change that this reserve is able to compensate for with its adaptive plasticity. To calculate the actual underlying cognitive change that is occurring is not clinically possible but it is interesting to consider as there may be effects occurring that are not detectable.

Some patients had artefact on their imaging; due to RF artefact ("zipper artefact), wrap-around artefact and patient movement (Iwama et al. 1989, Graves et al. 2013 and Krupa et al. 2015). Although mostly subtle, two had large distortions requiring repeat scans (which were satisfactory). Still, subtle changes may have increased the blur (with patient movement) around WMH and artificially increased the apparent volume (with RF artefact). Although there were some instances of wrap around artefact, it was not severe enough to degrade the WMH volume (The nose was but off at the front and reappeared behind the head but didn't impact on visible WMH). An overall increase or decrease in brightness due to artefact can impact WMH brightness when the intensity normalisation step is applied.

Due to our study population, patterns within groups were not examined. Age was measured on a continuum, for example; with larger numbers, age ranges 60-70 and 70-80 and 80+ could be investigated. Similarly, effects within other groups such as gender, obesity were not examined with general linear models as larger numbers were needed. Finally, as a result of this numerical restriction, a model that included every single factor was not possible. Models were built instead based on hypothesis, logic and relationships outlined previously in the literature. As such an all-inclusive model may be very difficult to interpret and apply to the general population. The current method of using a general linear model with multiple covariates may be slightly limited, but it enables fair conclusions to be made. An effect observed can be corrected for a few covariates, while remaining simple enough to be widely applicable and also more logical to interpret. As more factors are included, it is more likely that there are multiple interactions that need to be examined and possible included in the model.

8.3 Overall implications

8.3.1 Clinical results

With our study, we have not shown an effect of physical activity on WMH progression. We have however consistently demonstrated a very strong effect of baseline volume upon WMH progression. Given the correlations we have shown with Systolic Blood pressure), and the growing knowledge of vascular risk, lifestyle factors and genetics upon WMH volumes, it is still likely that lifestyle modification and VRF control have an effect on WMH. The significant correlation of WMH progression volume with executive function is in line with the literature; however the negative correlation of WMH and anxiety is a new finding.

8.3.2 Methods

With no major difference between outcomes for either method, the use of side-by-side manual segmentation cannot be recommended. The extra time spent on this method cannot be justified for a team who is educated and consistent with manual segmentation already. There may be some use for this method for educating readers as they learn to consistently manually segment, but this can also be said for just doing a large number of cases with professional coaching. Conventional manual segmentation, when reviewed with an expert neuroradiologist has been proven robust and should remain the standard to which other methods are compared.

8.4 Future directions

The most important future step will firstly be analysing the compliance data. This will give a more accurate account of who completed their prescribed activity regimen, and also those who did not do all activities. The additional use of questionnaire and adherence data will also be able to determine what type of and intensity of physical activities were performed. This may enable some activity subgroup analysis and show some forms of activity and intensities are more beneficial than others. Also, the pedometer data along with questionnaire results from the control group will enable calculation of how much daily activity both groups performed. This is beneficial as it will give activity levels across the whole cohort, and physical activity will then become a continuous variable instead of binary, which may yield yet further information. With a larger group, all with known activity levels, the statistical power will be greater, particularly when using subgroups of WMH progression. Saczynski et al. (2008) demonstrated cognitive effects in the highest quartile versus the lower three, and a similar division with our data might be needed to account for the non-linear accumulation of WMH, that is: baseline WMH significantly influencing progression in our data, and thus accumulation accelerates with higher WMH volumes. Division of WMH volumes would also help account for possible floor and ceiling effects: Minimal effect with low WMH volumes and little further effect once a significant volume has accumulated.

Another method for WMH analysis not utilised in this thesis is subregion analysis. Functionally distinct regions are an interesting thought and warrants further consideration. Consideration of anatomical regions with their subsequent cognitive domains could reveal deeper understandings of the impact of physical activity and the co-involvement of other covariates already examined in this thesis. These along with additional imaging paradigms such as rate of atrophy, DTI and fMRI will be utilised to explore the whole effect of physical activity (outside WMH and including grey matter) and can look into subregions which is increasingly showing promise with WMH and physical activity research.

The frontal lobe particularly is showing a number of interesting associations. Frontal lobe white matter hyperintensities have been independently associated with frontal grey matter atrophy (Rossi et al. 2006, Ha et al. 2012) and gait disturbance (Annweiler et al. 2012). Global atrophy has also been linked to frontal and parietal WMH (Lambert et al. 2016). Although slightly contradictory, It is interesting that there is more posterior (i.e. occipital lobe versus frontal lobe as a ratio) accumulation in MCI/AD patients than cognitively normal individuals (Yoshita et al. 2012), and that posterior WMH are more associated with cognitive decline in a study by Kim et al. 2011b. Despite this, frontal WMH volumes are largest in AD, followed by MCI then cognitively normal individuals (Meier et al. 2012 and Zhu et al. 2012). This complexity firstly suggests differing causes for cognitive decline, gait disturbance and atrophy, all of which have been traditionally associated with overall WMH volumes. It also suggests an anatomically specific accumulation pattern, which may change as the disease progresses. Regional mapping and more complex algorithms may be the method needed to examine this phenomenon further.

Another interesting area to examine would be the effect upon cognition. With the acquisition of follow up data, an association between cognitive decline/preservation and WMH volume at baseline and progression could be examined. It would be imagined that those with a higher volume at baseline would deteriorate more. Cognitive deterioration could also be correlated with WMH progression. Perhaps there is even a group with relatively preserved cognition, who, despite their large baseline volume of WMH, have little progression.

Further imaging data is already available, along with biomarker data, dietary data. Additional sequences available in our cohort include Arterial Spin Labelling (ASL), Diffusion Tensor Imaging (DTI), functional MRI (fMRI) and perfusion imaging. These would be interesting to consider in with the other factors examined against WMH in this thesis, but their relationship to WMH directly would also be interesting. Blood biomarkers including IL-6, TNF-α, sICAM-1, sVCAM and others are measures of inflammation and vascular damage and will be interesting to compare with WMH volumes. The availability of secondary measures at the conclusion of this study will also enable some consideration of an effect of exercise on measured inflammation and vascular damage. Finally, as dietary outcomes are a hot discussion topic of late, they will be interesting to incorporate. Diet data could be used in a number of ways. The effect of baseline diet on WMH baseline volumes could be examined, along with average diet over 2 years on WMH progression. A confounding factor would be the healthy living advice given to all participants, as hopefully all involved are eating better by the conclusion of the study. A side though is to consider the effect of healthy living advice on diet changes, factors that cause resistance to change could be examined. Do these factors correlate with WMH progression? Are less adaptive participants more likely to suffer cognitive decline? There remains a great wealth of factors to be considered.

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CHAPTER 10 APPENDIX

10.1 CmsWMH distribution and transformations

As volumes of cmsWMH (normally in units of mm^3) are all corrected for intracranial volume (also in mm^3), the units cancel out and results represent a ratio of volumes to intracranial volume (absolute for baseline volumes and per year for progression volumes).

The distribution of baseline cmsWMH is given below in Figure 10.1.1. As it can be seen, the distribution has a significantly positive skew (of 4.4) with a large number of participants having low levels of white matter hyperintensities. As such, the distribution was not normally distributed (Kolmogorov Smirnov value of 0.000). The values for cmsWMH volumes are so small because they are corrected for head size, which means dividing the cmsWMH volumes by the much larger volume of head size (Estimated Total Intracranial volume, ETIV from Freesurfer). After taking the natural log of the baseline ICV corrected cmsWMH values, as can be seen in figure 10.1.2, the distribution became normally distributed (Kolmogorov Smirnov value of 0.200).

Progression values are corrected for head size, and also corrected for the time elapsed between both scans for each patient. The values are therefore displayed as cmsWMH volume change, corrected for ICV (using ETIV volumes from Freesurfer), per year. Similarly, the progression of cmsWMH values also requires a natural log transform to become naturally distributed. Figure 10.1.3 shows the values of cmsWMH progression; again the distribution has a strong positive skew (2.3) and is not normally distributed (Kolmogorov Smirnov value of 0.000). Figure 10.1.4 demonstrates the distribution of cmsWMH volumes (per year, ICV) after natural log transformation. Although the distribution has a slight negative skew (-0.482), the values are now normally distributed (Kolmogorov Smirnov value of 0.200).

For both baseline and progression cmsWMH results onwards, natural log values will be used.

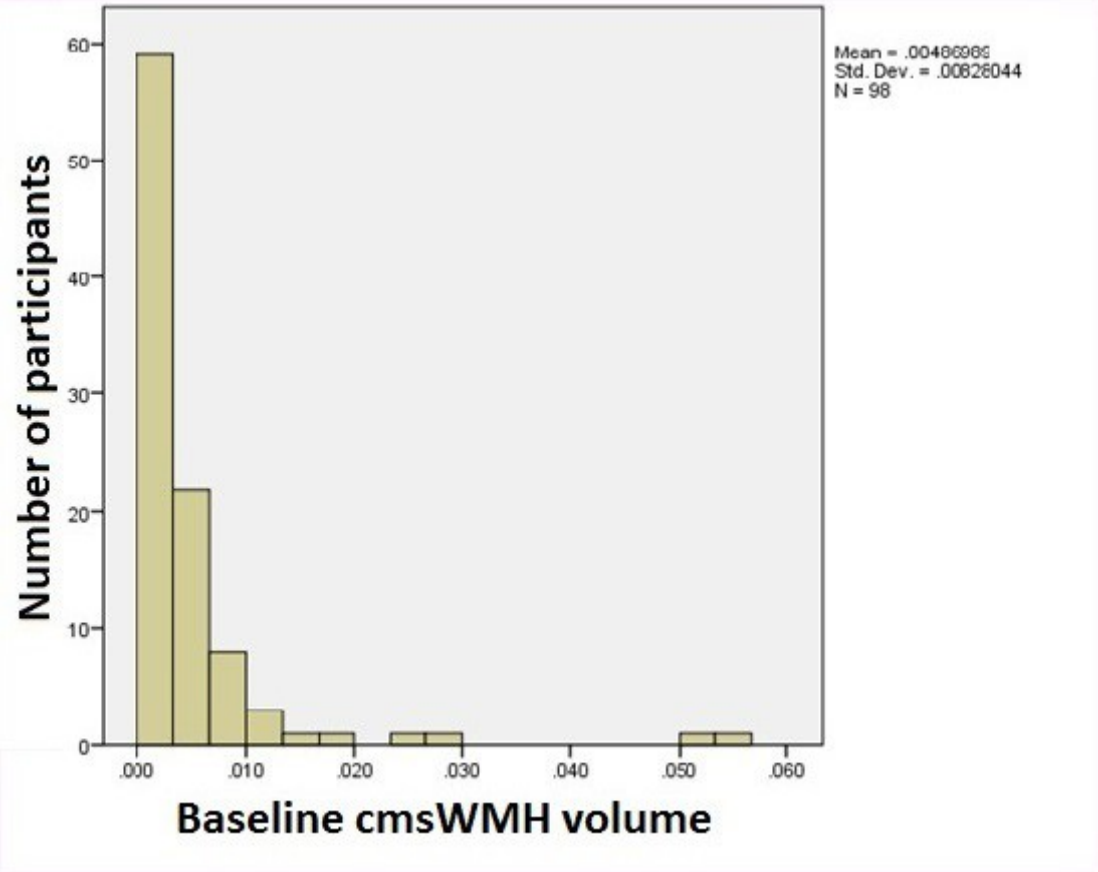

Figure 10.1.1 Baseline cmsWMH (ICV corrected) versus number of participants

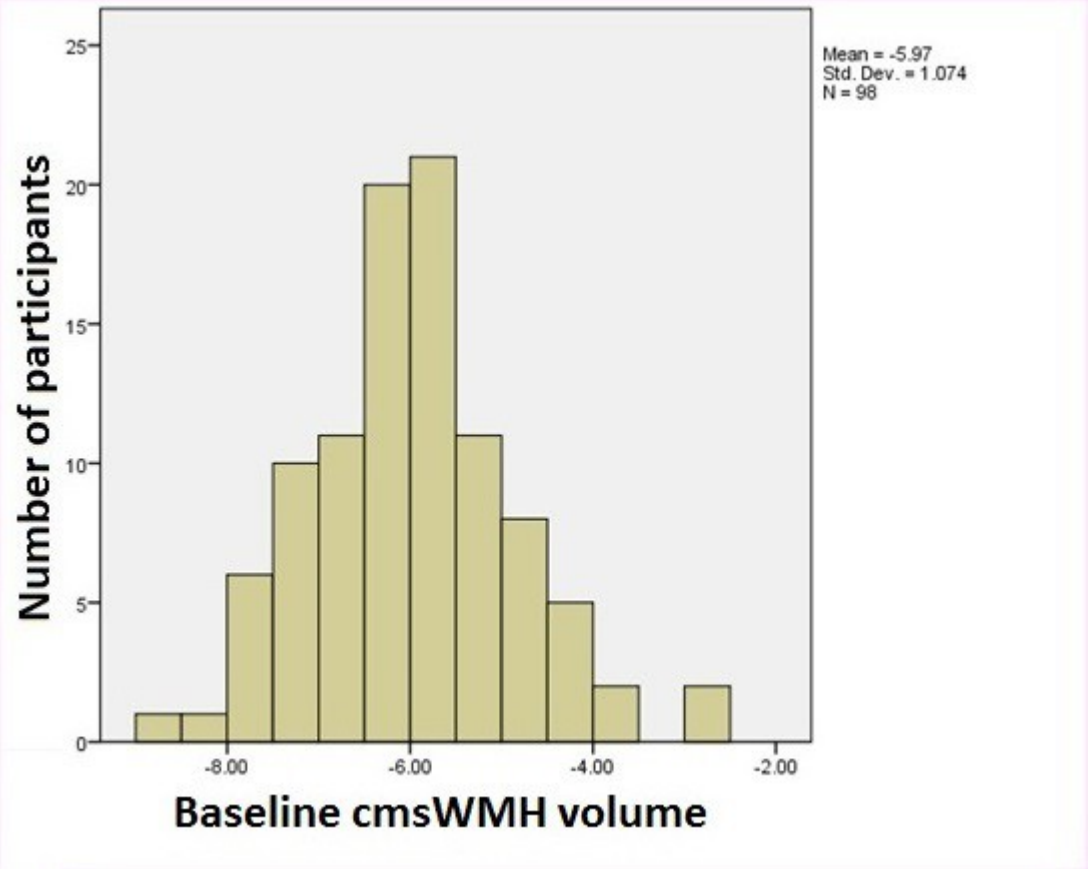

Figure 10.1.2 Baseline cmsWMH volume (natural log, ICV corrected) versus number of participants.

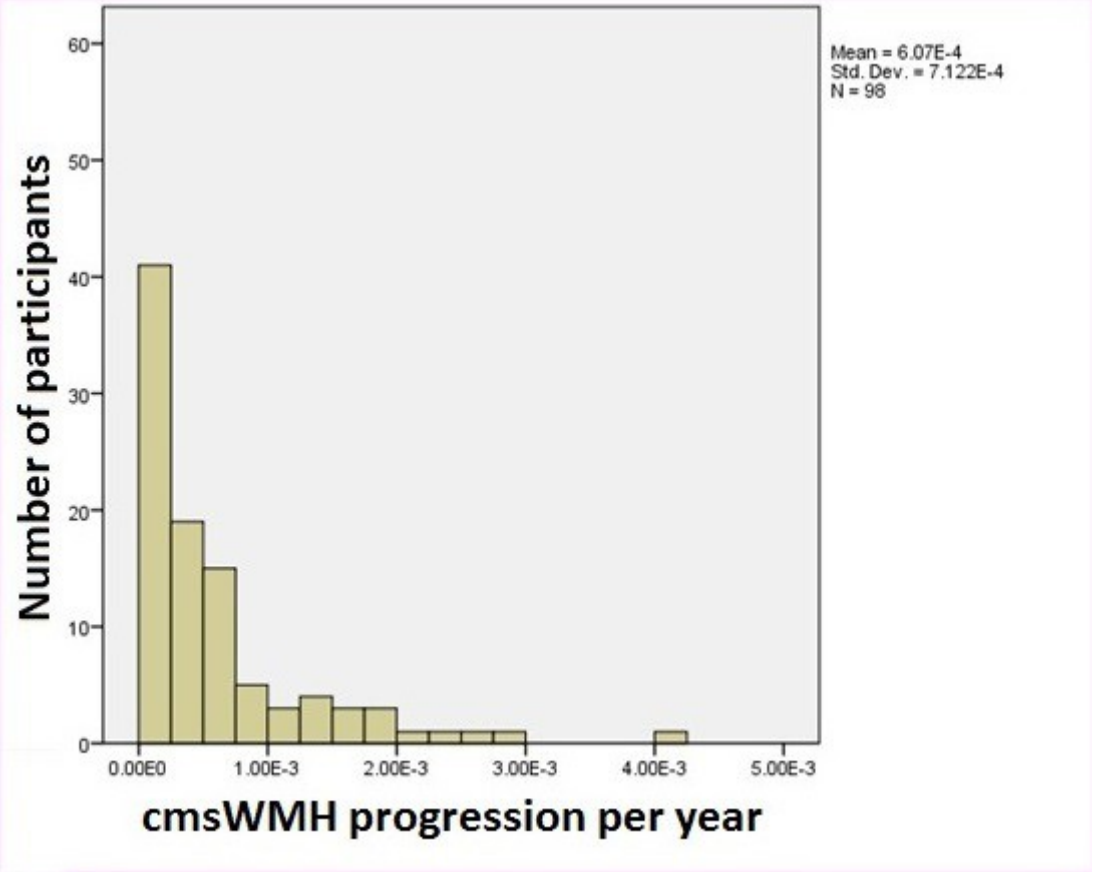

Figure 10.1.3 Yearly CmsWMH volume progression (ICV corrected) versus number of participants. (Same scale used for sbsWMH progression in chapter 5)

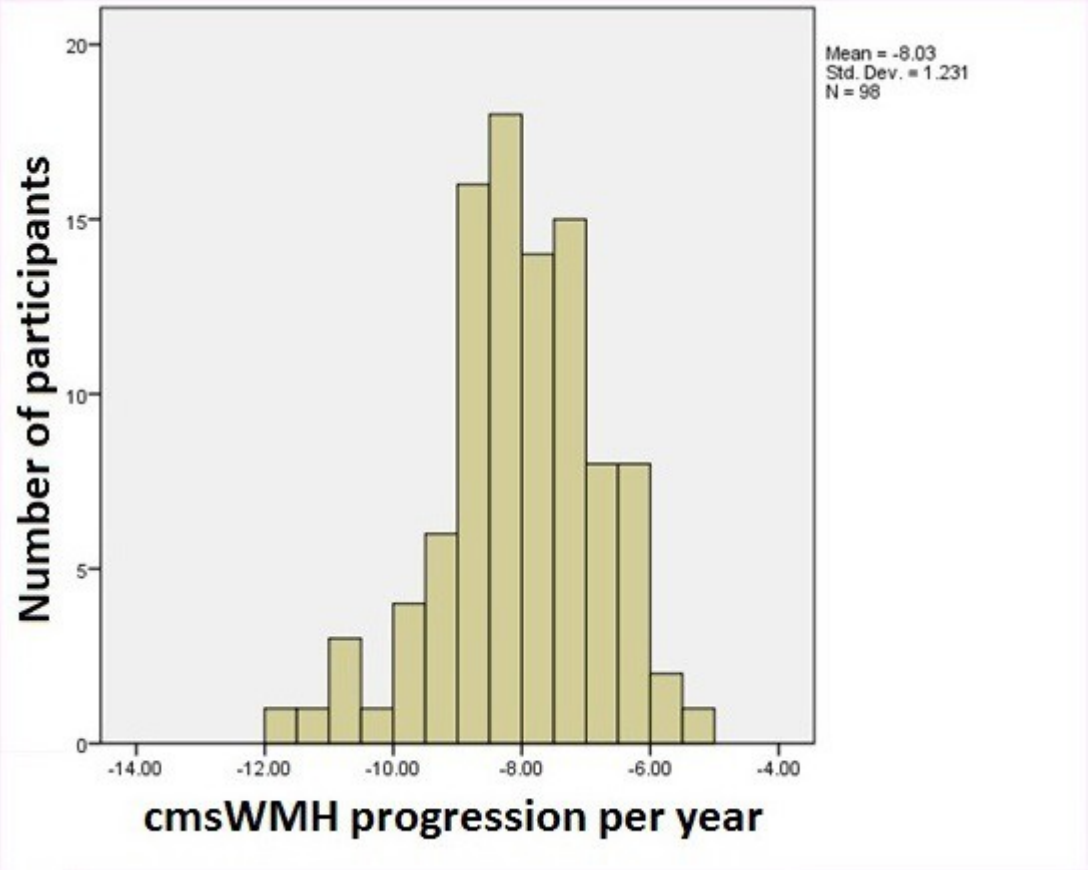

Figure 10.1.4 Yearly CmsWMH volume progression (natural log, ICV corrected) versus number of participants

10.2 SbsWMH volume distribution and transformation

As volumes of sbsWMH (normally in units of mm^3) are all corrected for intracranial volume (also in mm^3), the units cancel out and results represent a ratio of sbsWMH volume to head size (absolute in the case of baseline volumes and per year in the case of progression volumes).

The baseline distribution of sbsWMH is presented below in Figure 10.2.1. This relationship has a strong positive skew (of 4.3), with the majority of participants having low volumes of sbsWMH at baseline. Due to this, baseline sbsWMH volumes are not normally distributed (Kolmogorov Smirnov value of 0.000). The volumes corrected for head size are small because they are corrected for head size, which involves dividing the sbsWMH volume by the much larger volume of estimated intracranial volume results (obtained from Freesurfer). Once the baseline sbsWMH volumes were log transformed (using natural log), it can be seen that the distribution changes towards normality (Figure 10.2.2). This was confirmed with a Kolmogorov Smirnov value of 0.200.

Progression values are not only corrected for intracranial volume, but for time elapsed between each scan. This creates progression values as volume change (corrected) per year, and corrects for potential further sbsWMH progression with a larger time elapsed between scans. The distribution of corrected sbsWMH volume progression is shown in Figure 10.2.3. This distribution is also positively skewed (skew of 2.3) and not normally distributed (Kolmogorov score of 0.000). A natural log transform of sbsWMH progression is presented in Figure 10.2.4. This distribution resembles a normal distribution but appears to suffer from a negative skew. This was confirmed with a skewness value of -0.853. Despite its appearance, this distribution is not normally distributed (Kolmogorov-Smirnov value of 0.003). Using all other possible transformations to normality failed to transform the sbsWMH volume to normality. As such, subsequent simple correlations will be performed using non-parametric measures. The natural log values will still be used as these values provided a better fit of residuals (being normally distributed).

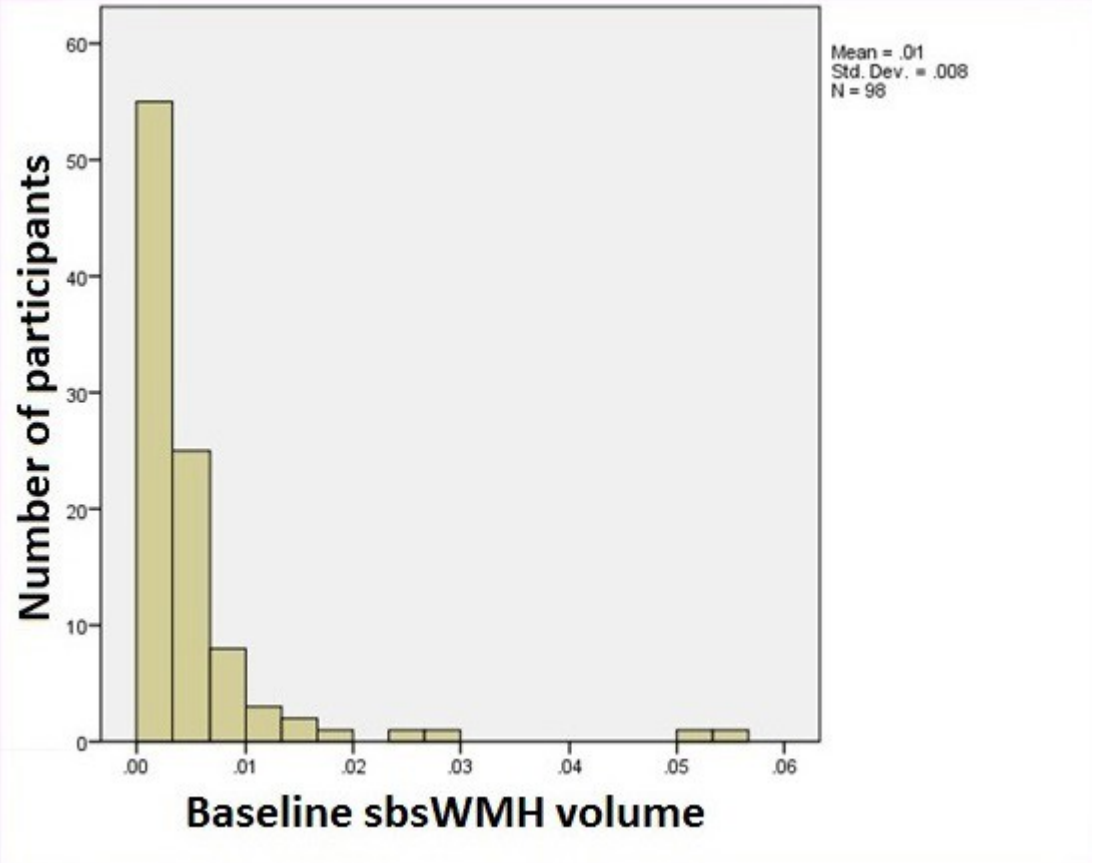

Figure 10.2.1 Baseline sbsWMH volume (ICV corrected) versus number of participants.

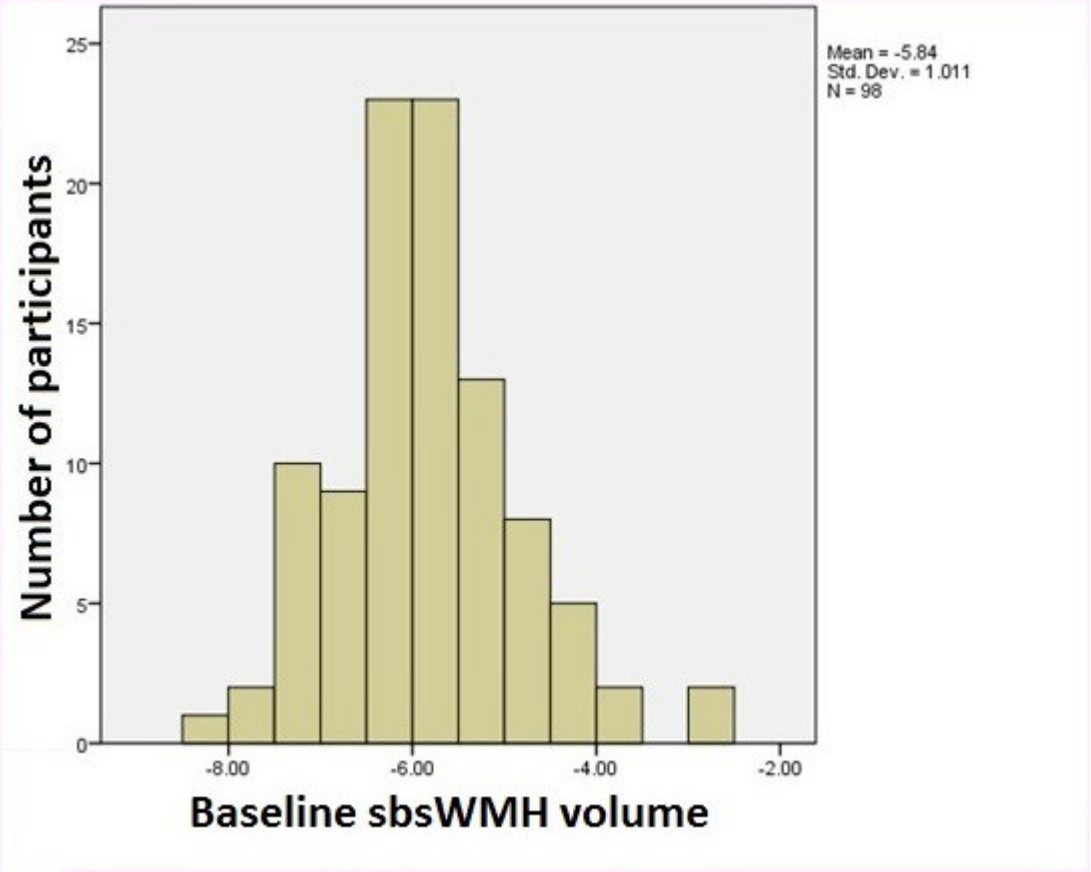

Figure 10.2.2 Baseline sbsWMH volume (Natural log, ICV corrected) versus number of participants.

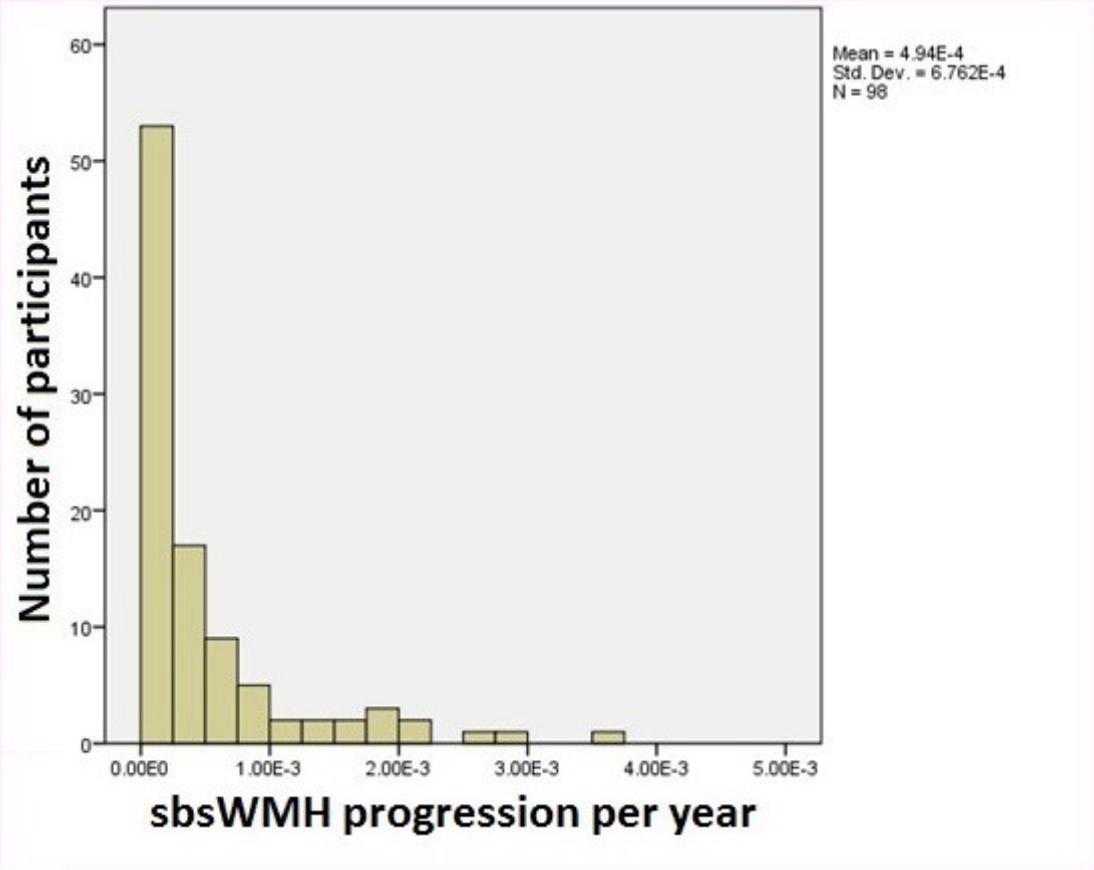

Figure 10.2.3 Yearly SbsWMH volume progression (ICV corrected) versus number of participants.

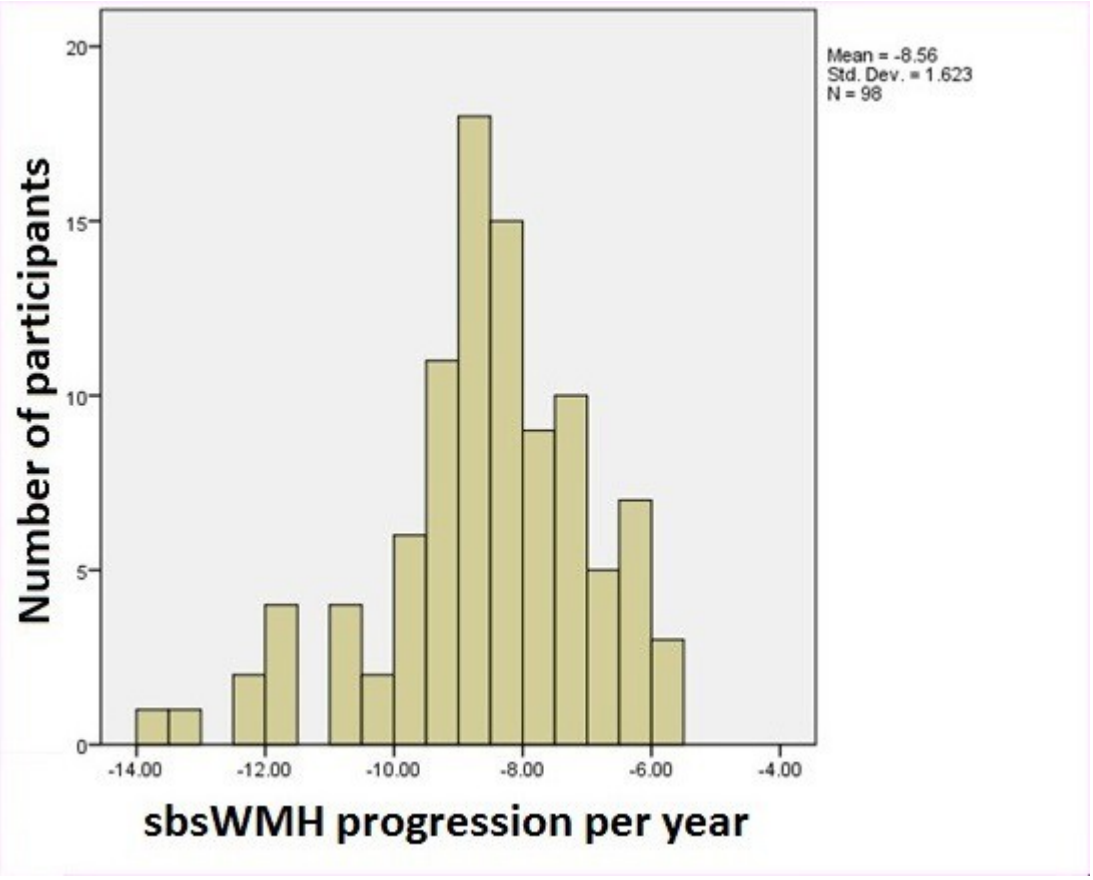

Figure 10.2.4 Yearly SbsWMH volume progression (natural log, ICV corrected) versus number of participants.