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**VASCULAR RISK AND DEPRESSION IN OUTPATIENTS AT
GROOTE SCHUUR HOSPITAL MEMORY CLINIC**

H KINNEAR (RNGKEL001)

A dissertation submitted in partial fulfillment of the requirements for the award of the
degree of Master of Arts (Clinical Psychology)

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COMPULSORY DECLARATION

This work has not been previously submitted in whole, or in part, for the award of any degree. It is my own work. Each significant contribution to, and quotation in, this dissertation from the work, or works, of other people has been attributed, and has been cited and referenced.

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ABSTRACT

Background and Objective: Depression in the elderly has been linked with stroke, and with white matter lesions, particularly in frontal-subcortical regions responsible for mood regulation. Such evidence of vascular disease has in turn been associated with vascular risk factors such as diabetes, hypertension, smoking, high cholesterol and heart disease. The vascular depression hypothesis (Alexopoulos et al., 1997) proposes that individuals with late-onset depression and vascular risk factors have more apathy, fewer ideational symptoms, and more functional and cognitive impairment. Recent studies offer only limited support for this proposal, perhaps due to lack of comparability of studies, lack of control for factors such as age, medical co-morbidity and functional impairment, and exclusion of patients with cognitive impairment. The current study aimed to test the vascular depression hypothesis in a non-Western sample by examining (a) whether a specific depression symptom profile exists in patients with vascular risk factors, and (b) the relationship between vascular risk, depression and cognitive and functional ability.

Method: Retrospective data were gathered from 184 individuals (age ≥ 55 , MMSE ≥ 17) who had been evaluated at the Groote Schuur Hospital Memory Clinic. Correlational and multiple regression analyses tested relationships between a cumulative vascular risk index, scores on the Cornell Scale for Depression and the Bristol Activities of Daily Living Scale, physical evidence of heart disease and 4 executive function tests (Trail Making Test, category fluency, CLOX1, and an initiation/perseveration index).

Results: Vascular risk and depression were significantly related, even after controlling for age and functional impairment. However, using a vascular risk model of vascular depression, the data provided no further support for the vascular depression hypothesis either in terms of (a) a specific depression profile, or (b) the impact of vascular risk and depression on cognitive and functional impairment. There were, however, significant relationships between heart disease and executive function measures, and between all cognitive measures and ADL functioning.

Conclusion: The current findings imply there may be a threshold of severity of vascular burden before clinically significant symptoms become apparent. However, the findings may also be explained by a common underlying mechanism (either biological or psychosocial) linking vascular disease and depression. Prospective longitudinal studies are required to clarify causal mechanisms.

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INTRODUCTION

The 'vascular depression' hypothesis was outlined by Alexopoulos et al. (1997) as an attempt to formally conceptualise the frequently observed co-occurrence of late-onset depression with cerebrovascular disease. Depression following stroke has been documented since the early 1900's, and with the relatively recent emergence of imaging technology it has also been possible to demonstrate an association between depression and silent stroke, which is radiological evidence of stroke in the absence of neurological signs (Fujikawa, Yamawaki, & Touhoda, 1993). These small strokes, symptomatic of small vessel disease, affect mainly frontal-subcortical grey and white matter, and as a result they are considered likely to disrupt frontal-subcortical neurological pathways important in the regulation of mood (Newberg, Davydow, & Lee, 2006). Mood dysregulation is a common feature in a variety of neurological disorders affecting frontal-subcortical pathways, including vascular dementia, multiple sclerosis, Parkinson's disease and Huntington's disease (Salloway et al., 1996). Given the above, and because vascular disease and stroke is associated with a range of vascular risk factors, it seemed reasonable to suppose that depression in late life might also be associated with vascular risk factors. This would be useful to demonstrate, as radiological investigation is not routine in the assessment of depression in late life (Licht-Strunk et al., 2004). Moreover, where late-onset depression occurs in older adults with vascular risk factors, the implications for treatment might entail a more focused intervention that addresses both the symptoms and the presumed cause. Without successful intervention, patients with vascular depression are thought to be at higher risk of progression to vascular dementia (Barnes, Alexopoulos, Lopez, Williamson, & Yaffe, 2006), the only dementia considered potentially preventable (Looi & Sachdev, 1999; Meyer, Judd, Tawaklna, Rogers, & Mortel, 1986). Because of this increased risk, there has been an increasing body of research aimed at elucidating a clear syndrome or diagnostic entity with a view to more tailored treatment for a specific group of patients.

Depression in the elderly

According to Alexopoulos (2005), between 1 and 4 percent of older adults (i.e. those over the age of 65 years) suffer from major depressive disorder and between 4 and 13 percent from minor depression. These figures double in the 75-85 age group, but in general the prevalence of depression in later life is slightly lower than in middle age, in which depressive disorders

have a prevalence of between 8 and 16%. There is however a concern that depression may be under-diagnosed and under-treated in the elderly, as amongst this age group there appears to be some reluctance to seek help for depression, and general practitioners are blamed for spending too little time assessing for depression in the elderly (Alexopoulos, 2005). This may be a function of the fact that among somatically ill patients, regardless of age, depression tends to be under-diagnosed (Nuyen et al., 2005). In older adults, depression is often associated with medical morbidity, with 10-12% of medical inpatients suffering from depression compared with 6-9% in primary care settings. Among nursing home residents this rises further to around 12-14%. Depression also significantly affects the outcome of a number of medical illnesses, particularly heart disease, in which mortality is increased in the presence of depression, as well as outcome following stroke (Alexopoulos, 2005; Robinson, 2003). Depression frequently accompanies dementing illnesses, with prevalence rates ranging from around 20-30% in clinical populations (Alexopoulos, 2005; Barnes et al., 2006), but with a far higher prevalence and worse course among vascular dementia as opposed to dementia of the Alzheimer's type (Li, Meyer, & Thornby, 2001; Newman, 1999).

Definition of vascular depression

The term 'vascular depression' was first put forward by Alexopoulos and colleagues in 1997 in an attempt to delineate a group of patients who fulfil the clinical criteria for depression, but who also have vascular factors. This was based on research evidence suggesting that patients with late-onset depression have more vascular disease (Fujikawa, Yamawaki, & Touhoda, 1994), exhibit a specific depression profile (K. R. Krishnan, Hays, Tupler, George, & Blazer, 1995) and less family history of depression (Mendlewicz & Baron, 1981). Alexopoulos and colleagues (1997) predicted that this group of patients would also have more cognitive and functional impairment. They therefore selected for study a group of patients who presented with unipolar depression with first onset after the age of 60, and the presence of at least one vascular risk factor. Based on their hypotheses they predicted this patient sample would have:

1. Greater cognitive impairment, especially executive functions and psychomotor slowing
2. Lack of family history of depression

3. More functional impairment
4. More motivational and vegetative symptoms of depression (e.g. sleep, appetite disturbance, apathy) and fewer ideational symptoms (e.g. guilt, suicidal ideation)

Using two groups of patients from a clinical setting, Alexopoulos et al. (1997) found evidence to support all these hypotheses, albeit with small sample size (33 'vascular' and 32 'non-vascular' depressed patients). Attempts at replication have yielded mixed and often inconsistent results, with some hypotheses supported and others not. The following discussion will review the evidence regarding post-stroke depression, links between depression and vascular disease as evidenced by radiological or neuropathological data ('silent' stroke), and the relationship between depression and vascular risk factors.

Post-Stroke Depression

Stroke is the third leading cause of mortality in adults (Newberg et al., 2006). In developed countries, the annual incidence of stroke among 55-65 year olds is around 10-20 per 10000, but escalates with age to around 200 per 10000 in over 85's. Improved control of vascular risk factors, particularly hypertension, is thought to have been the cause of a decline in stroke incidence and mortality in developed countries over the past 20 years (Robinson, 2003). Depression affects roughly one-third of individuals post-stroke, though this varies depending on depression criteria (Hackett, Yapa, Parag, & Anderson, 2005; Paolucci, 2008; Robinson, 2003). Most studies of post-stroke depression exclude aphasic patients owing to communication difficulties, which may result in an under-estimate of depression prevalence (Paolucci, 2008). It is unclear what is the impact of disability more generally on the probability of depression after stroke, as not all studies control for disability, though it has been observed that depression occurs more commonly following stroke than following other medical conditions with comparable disability, such as orthopaedic surgery (Folstein, Maiberger, & McHugh, 1977). Longitudinal studies also show that despite improvements in disability in the weeks to 3 months post-stroke, the prevalence of depression increases (Paolucci, 2008). In a large ($N=1134$), randomised, community-based longitudinal study, incident stroke was associated with a 6-fold increased risk of depression after controlling for vascular risk factors and disability (Whyte, Mulsant, Vanderbilt, Dodge, & Ganguli, 2004). Adding complexity to this area of research is the observation that in medical populations it is often difficult to separate out some of the depression scales' criteria from medically derived

symptoms such as lack of energy, sleep and appetite disturbance (Robinson, 2003). The assessment of post-stroke depression thus varies across studies, with some opting to use existing measures unchanged, and others attempting to control for medical disability by modifying certain scale items.

Relationship between depression and vascular disease (radiological and pathological)

Whereas the temporal relationship between stroke and depression by nature lends itself to hypotheses regarding causality, examinations of relationships between radiological evidence of silent stroke and depression are by nature correlational (Newberg et al., 2006). Silent stroke is 5 times more common than symptomatic stroke, and is linked with a doubled risk of dementia when compared with those without stroke. Radiological evidence of silent stroke comprise areas of hyperintensity, most commonly subcortical, and includes both lacunar infarcts (lesion volume < 15mm), commonly in the basal ganglia, and white matter lesions (Roman, 2006). The decision to include white matter lesions (WML) as evidence of vascular disease has been controversial, as other possible etiologies for WML cannot be excluded, for example demyelination or dilation of peri-vascular spaces (Baldwin, 2005; Kales, Maixner, & Mellow, 2005). WML are strongly related with age, with a prevalence among older adults of between 60 and 95% (Roman, Erkinjuntti, Wallin, Pantoni, & Chui, 2002). In an attempt to clarify the nature of WML in depressed patients, Thomas et al (2002) conducted a post mortem study of the brains of 20 depressed patients and 20 controls. Their results showed that *all* the white matter lesions in depressed patients were ischemic in origin, compared with less than a third in the control group. From these findings the authors concluded that WML have a strong link with depression, and should be considered evidence of vascular disease in depressed patients.

The evidence for increased rates of depression amongst older adults with white matter and basal ganglia abnormalities is mixed, with numerous studies, some quite large, providing both positive and negative results. In the community-based Rotterdam scan study (de Groot et al., 2000), in which 1077 elderly (age range 60-90) Dutch subjects were investigated, most had white matter lesions, but those with severe WML were 3-5 times more likely to have major depression than those with mild or no WML. This relationship remained even after

controlling for stroke, cognitive functioning and overall severity of cerebral atrophy. Later age of onset of depression was linearly associated with severity of subcortical (but not periventricular) -WML, with those patients with later onset of depression having more severe subcortical WML. Another large community based study, ($N=629$), the LADIS study (Firbank et al., 2005) found that severe as compared with mild WML were significantly associated with depression after controlling for quality of life. This study excluded subjects with no or minimal vascular risk factors, which according to the authors possibly weakened the relationship found.

There are also large studies with some negative findings; for instance, the Cardiovascular Health Study ($N=3660$) found that a significant relationship between depression and WML was no longer significant after controlling for age, cognitive status, medical illness and functional impairment (Steffens, Helms, Krishnan, & Burke, 1999). The relationship between basal ganglia lesions and depression did however remain significant. Another large prospective Dutch study ($N=527$), the PROSPER study (Versluis et al., 2006) found no relationship between increasing severity of WML and worsening depressive symptoms, but acknowledged that the exclusion of patients with cognitive impairment (Mini-Mental State Exam [MMSE] score < 24) could have impacted on this finding, as their depression rates were unexpectedly low. The VITA study (Rainer et al., 2006) found no relationship between white matter or small grey matter lesions and depression in 606 non-demented 75-year olds, but did find a relationship between depression and brain atrophy, causing them to conclude that late-onset depression is probably organic but not necessarily vascular.

In terms of smaller studies, and those using clinical samples, Coffey, Figiel, Djang & Wiener (1990) found more subcortical hyperintensities on magnetic resonance imaging (MRI) among 51 elderly depressed patients who had been referred for electroconvulsive therapy (ECT), compared with 22 normal controls. Rabins, Pearlson, Aylward, Kumar & Dowell (1991) found more atrophy and basal ganglia lesions in 21 elderly depressed inpatients compared with 14 controls, but no difference in degree of periventricular hyperintensities. Another small cross sectional study by Taylor et al. (2003) showed that WML in the frontal lobes was related to depression in 87 depressed patients compared with 47 controls. Fujikawa et al.

(1993) found that among 205 patients with late-onset depression, 93% had MRI evidence of silent infarcts vs. 65% of those with early onset of depression. There were no controls for medical co-morbidity in these latter studies. In summary, the evidence regarding links between depression and radiological evidence of vascular disease is somewhat inconclusive. The preponderance of evidence suggests there is a relationship, but especially where white matter disease is concerned there appears to be still a degree of uncertainty.

In terms of post-mortem studies of vascular disease and depression, Thomas, Kalaria, and O'Brien (2004) argue that their own studies show there are strong links, with atheromatous disease as well as post-ischemic inflammation more prevalent in autopsy findings of those with depression than those without.

The relationship between lesion location and depression has long been the subject of debate. Carson et al. (2000) performed a review of studies examining whether left-sided lesions were more likely to cause depression than right-sided lesions. They found that some supported this theory and others did not. However they did not specifically examine infarcts affecting subcortical or white matter. A later review by Vataja et al. (2004) concluded that lesions of the globus pallidus and caudate, especially on the left, were far more likely to be associated with depression, with an odds ratio of 7:2. They also argued that previous reviewers had included a preponderance of reports based on CT rather than MRI, which is insensitive to white matter disease and smaller infarcts. Their review is consistent with the view that frontal-subcortical circuits are implicated in the etiology of depressive disorders.

Finally, further evidence for the link between vascular disease and depression is the significantly higher association between depression and vascular dementia (>20%) when compared with that between depression and dementia of the Alzheimer's type (3%) (Newman, 1999). A longitudinal study also demonstrated that depression worsened over a 3.5 year period in patients with vascular dementia whereas depressive symptoms improved in patients with dementia of the Alzheimer's type (Li et al., 2001).

Relationship between depression and vascular risk factors

Stroke and vascular disease have been traditionally associated with a range of vascular risk factors, with the risks increasing with advancing age (Baldwin, 2005; Mast, Azar, & Murrell, 2005). Most studies rely on a combination of self-report and informant interview for information on vascular risk factors. Those that have been included in one form or another in the studies reviewed are; smoking (may be recorded as current or past history, presence or absence of smoking, or pack-years), hypertension (HPT, may be self report, presence or absence of systolic hypertension, or graded on degree of control with antihypertensive medication), diabetes mellitus (DM), atrial fibrillation (AF; a common type of abnormal heart rhythm involving the upper chambers of the heart), hypercholesterolemia (high cholesterol, some studies have also examined the impact of low cholesterol levels on depression), left ventricular hypertrophy (LVH; thickening of the muscle of the left ventricle of the heart), as assessed by electrocardiogram, ischemic heart disease (IHD; heart disease characterised by reduced blood supply to the heart muscle), atherosclerosis (evidence of hardening of the arteries caused by formation of plaques within the arteries), claudication (cramps in legs suggestive of peripheral arterial disease), history of previous stroke, history of transient ischemic Attack (TIA, a period in which neurological signs suggestive of stroke are present for a period not exceeding 24 hours), and a history of vascular surgery.

Most studies have examined some composite of these elements, and others have looked at specific vascular risk factors. Most are cross-sectional but there are some fairly large longitudinal studies, and the latter will be examined first.

Kim et al. (2006) studied 661 community participants over 65 years without depression at baseline in a prospective 2 year study. At follow up they found that incident depression (in 63 participants) was significantly associated with pre-existing heart disease, incident stroke, and raised cholesterol, but that only a trend existed for hypertension and diabetes. The prospective community-based Health, Aging and Body Composition Study (Mast et al., 2008) demonstrated that even with a short follow up interval (2 years), baseline vascular risk factors were linked with increased risk of incident depression in older adults (age 70-79) who were free from depression and functional impairment at baseline. In this large ($N=1796$)

study the authors used a cumulative vascular index and demonstrated a dose-response relationship. A similar study, the Hispanic Established Population for the Epidemiological Study of the Elderly (Zimmerman, Mast, Miles, & Markides, 2008), examined 964 Mexican-American patients with vascular risk factors but without depression and cognitive impairment at baseline. Using a cumulative vascular risk index, patients were followed up for 2 years, and the authors found increased incidence of depression at follow up with increased cumulative vascular risk index after controlling for demographic data, medical conditions and physical functioning. The vascular risk factors making up the index included previous stroke and heart attack together with hypertension, diabetes and smoking. A small longitudinal study found support for the relationship between baseline vascular risk factors (diabetes, atrial fibrillation and hypertension) and later development of depression in 100 mostly African-American geriatric rehabilitation patients (Mast, Neufeld, MacNeill, & Lichtenberg, 2004). Comparing patients with no- or one vascular risk factor with those with two or three vascular risk factors, the authors found the latter group were approximately 5 times more likely to be depressed at 6-month and at 18-month follow up, after controlling for baseline depression, co-morbid medical burden, cognitive impairment and functional impairment (ADL). In the Longitudinal study of Aging in Amsterdam (LASA), the authors found more depression in those with a history of vascular or cardiac events compared with those without (Licht-Strunk et al., 2004).

In terms of correlational studies, Whyte et al. (2004) found depression to be associated with a history of stroke, and with diabetes, but with none of the other vascular risk factors they studied (hypertension, smoking, atherosclerotic heart disease). A study among the oldest-old in a retirement community ($N=181$, average age 83.2) showed that vascular risk factors were correlated with depression at baseline (M. Krishnan, Mast, Ficker, Lawhorne, & Lichtenberg, 2005). A cross-sectional study examining the relationships between vascular risk factors, depression and executive dysfunction in 448 primary care patients found a relationship between vascular risk factors and depression but this relationship was no longer significant after controlling for overall medical burden (Sanders, Lyness, Eberly, King, & Caine, 2006). An Australian study (Almeida et al., 2007) examined 4204 men between the ages of 71 and 89 and found that those with depression were more likely to have diabetes, angina, MI, stroke and to be current smokers.

An unexpected finding in a recent Dutch study (Nuyen et al., 2007) was that the link between vascular risk factors and depression was mediated by specific age group. This study examined 286 patients with first episode of depression after age 60, and found a strong relationship between vascular risk factors and depression in the 50-69 age group, but that this relationship no longer held after age 70, as depression was less frequently diagnosed beyond this age. The authors noted that in this retrospective study depression diagnosis was made by general practitioners, and that in one of their previous studies they found that in the presence of somatic illness, depression tends to be under-diagnosed in general practice.

In terms of studies that examined individual vascular risk factors, a longitudinal study of 2584 hypertensive volunteers aged 55-74 did not find any relationship with incident depression at 5-year follow up (Cervilla, Prince, & Rabe-Hesketh, 2004), but did find a link between depression and baseline smoking and low serum cholesterol, which the authors did not consider vascular risk factors. The large ($N=3660$) Cardiovascular Health Study (Steffens et al., 1999) found a significant relationship between depression severity and presence of hypertension, but because hypertension was associated with every other variable in their model (e.g. age, smoking, obesity) it lost significance on its own.

A large study ($N=1008$) was conducted in a tightly defined population of citizens all born in 1935 from a small Finnish town in order to assess the link between both diagnosed and undiagnosed diabetes and depression (Rajala, Keinanen-Kiukaanniemi, & Kivela, 1997). The authors found depression to be linked only to diagnosed diabetes, which they suggest indicates psycho-social reasons for depressive symptoms, but noted also that undiagnosed diabetes represents a less severe form of the disease (Rajala et al., 1997).

The relationship between depression and raised cholesterol as a vascular risk factor is complex, as there are many different kinds of measures of cholesterol and some confusing findings, including the observation that both high (Kim et al., 2006) and low (Cervilla et al., 2004) cholesterol has been associated with depression. Mast et al. (2008) found that incident

depression at 2-year follow up was associated with low baseline high-density lipoprotein in models adjusted for demographic variables and cognitive impairment.

The mechanism of the relationship remains unclear but substantial prospective evidence exists to suggest a bi-directional relationship between heart disease and depression.

Indications are that the prevalence of depression is approximately 45% following myocardial infarction (MI), and that conversely depression as a predictor of subsequent cardiac events is equivalent as a risk factor to smoking, history of previous MI or left ventricular dysfunction (Grippe & Johnson, 2002).

Studies in which no relationship at all was found between vascular risk factors and depression include that of Lyness et al. (1999), in which neither a cumulative vascular score nor the individual risk factors were related with depression score. The vascular risk factors included left ventricular hypertrophy, hypertension, cardiovascular disease, diabetes, atrial fibrillation and smoking. However most patients in their cross sectional study were non-depressed (only 31 of the 214 patients were depressed), and in a follow-up study a year later with the same patient group, the authors found that the overall vascular score did in fact predict incident depression (Lyness, King, Conwell, Cox, & Caine, 2000). In one of the few studies involving a non-Western sample, (287 Caribbean-born UK patients), no relationship was found between vascular risk factors and depression (Stewart, Prince, Mann, Richards, & Brayne, 2001).

Attempting to summarise the evidence regarding vascular risk and depression is complex, as the identification of variables as vascular risk factors is an area that varies greatly from one study to another for reasons that are not always clear. Because of lack of comparability, the findings with respect to vascular risk and depression remain inconclusive but generally appear weaker than the findings with respect to radiological evidence of vascular disease and its link with depression (Thomas et al., 2004). Nevertheless there appear sufficient evidence to warrant further interest; in particular the longitudinal evidence shows promise as a line of investigation.

Direction of causality – evidence for a bi-directional relationship between depression and vascular disease?

The majority of studies examining links between depression and vascular disease have been correlational. Along with an early emphasis on late age of onset of depression within the vascular depression model, the assumption has been that vascular risk factors may predispose, precipitate or perpetuate depression in later life (Alexopoulos et al., 1997). Conversely, there is quite a large body of longitudinal evidence in support of a causal relationship between depression and incident stroke, suggesting a possible bidirectional relationship (Baldwin, 2005; Thomas et al., 2004). The Alameda County Study (Everson, Roberts, Goldberg, & Kaplan, 1998) was one of the earliest large ($N=6676$) longitudinal community-based studies to demonstrate baseline depression as a predictor of stroke. The authors showed that reporting five or more depressive symptoms at baseline almost doubled the risk of stroke over 29 years, and that each additional symptom conferred an additional 8% risk. Perhaps the strongest relationship between depression and vascular disease was demonstrated in a longitudinal study conducted using the Taiwanese national health database ($N=827$), in which patients (aged 18-44) hospitalised for depression incurred a five-fold higher risk of stroke at 5-year follow up. (Lee, Lin, & Tsai, 2008). This is an impressive finding given the infrequency of stroke in this age group. A 10-year follow-up study in a Japanese population (Ohira et al., 2001) found an increased rate of incident ischemic stroke in 901 patients aged 40-78 with depression at baseline (odds ratio 2.7). This was after controlling for vascular risk factors, and patients with a history of stroke at baseline were excluded from the study. Similar results were found in a 22-year follow-up study of 6095 patients aged 25-74, in which baseline depression was associated with a 50 -160 percent increased chance of stroke (Jonas & Mussolino, 2000). Another large ($N=4120$) community-based prospective study, the Framingham Stroke Risk Study, demonstrated a more than 4 times greater risk of stroke or TIA at 8-year follow-up in patients with depression at baseline. This was after controlling for education and vascular risk factors (Salaycik et al., 2007). A smaller ($N=181$) longitudinal study among the oldest-old in a retirement community (average age 83.2) showed that using logistical regression and path analysis, depression at baseline not only predicted incident stroke, but was also the strongest variable in the model, with 58 percent of the depressed group and only 4 percent of the non-depressed group developing incident stroke (M. Krishnan et al., 2005). The Baltimore Epidemiologic Catchment Area

Study ($N=1703$) reported a 2.6 times greater risk of stroke in depressed compared with non-depressed patients at 13 year follow-up (Larson, Owens, Ford, & Eaton, 2001). May et al. (2002) found a measure of psychological distress, the general health questionnaire, to predict an increased rate of fatal stroke in 2201 men at 5 year follow up (relative risk 2.6 after controlling for vascular risk factors and pre-existing vascular disease or events). To summarise, there appear to be persuasive longitudinal data to suggest that depression is a strong predictor of vascular events.

Role of depression onset within the vascular depression hypothesis

Early studies into the vascular depression hypothesis placed greater emphasis on the age of onset of depression as an important feature of the model. However because age of first onset of depression has proved extremely difficult to establish with any reliability, more recent studies have shifted focus to 'late-life depression' without reference to age of onset. It is nevertheless worth mentioning some of the findings with respect to late-onset depression as not all studies rely on self-report alone. It has also represented a different angle from which to approach the question of the relationships between depression and vascular disease in a field in which there is still uncertainty about the relative importance of variables concerned as well as direction of causation.

In a study combining self and family report of depression after age 50, silent infarcts were found in 93% of patients with late-onset depression compared with only 65% of those with early-onset depression (Fujikawa et al., 1993). Using a combination of self-report, family collateral, and past medical records, Salloway et al. (1996) found that cognitive performance, subcortical hyperintensities and depression scores were predictive of group membership (early vs. late-onset depression) in a discriminant analysis model. Their cut-off age for late-onset was age 60. The Rotterdam scan study ($N=1077$) demonstrated that age of onset of depression (as determined by self reported history of treatment for depression by GP, psychologist or psychiatrist) was correlated in a linear manner with WML severity, so that more severe WML was associated with a later age of depression onset (de Groot et al., 2000). Subcortical lesions have also been found to be more common in late-onset than early-onset

depression in two smaller studies (K. R. Krishnan, Hays, & Blazer, 1997; Lavretsky, Lesser, Wohl, & Miller, 1998).

Role of depression profile within the Vascular Depression hypothesis

Apathy and psychomotor slowing are factors that have been traditionally associated with the profile of vascular dementia and of other subcortical degenerative processes such as Parkinson's disease (Levy & Dubois, 2006). Accordingly it was hypothesized by Alexopoulos and colleagues (1997) that patients with late-onset depression and vascular risk factors, or 'vascular' depression, might exhibit more vegetative and motivational, and less ideational features of depression, presumably with the underlying implication that vascular depression has an organic basis. Their study demonstrated that within their sample this profile of depressive symptoms did indeed characterise patients with 'vascular' depression. On balance, most studies have been unable to replicate these findings, with some confirmation of increased motivational symptoms but largely negative findings with respect to fewer ideational symptoms. The large (total $N=2220$) Rotterdam scan study, combined with data from the Amsterdam study of the elderly (AMSTEL), both community-based samples, demonstrated that depression with vascular risk factors was associated with more loss of energy and more appetite disturbance, but no specific differences in 'mood' symptoms were found. Loss of energy was linked specifically with myocardial infarction and peripheral arterial disease (Naarding et al., 2007). Schreiner and Morimoto (2002) found that among post-stroke patients, the Cornell Scale for Depression (CSD; Alexopoulos, Abrams, Young and Shamioan, 1998), items most frequently identified were irritability, anxiety and sadness, sleep disturbance and psychomotor retardation, a mix of ideational and vegetative symptoms. Yamashita, Fujikawa, Yanai, Morinobu and Yamawaki (2001), found no difference in Hamilton Depression Scale (Hamilton, 1960) profiles in patients with vs. those without silent cerebral infarcts. Similarly, Krishnan et al. (2004) found no differences in ideational symptoms in patients with early-onset vs. late-onset depression and subcortical changes on MRI, although "lassitude" or apathy was more prevalent in the late-onset group. A longitudinal study (Licht-Strunk et al., 2004) found no difference in depressive symptom profile among depressed patients with vs. those without vascular disease. Another longitudinal study (Kim et al., 2006) found that heart disease and stroke were associated with ideational rather than vegetative symptoms of depression; this is the opposite of what the

vascular depression hypothesis would predict. Again contrary to expectations, core features of depression in stroke patients were anhedonic in a large epidemiological study, (Whyte et al., 2004). To summarise, there is some evidence confirming the prediction of more vegetative and motivational features in 'vascular' depression but mostly negative or non-significant findings regarding the prediction of fewer ideational features.

Treatment response in vascular depression

A frequent statement in literature reviews motivating for research in vascular depression is that late-onset depression with vascular risk factors is associated with a poorer response to antidepressants (Alexopoulos et al., 1997; Firbank et al., 2005). This statement must be qualified by pointing out that larger clinical trials of antidepressant drugs are generally not aimed at the older adult population, so it is difficult to comment on comparable success rates more generally between younger and older adults. There are a few studies examining treatment of post-stroke depression and a few examining treatment of late life depression in the presence of vascular disease, and these will be discussed in more detail.

Studies of post-stroke depression generally show significant improvement of depression symptoms in patients taking antidepressants compared with those taking placebo. A recent review that combines data from the available randomised controlled trials demonstrated that both treatment and placebo groups show significant improvement in the weeks immediately following stroke, but that with longer follow-up the differences between the treatment and placebo group become larger. This suggests that recovery from depressive symptoms in the early stages may partly be neurological. The finding that longer duration of treatment was associated with greater recovery implies that the usual 6 to 8 week trial period for remission of symptoms may be inappropriate in this patient population if significant effects are to be observed (Paolucci, 2008). An important outstanding question is what constitutes 'remission' in post-stroke patients since there is a degree of overlap in the residual physical symptoms following stroke, and common depression scale items such as lack of appetite, loss of energy, or sleep disturbance (Paolucci, 2008; Robinson, 2003).

In terms of treatment response where patients have either vascular disease or vascular risk in the absence of clinical signs of stroke, there is mixed evidence. Yamashita et al. (2001) found worse treatment response in patients over 50 with silent cerebral infarcts as opposed to those of any age group without silent infarcts. There was no relationship between age and treatment response in their sample. Iosifescu et al. (2005) showed that of a group of 355 patients with major depressive disorder age 19-65, response to fluoxetine over 8 weeks was worse in patients with vascular risk factors than those without. Vascular risk factors accounted for 10% of variance in response rates; however age was treated as a vascular risk factor, which is unusual. The only vascular risk factor independently associated with poor treatment response was high cholesterol. The study most frequently cited regarding claims of poor treatment response in the presence of vascular disease is the small study by Simpson, Baldwin, Jackson and Burns (1998). Their study was designed to predict group membership in terms of responders vs. non-responders to antidepressants. Using 28 controls and 75 depressed patients, the authors demonstrated that initial monotherapy appears to have a lower success rate at 12 weeks in those patients with MRI evidence of subcortical vascular disease. A variety of SSRI and tricyclic antidepressants were used as first line treatment. Two disease marker variables exerted a particularly strong predictive impact on treatment resistance; basal ganglia lesions, and presence of extra-pyramidal signs. The authors report that second line augmentation and/or alternative treatment improved the rate of response considerably. By way of contrast, a study by Salloway et al. (2002) found no difference in response to Sertraline (an SSRI) in older depressed outpatients with subcortical hyperintensities compared with those without, and Krishnan et al. (2004) found no difference in response at 6- and 12-month follow up in patients defined as having 'subcortical ischemic depression' (as defined by late onset of depression and presence of subcortical vascular disease on MRI) compared with depressed patients without subcortical vascular disease. Finally, Miller et al. (2002) found no difference in response to antidepressants in patients with vascular risk factors and late onset of depression.

In summary, when comparing treatment response with antidepressant therapy vs. placebo in patients with vascular risk and vascular disease, there are clear benefits to treatment. When comparing response to antidepressant treatment in those with vs. those without vascular disease, the evidence is inconclusive, with some studies suggesting it appears more difficult

to treat depression in the latter group and other studies showing no difference in treatment response.

Natural Course of Vascular depression

A key implication of the vascular depression hypothesis is that this is a disease entity with a specific prognosis, with the likely end-result vascular dementia. In a large ($N=2220$), 6-year follow up study, the cardiovascular health study (Barnes et al., 2006), in patients aged 64-92, those with depression had a higher risk of progressing to mild cognitive impairment (MCI) with the risk increasing with depression severity. (The authors used a broad definition of MCI rather than the more restrictive 'amnesic' MCI definition). Interestingly, despite the fact that the presence of vascular disease on MRI at entry increased odds of developing MCI by 50-60%, the relationship between depression and cognitive impairment in this large sample was independent of vascular disease, which again highlights questions around causality. In a smaller retrospective study, 71 patients that had been hospitalised for depression 25 years previously, as well as 50 controls, were investigated (Brodaty et al., 2003). The authors found that 10 of the depressed group but none of the controls had dementia at follow up, with vascular dementia being the most common outcome.

Summary of evidence

The evidence thus far that has bearing on the validity or otherwise of the vascular depression hypothesis may be summarised as follows:

1. Vascular risk factors increase with age
2. White matter disease increases with age
3. Vascular risk factors are linked with stroke but the nature/degree of the relationship between vascular risk factors and white matter disease is still insufficiently defined
4. Depression does not increase with age; indeed, empirical evidence suggests a decrease in depression with age
5. There is good prospective evidence for stroke as risk for subsequent depression

6. There is very strong prospective evidence for depression as risk for subsequent stroke
7. There is a correlation between silent stroke (radiological evidence of subcortical infarcts) and depression
8. There are inconsistent findings regarding the relationship between vascular risk factors and depression
9. There are inconsistent but mostly negative findings regarding a specific depression profile where vascular disease or vascular risk
10. There is inconsistent evidence as to whether depression in the presence of vascular disease is more refractory to treatment.
11. Prognosis of depression in the presence of vascular disease with respect to cognitive outcomes appears poorer in terms of progression to dementia.
12. Medical prognosis is also poorer (higher morbidity) in the presence of depression post-stroke.

There are a number of issues to be examined in order to attempt to understand the lack of consistency in this area of research, and beginning with some general comments, a few key issues that have bearing on this study will be discussed in more detail.

One over-arching issue concerns the definition of the sample in question; what constitutes a 'vascular depression' sample. Exclusion and inclusion criteria may vary widely from one study to another, depending on which aspect of the theory is under investigation. One example is age of onset, in which lack of consensus as to what constitutes 'late' onset of depression is likely to have impacted on comparability of studies. According to Baldwin and O'Brien (2002), generally UK authors use 65 and US authors age 50, but some even define late onset as that occurring after age 40 (K. R. Krishnan et al., 1997). More recent studies have not included age of onset at all in defining a vascular depression patient sample.

Where a variable might exert a possible confounding influence, a decision has to be made as to whether to exclude it entirely, or to measure its contribution. As an example, some studies may exclude patients with a history of stroke, where others choose to measure its individual contribution to depression. The reason to exclude stroke may be owing to the fact that it is indicative of already established vascular disease rather than vascular risk; or because it exerts a possible confounding influence in terms of functional impairment and medical co-morbidity, which is strongly linked with depression. In a strongly worded criticism of the vascular depression hypothesis, Almeida (2008) argues that it is possible that the relationship between vascular disease and depression is mediated almost entirely by overall medical burden and functional impairment. In support of his argument, some large studies have found significant relationships between vascular risk or vascular disease and depression, but once overall medical burden was taken into account, these variables no longer exerted a significant influence on depression scores (Steffens et al., 1999). Almeida (2008) further argues that according to the vascular depression hypothesis, because vascular risk factors increase with age, depression ought also to increase with age, but since it does not, the relationship must be spurious, and the vascular depression hypothesis therefore is a myth. This is a persuasive point, but the logical extension of this argument is that because burden of medical illness increases exponentially with age, and depression does not, then there cannot be a relationship between these variables either. Lyness et al. (2000) have framed the dilemma more cautiously, saying that it is difficult to extricate vascular disease from overall medical burden, thus making it difficult to draw conclusions.

Vascular disease vs. Vascular risk

Confusingly, measures of vascular risk and indicators of vascular disease are sometimes conflated. There appear stronger data to support a relationship between depression and radiological evidence of vascular disease, but vascular risk is not the same thing – it is the risk of acquiring vascular disease (Lucchi, Bellelli, Magnifico, Guerini, & Trabucchi, 2005). The assumption within the vascular depression hypothesis seems to be that where there are multiple vascular risk factors there may be sub-clinical vascular disease, but obviously one may not be taken for evidence of the other (Kales, Maixner, & Mellow, 2005). There is very little overlap between some studies in terms of what qualifies as vascular risk. Alexopoulos's 1997 study used the Cumulative Illness Rating Scale (CIRS) definition of vascular risk

factors which comprised hypertension, evidence of stigmata of atherosclerosis, a history of transient ischemic attack (TIA) or surgery for vascular disease. Other studies e.g. Sanders et al. (2006), use the American Heart Association Stroke Risk prediction chart, which includes hypertension, diabetes, atrial fibrillation, left ventricular hypertrophy, smoking, cardiovascular disease and being on anti-hypertensive medication. Studies that have used smoking, hypertension, diabetes, heart disease and raised cholesterol as vascular risk factors, such as Salloway, Correia et al. (2002), might be expected to pick up cases at the milder end of the disease spectrum than for example the Zimmerman et al. study (2008), which included previous stroke and heart attack as vascular risk factors.

Because of small sample sizes and the large number of predictor variables involved in examining each risk factor separately, most studies use a cumulative vascular risk index, which may either be an existing scale, or may simply be a continuous variable from 0 (= no vascular risk factors), up to around 5 or 6 risk factors. The reason for combining vascular risk factors may be a statistical necessity, but it has the effect of equalising each of the variables. A factor such as surgery for existing vascular disease may be given equal weight as having a history of smoking, with obvious consequences for comparability of findings. An added confounding factor is that certain vascular diagnoses may confer poorer quality of life, for example dietary restrictions with diabetes, whereas others may be more insidious, such as hypertension.

Choice of Demographic

A related and apparently un-researched issue is the degree of control of vascular risk factors within a particular patient population and likelihood of progression to disease within that population. Risk factors such as hypertension may be well controlled and might never progress to vascular disease. It is therefore of interest to this field of research that vascular risk factors tend to be more poorly controlled in developing than developed nations. Poor control of vascular risk factors is thought to underlie the observation that vascular dementia is more prevalent in developing countries such as India, Japan, China and African countries than it is in the developed world (Loeb & Meyer, 1996; Roman et al., 2004; Xu et al., 2004). It seems worth investigating whether in populations with poor control of vascular risk factors,

there is a higher prevalence of vascular-related depressive disorders. There are a few studies examining this, some with non-Western samples and others using groups of individuals with reportedly higher vascular risk that are resident in Westernised countries. A study investigating a Caribbean-born population in the UK with a relatively high prevalence of vascular risk factors found that MRI-defined vascular disease was associated with depression but that vascular risk factors were not (Stewart et al., 2001). However the authors did not use a global measure of vascular risk, but instead examined individual risk factors while acknowledging at the same time that their study did not actually have the power to detect relationships between depression and individual vascular risk factors. A longitudinal study with mostly African-American patients in whom there are reportedly higher levels of vascular risk, demonstrated strong links between baseline vascular risk factors and depression symptoms at 18 month follow up (Mast, Neufeld et al., 2004). Similarly a recent study with a Mexican-American sample demonstrated prospective evidence of vascular risk factors as a cause of incident depression (Zimmerman et al., 2008). Two studies with non-Western samples found strong prospective evidence for depression as a risk factor for later vascular events (Lee et al., 2008; Ohira et al., 2001), while another large study with a non-Western sample found evidence for vascular risk factors as a cause of incident depression (Kim et al., 2006).

Studies from clinical samples have tended to demonstrate more robust relationships between vascular risk factors and depression than are typically found in community or population studies. Additionally clinical samples vary, from those recruited from memory clinic settings to outpatient geriatric rehabilitation settings, in which there is high medical co-morbidity. There are few community based studies and even fewer that are both community based and longitudinal, such as the Rotterdam scan study (Naarding et al., 2007). The relative benefit of using a longitudinal method was demonstrated quite clearly in the study by Lyness et al. (1999), in which they found no cross sectional relationship between vascular risk and depression but a year later in that same patient population (Lyness et al., 2000) found that baseline vascular risk was a significant predictor of depression. Samples also vary greatly in terms of size, and many smaller studies do not have the power to detect relationships, particularly to examine individual vascular risk factors rather than a cumulative risk index.

Conversely many studies acknowledge performing numerous analyses on relatively small samples, risking type I errors.

The role of cognitive impairment in the vascular depression hypothesis

Cognitive impairment has largely been overlooked or factored out, rather than considered as a key component of the vascular depression hypothesis (Mast, Yochim, MacNeill, & Lichtenberg, 2004). Krishnan et al. (1997) used a MMSE cut-off of 26, and found no differences in apathy among patients with compared with those without MRI-defined vascular pathology. Miller et al. (2002) excluded patients with an MMSE < 27/30 and subsequently found no evidence of psychomotor retardation in depressed patients with vascular risk factors as opposed to those without. In their effort to reduce the 'confounding' variable of cognitive impairment, these authors may have unwittingly selected a group of depressed patients with less severe frontostriatal dysfunction, i.e. those whose impairment is not severe enough to produce cognitive impairment. This possibility was acknowledged by Miller et al. (2002). Because of the concern raised above, and with particular reference to the inconsistency of findings in the relationship between vascular risk factors and depression, Mast et al. (2004) set out to test whether executive dysfunction perhaps moderated this relationship. They found that patients with poorer scores on the initiation-perseveration (IP) subscale of the Mattis Dementia Rating Scale (MDRS; Mattis, 1988) together with a higher number of vascular risk factors had worse depression scores than those with better scores on the MDRS and fewer vascular risk factors. There was a significant interaction effect between IP scores and vascular risk, suggesting a possible reason for some of the negative findings in the literature.

The lack of emphasis on cognitive functioning within the field is surprising given fairly widespread acceptance of the role of frontostriatal pathways in mood regulation (Alexopoulos, 2003; Tekin & Cummings, 2002). Frontostriatal dysfunction is thought to underlie both executive dysfunction and depression, not only in vascular dementia, but also Parkinson's disease, Huntington's disease and HIV-related cognitive disorders (Tekin & Cummings, 2002). A number of studies detail a relationship between vascular risk factors and cognitive impairment. For instance, in the Framingham heart risk study ($N=198$), Smith et al.

(2007) found that diabetes, hypertension and smoking were associated with worse performance on tests of executive functioning in middle-aged and older patients with major depressive disorder. Similarly, in a large ($N= 10, 963$) study investigating atherosclerosis risk in middle-aged participants, Knopman and colleagues (2001) found that declines in cognitive performance over a 6-year period were greater in participants with diabetes, hypertension and stroke than those without such vascular risk factors. These authors noted however that the declines themselves were small and not clinically significant. Sheline et al. (2006) demonstrated that depression and vascular risk factors were both independently related to executive function and processing speed. Further analysis revealed that processing speed mediated the relationship between vascular risk and executive functioning, and thus concluded from their findings that processing speed is a core feature of late life depression, underlying other cognitive deficits . Finally Sanders et al. (2006) found that vascular risk factors were associated with the MDRS IP score and part A of the Trail Making Test (Reitan, 1993), after controlling for medical burden.

Rationale and goals for study

This research is bounded by the protocol adopted by the Memory Clinic at Groote Schuur Hospital, and the data captured according to that protocol. It is cross-sectional in nature, and sample size is limited by the number of patients captured into the Clinic database as at December 2008. Nevertheless this study aims to contribute to the field in the following manner:

1. This is the first South African study in the field of vascular disease and depression. The lack of non-Western samples in the literature is a gap that requires filling, particularly in the light of poor control of vascular risk factors in resource-poor countries such as South Africa. In this country access to primary health care remains a challenge, with poverty, transport difficulties, long queues and language barriers as well as poor education all contributing to poor compliance with medication for high blood pressure, diabetes and high cholesterol.
2. This study includes measures of cognitive, particularly executive functioning, as an integral part of the vascular depression investigation. Not only does this make theoretical sense but findings of a relationship between executive function and

vascular risk suggest that a brief cognitive screen may be a useful tool to support a suspected diagnosis of vascular depression where MRI is not indicated.

Hypotheses to be tested

The first specific hypothesis to be tested is that in the sample of older adults, higher vascular risk factor scores will be associated with:

1. More depression and
2. A particular depression profile, i.e.
 - a. More symptoms of impairment on 'motivational' items, namely retardation, loss of interest, and loss of energy, as measured by the Cornell Scale for Depression (CSD; see Appendix 1)
 - b. Less 'ideational' disturbance, such as sadness, loss of self esteem and pessimism, as measured by the CSD;

The next specific hypotheses to be tested are that in the sample of older adults, higher vascular risk factor scores and depression will be associated with:

3. Lower scores on the Bristol Activities of Daily Living Scale (BADLS, Bucks, Ashworth, Wilcock and Siegfried, 1996; see Appendix 2), indicating greater functional impairment;
4. Poorer performance on measures of executive function; specifically
 - a. Poorer completion times on the Trail Making Test part A, indicating greater psychomotor slowing;
 - b. Poorer completion times on Trails B, indicating impairment in cognitive flexibility;
 - c. Poorer performance on a category fluency task, suggesting poorer motivation and persistence and increased apathy;
 - d. Poorer scores on the CLOX1 (Royall, Cordes & Polk, 2005), which measures executive control more broadly;
 - e. Greater difficulty on tasks measuring initiation and perseveration, this includes two of Luria's motor sequencing tasks, and two of Luria's recursive figures.

METHOD

Subjects

Participants in this study were enlisted through the Groote Schuur Hospital Memory Clinic, a tertiary hospital service linked to the University of Cape Town. The Memory Clinic serves the greater population of Cape Town and provides data for the Albertina and Walter Sisulu Institute for Ageing in Africa (IAA). This database is a source from which researchers can examine the presence and characteristics of dementing illnesses in a South African population. A standard research protocol was implemented at the clinic from 2003, and participants for this study represent those enrolled in the database during the period January 2003 through December 2008. The initial patient interview and assessment comprises a detailed demographic and health questionnaire, a physical examination, and a number of cognitive and behavioural tests and scales that are described in more detail below. The data has been collected over this time period by numerous clinicians and researchers including myself.

Ethical Considerations

Ethical approval for the collection and use of the research data obtained from the GSH Memory Clinic population was obtained from the University of Cape Town's Faculty of Health Sciences. Patients attending the Memory Clinic give consent for their information to be used for research purposes. All participants are assured of confidentiality and no names were used in this research. There are no risks to the patient in allowing their data to be kept in the database as this information is not shared with any other agency. There is no impact on treatment and there are no benefits to the patient in return for consenting to have their information captured in the Memory Clinic database.

Sample Demographics

The Memory Clinic database contained information for 360 patients at the cut-off date of 16 December, 2008. Patients with sensory impairment were excluded; 39 patients for faulty vision and 33 for faulty hearing (six had both). Two records were omitted as they had only a record number and no further data. This left a sample of 281 patients for further analysis. A

minority ($n=26$) of participants in the study were aged under 55 and were excluded, as this study is concerned with investigating vascular risk and depression in older adults rather than the general population. Of the remaining sample of 255 patients, a further 73 patients were excluded on the grounds of moderate to severe cognitive impairment ($MMSE < 17$), and another 26 were excluded on the grounds that they could not complete the MMSE. An MMSE cut-off score of 17 was used so as not to exclude patients with some cognitive impairment due to vascular disease, as one of the main premises of the vascular depression hypothesis is that such patients have higher levels of cognitive impairment (Alexopoulos et al., 1997). This left a final sample for analysis of 160 patients.

A decision was taken not to exclude patients on the basis of other dementia diagnoses, for example dementia of the Alzheimer's type. This decision was made partly due to the fact that there are only consensus conferences for some patient's diagnoses, radiological data is also only available for some patients, and the Memory Clinic does not have the facility for neuropathological confirmation of diagnosis. Another important and related consideration is that vascular disease overlaps considerably with other dementias, particularly with advancing age. At least one-third of patients who present at autopsy with AD pathology, have concomitant vascular disease (Fernando & Ince, 2004; Korczyn, 2005). In summary, regardless of whatever other pathological process may be underway, it remains of interest whether depression in the presence of vascular risk factors has a specific symptom profile, as well as a significant influence on cognitive and functional impairment.

Measures

It is important to emphasize at the outset that these measures were not chosen specifically for this study, and this study's aims and hypotheses were constrained by the data available. These measures were chosen by the IAA team for the Memory Clinic, after reviewing measures used in other memory clinics worldwide. These measures were created with English-speaking, Westernised populations in mind, whereas the GSH Memory Clinic population is linguistically and culturally diverse. Notwithstanding the above, although most clinic patients speak Afrikaans as a first language, most are able to converse in English, and these measures are regularly used in both research and clinical practice in South Africa. A review is held

from time to time with clinicians and researchers that administer the memory clinic battery, to ensure that the measures contained therein have face validity in our current setting. Items that are consistently poorly understood by respondents may therefore have been amended.

Because the Memory Clinic battery is an evolving instrument, not all the tests and scales that are currently used have been in use since the outset. Thus the data for the trail making test for example is only available for the past two years, and letter fluency for the past few months, whereas data is available for most other measures used in this study for the past 6 years.

There are still some domains that the Memory Clinic battery does not yet fully cover. Variables of interest to this study that have been used by other researchers but that were not available in the database include time of onset of depression, family history of depression, history of stroke or surgery for vascular disease. In addition, the assessment battery does not include any scales to assess cumulative burden of illness. Finally, as previously discussed, there are seldom radiological investigations carried out among this patient population, therefore it has not been possible to examine MRI or CT evidence of vascular lesions for this patient sample.

Assessment of depression

The Cornell Scale for Depression (CSD; Alexopoulos, Abrams, Young and Shamoian, 1998) is a widely-used measure of depression originally designed for use in elderly patients with dementia (refer to Appendix 1). It is administered by a clinician using information from both the patient and a caregiver, and consists of 19 items each relating to a symptom that must be rated as absent, mild, severe or unable to be evaluated. The CSD assesses symptoms from five domains – four mood related symptoms, four behavioural, three physical, four relating to cyclic functions and four relating to ideational disturbance. The CSD has been validated on a variety of patient populations and found to be equally valid in both demented and non-demented elderly (Korner et al., 2006). A higher score indicates more depressive symptoms.

Functional Assessment

The Bristol Activities of Daily Living Scale (BADLS; Bucks, Ashworth, Wilcock and Siegfried, 1996) was designed as a carer-rated instrument, measuring 20 different daily living abilities (refer to Appendix 2). It was designed as a rating scale for use in patients with dementia that is quick to administer, and comprises items that measure both basic and instrumental activities of daily living (basic or BADL items being those relating to activities such as feeding and toileting, and instrumental or IADL items relating to higher-order functions such as shopping or managing one's own financial affairs). A higher score indicates more impairment. The BADLS has been shown to correlate well with cognitive change over time in dementia patients (Byrne et al, 2000).

Vascular Risk Factors

This is an area that has, as discussed earlier, varied widely in research into the vascular depression hypothesis, as has been discussed earlier. Vascular risk factors in this study are determined by the research protocol, and are self- or carer-reported presence of risk factors. The risk factors included are diabetes, heart disease, hypertension, claudication, hypercholesterolemia, atrial fibrillation, and smoking.

Physical measures

This category refers to clinician-observed vascular disease and includes evidence of atherosclerosis, evidence of heart disease, evidence of valvular heart disease, evidence of cardiomyopathy, and presence of significant arrhythmias.

Screening for dementia

Mini-Mental State Exam (MMSE; Folstein, Folstein and McHugh, 1975).

The MMSE is a brief cognitive screening tool developed for the assessment of cognitive status. A cut-off of 24 is generally considered to indicate clinically significant cognitive impairment. The test takes less than 5 minutes to administer and provides a useful measure particularly for screening dementia of the Alzheimer's type. It is weighted toward more posterior cortical impairment rather than executive functioning, and for this reason, in studies in vascular dementia and depression, in which frontal-subcortical circuits are implicated, the

MMSE is usually supplemented or replaced with tests that tap executive functioning (Roman et al., 2002). For the purposes of this investigation its chief function was to assist in screening out patients with moderate and severe cognitive impairment. A cut-off of 17/30 was therefore used in accordance with the original study by Alexopoulos (Alexopoulos et al., 1997).

Tests of Executive Function

The Memory Clinic screening procedure includes a battery of neuropsychological tests that cover the domains of memory, language, visuo-spatial functioning, attention and executive functioning. This test battery takes approximately an hour to complete, and is administered by trained neuropsychologists. In accordance with the literature on vascular depression and vascular dementia, the focus of this investigation is on performance on tests of executive functioning. These tests are discussed below:

The *Trail Making Test* (TMT) was originally adapted for use part of the Army Individual Battery by Reitan in 1944 and now forms part of the Halstead-Reitan neuropsychological test battery (Reitan, 1993). It is a widely used measure of executive functioning, and is divided into two parts. Part A measures sustained attention, speed of visual processing, and sequencing abilities, while the more complex part B assesses the above together with response inhibition and mental flexibility. In part A, a series of numbers from 1 to 25 is distributed across an A4 page, and the respondent is required to connect the numbers in sequence with a pencil. In part B, there are both numbers and letters distributed across the page, and the respondent is required to join the letters and numbers in alternating sequence (e.g. 1-A, 2-B, etc). The test is timed, and time and number of errors may both form part of the scoring process (Strauss, Sherman, & Spreen, 2006). Errors are pointed out by the examiner, noted, and the patient instructed to continue, in accordance with the scoring method introduced by Reitan (Lezak, 2004).

Verbal fluency

The neuropsychological battery includes two tests that assess word generation. Participants are required to complete both a phonemic and a semantic fluency task. In the former, participants are required to list as many words as they can think of that begin with a particular

letter of the alphabet. In the latter participants must list as many animals and supermarket items as they can generate in a minute. Elderly controls should generate 12-16 words per letter for the phonemic fluency task and around 18-20 words for the semantic fluency task (Lezak, 2004). Unfortunately the test of phonemic fluency has been only recently introduced to the Memory Clinic test battery and so there are insufficient data to examine this at this stage.

CLOX (Royall, Cordes, & Polk, 1998)

The CLOX was designed as a test to discriminate between constructional difficulties of an executive nature and those of a visuo-spatial nature, thus helping to distinguish patterns of dementing processes. It has high inter-rater reliability and is strongly associated with other cognitive measures. The first part of the test (CLOX 1) reflects performance on an unstructured task, in which the patient is instructed to draw a clock, set to a specified time, on a blank piece of paper. In the second part (CLOX2) the examiner draws a clock face onto a pre-printed circle, with the patient watching, placing the numbers in an ordered sequence and setting the hands to reflect the same time as in the first task. The patient is then instructed to copy the examiner's example directly alongside it. Patients with executive dysfunction are expected to perform poorly on the unstructured CLOX1 but perform better on the CLOX2 copy task (Royall et al., 1998).

Luria manual sequencing task.

This involves a three-step series of hand movements that tap the ability to copy and persist on a motor task. Difficulties with this task may be a result of poor planning and execution abilities associated with the dorsolateral frontal circuit, but may also result from poor motivation and persistence associated with the anterior cingulate circuit. (Tekin & Cummings, 2002). Scoring is 2 for normal, 1 for borderline, and 0 for an abnormal performance.

Luria Recursive Figures

This test involves the continuation of two sequences, the first alternating triangles and squares, the second a series of loops. Perseveration may take the form of extra loops or

missed alternations. Scoring is 2 for a completely correct sequence to 0 for two or more perseverative errors.

Procedure

The Memory Clinic data were stored in numerous separate tables, from which variables of interest were extracted to create a dataset which could be exported to a spreadsheet package. From this, a number of derived variables were created. These variables are:

VascRisk: This is an index of self-reported cumulative vascular risk including the seven variables hypertension, diabetes, atrial fibrillation, hypercholesterolemia, heart disease, claudication and smoking (in the past 5 years). A minimum score of 0 indicates no vascular risk factors, and there is a maximum score of 7.

PhysEvHD: An index of cumulative heart disease variables from a physical examination of the patient, including evidence of atherosclerosis, heart disease, valvular heart disease, significant arrhythmias and cardiomyopathy. The minimum score is 0 and the maximum 5.

PrimReflexSum: These are reflex actions evident in infancy but not neurologically intact adults, as they are inhibited by intact frontal lobe functioning. A composite sum of 5 primitive reflexes; grasp, sucking, snout, palmar and glabellar tap. The minimum score is 0, and the maximum 5.

IPSum: A sum of the values of the two Luria motor sequencing tasks and the two Luria recursive figures, providing an additional measure of executive function designed to elicit difficulties with initiating and sustaining tasks and with perseveration. The minimum score is 0 and the maximum 4. A score of zero indicates maximum impairment.

AgeCat: Patients were assigned to age bands, for those under 50 years of age, between 50-59, 60-69, 70-79, and those 80+ years of age.

Data Analysis

All statistical analyses were performed using the software package Statistica version 8 (Statsoft, 2008).

The first hypothesis relates to the relationship between vascular risk factors as assessed by the cumulative risk factor index, and depression as assessed by the CSD total score. To test this relationship, a Pearson's product-moment correlation was performed.

The second hypothesis relates to the relationship between vascular risk factors and a specific profile of depression (more motivational and fewer ideational features). In order to test this, basic correlations were performed between three Cornell scale variables identified as 'motivational', namely retardation, loss of energy, and lack of interest and the cumulative vascular risk index. Similarly basic correlations were used to analyse the relationship between the vascular risk index and the three Cornell scale variables identified as 'ideational' features, namely pessimism, sadness, and loss of self-esteem.

The third hypothesis relates to the relationship between vascular risk factors and depression on the one hand and functional impairment as assessed by the BADLS on the other. To test this hypothesis, a multiple regression was performed with BADLS score as the outcome variable, and CSD score, vascular risk index and the heart disease index variable as predictors. The heart disease index was included as a predictor as it was felt it may contribute a measure of more severe vascular disease. The predictor variables of vascular risk, heart disease and depression were entered into this and subsequent regression models simultaneously because the vascular depression hypothesis is concerned with their simultaneous or combined contribution to functional and cognitive impairment in older adults. It was unfortunately not possible to examine separately the contribution of the predictor variables to basic (BADLS) and instrumental activities of daily living (IADLs), as the database provides only a total score. Most of the ADL scale items (12 out of the 17 items) measure basic ADLs and only 5 measure instrumental ADLs, so the instrument taken as a whole is weighted toward basic ADL's.

The fourth hypothesis relates to the relationship between vascular risk factors and depression, and executive functioning. Executive function comprises a collection of different abilities; with no one test capturing all these abilities. Therefore to test the 5 hypotheses that predict more executive impairment in the presence of vascular risk factors and depression, separate

multiple regression analyses were used, with the executive function measure as the outcome variable, and CSD score, vascular risk index and the heart disease index variable as predictors.

The following post-hoc analyses were also performed; ANOVA was used to examine the spread of vascular risk by age band. Pearson's correlations were used to examine the relationship between individual items of the Cornell depression scale and vascular risk index. Pearson's correlations were also used to examine underlying relationships between CSD score, BADLS score, MMSE score, vascular risk index, heart disease index and primitive reflexes. Finally point-biserial correlations were performed between each of the binary vascular risk variables and the CSD total score, in order to determine which of the vascular risk factors was independently associated with depression.

The significance level for all statistical analyses was set at .05. The following regression diagnostics were performed for all 6 multiple regression analyses: casewise diagnostics, tolerance, Cook's distance, Durbin-Watson test, and Mahalanobi's distance. For all the analyses, these values were within specified recommended ranges.

RESULTS

Descriptive Statistics

As noted earlier, the final sample comprised 160 patients (97 females and 63 males) who were aged 55 and over and who scored 17 or more on the MMSE. The demographic and clinical profile of this sample is presented in Table 1.

The youngest person in the sample was aged 55 and the oldest 88. With regard to education, most participants had completed between 8 and 11 years of schooling (only education range is captured, not number of years; the median and modal values were also in this range). Given South Africa's past education and other government policies which discriminated against people classified as 'non-white' and which forced many school-age children to find employment, the typical user of memory clinic services is better educated than the average person of their racial and ethnic background.

As can be seen in Table 1, most of the participants were Coloured, and a significant proportion were White. This is somewhat reflective of the racial mix in the Western Cape but Black African patients are under-represented in the sample at only 3.1%. compared with census data indicating 26.7% of the Western Cape population are Black African (Statistics South Africa, 2001). There were more females than males in the sample (97 females, 63 males), but amongst those with a Cornell depression score of 8 or more (indicating clinically significant depression symptoms), there were not significantly different numbers of males and females (28 male, 35 female, $X^2=0.77$, $p =0.37$). The average Cornell scale score in the sample was 7.5. The average MMSE score was 24, which is expected given this is a memory clinic sample.

With regard to vascular risk factors, Table 1 shows that 49 patients (30%) had no vascular risk factors and 111 (70%) had at least one risk factor. 42 patients had one. The spread across the different vascular risk factors is shown in Table 3. Table 2 shows means, standard deviation and ranges for all variables used in the multiple regression analyses.

Table 1:

Demographic and clinical characteristics of the final sample (N=160)

Variable	
Age (years)	70.80 (7.82)
Race	
Coloured	103 (64.00%)
White	48 (30.00%)
Black African	5 (3.10%)
Indian	3 (1.80%)
Other	1 (0.62%)
Vascular Risk Factors	
None	49 (30.00%)
One	42 (26.00%)
Two	36 (22.50%)
Three	20 (12.50%)
Four	10 (6.25%)
Five	2 (1.25%)
Six	1 (0.62%)
Seven	0 (0.00%)
Depression (CSD score $\geq 8^a$)	
Women	35 (55.00%)
Men	28 (45.00%)

Note. For the variables Age and Education, means are presented with standard deviations in parentheses. For the other variables, raw numbers of participants are presented with corresponding percentage of the sample in parentheses.

^aScores above 8 on the Cornell Scale for Depression suggest the individual experiences clinically significant depressive symptoms.

Table 2:

Valid N, Means, standard deviation and range of outcome variables used in the regression analyses

	Valid N	Mean(SD)	Range
BADLS	155	7.05(7.72)	0-40
Category Fluency	157	9.37(4.43)	0-29
CLOX1	155	10.10(3.26)	0-15
LuriaRecur1	155	1.44(0.81)	0-2
LuriaRecur2	155	1.25(0.90)	0-2
Luria 1	155	1.82(0.48)	0-2
Luria 2	155	1.03(0.85)	0-2
Trails A Time	84	85.2(50)	27-240
Trails B Time	76	201(54)	70-240

Note: where values are blank, they are excluded, which accounts for the fact that not all values have a total N of 160.

Table 3:

Distribution of vascular risk factors within the sample

	Present	Absent
Diabetes	39 (24%)	120 (76%)
Heart Disease	41 (26%)	118 (74%)

Hypertension	96 (60%)	63 (40%)
Claudication	15 (9%)	144 (91%)
Hypercholesterolemia	31 (20%)	127 (80%)
Atrial Fibrillation	7 (4%)	152 (96%)
Smoking	38 (24%)	121 (76%)

Hypotheses tested

Hypothesis 1: Relationship between vascular risk and depression

The first prediction was that there is a relationship between the cumulative vascular risk index and the Cornell Scale for Depression. A Pearson's correlation ($r = 0.23$, $p = 0.003$) confirmed this hypothesis, indicating depression and vascular risk are indeed associated.

To examine whether this relationship was still significant after taking into account age and functional impairment, a multiple regression was performed, with vascular risk, age and BADLS as the predictors and Cornell score as the outcome variable. The results of this analysis showed that vascular risk remained significantly associated with depression ($\beta = 0.24$, $p = 0.001$) after controlling for age ($\beta = -0.26$, $p = 0.001$) and ADL's ($\beta = 0.1$, $p = 0.1$). The overall model was also significant (adjusted $R^2 = 0.10$, $p = 0.0002$).

Because the relationship between depression and vascular risk factors was found to be significant, it was of interest which risk factors are associated with depression and which not. Point-biserial correlations were performed between depression and each of the binary vascular risk variables, in which significant relationships were found between depression and diabetes ($r = 0.19$, $p = 0.01$), and depression and heart disease ($r = 0.2$, $p = 0.009$), and a trend between depression and raised cholesterol ($r = 0.14$, $p = 0.07$) and depression and claudication ($r = 0.15$, $p = 0.051$). There was no relationship between depression and

hypertension ($r = 0.05, p = 0.4$).or between depression and smoking ($r = 0.09, p = 0.4$), or atrial fibrillation ($r = 0.03, p = 0.7$).

To summarise, vascular risk factors were associated with depression even after controlling for age and functional impairment, and of the individual vascular risk factors, only diabetes and heart disease were independently associated with depression.

Hypothesis 2: Vascular risk and depression associated with more 'motivational' and fewer 'ideational' symptoms of depression

The first prediction related to this hypothesis is that patients with more vascular risk factors would exhibit more 'motivational' features of depression. More specifically, those individuals with more vascular risk factors would be more likely to endorse CSD items related to retardation, lack of energy and loss of interest. As Table 4 shows, this prediction was partially confirmed; Pearson's correlations showed that the CSD item related to loss of interest was the only one not statistically significantly associated with vascular risk factors.

The second prediction related to this hypothesis is that patients with vascular risk factors would exhibit fewer of the ideational features of depression. More specifically those individuals with more vascular risk factors would be less likely to endorse CSD items related to sadness, pessimism and loss of self-esteem. Contrary to predictions, Pearson's correlations showed these patients exhibited significantly *more* sadness and pessimism and were not significantly different in terms of poor self-esteem.

The hypothesis of a specific depression profile for patients with vs. those without vascular risk factors was therefore generally not upheld, as shown in Table 4. The data indicate that vascular risk is associated with both increased vegetative and increased ideational features of depression.

Also of interest in terms of the relationship between CSD items and vascular risk factors was the association between cyclical sleep functions and vascular risk (See Appendix 1, items 12-

15). As shown in Table 4, Pearson's correlations showed significant relationships between vascular risk and sleep onset difficulty, multiple awakenings, and early morning awakenings. There were no CSD items that were significantly *less* frequently endorsed in the presence of vascular risk factors. The above findings serve to reinforce the finding of more severe depression in the presence of vascular risk as demonstrated by hypothesis 1.

Table 4:

Cumulative Vascular risk and relation with individual Cornell items

Overall CSD score	$r = 0.23$	$P = 0.003^{**}$
Motivational items		
Retardation	$r = 0.18$	$p = 0.026^*$
Loss of interest	$r = -0.10$	$p = 0.218$
Lack of energy	$r = 0.17$	$p = 0.038^*$
Ideational items		
Sadness	$r = 0.22$	$p = 0.009^{**}$
Pessimism	$r = 0.18$	$p = 0.033^*$
Poor self esteem	$r = 0.09$	$p = 0.262$
Sleep items		
Multiple awakenings	$r = 0.23$	$p = 0.005^{**}$
Sleep onset difficulty	$r = 0.20$	$p = 0.018^*$
Early morning awakening	$r = 0.25$	$p = 0.002^{**}$

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Hypothesis 3: Patients with more vascular risk and depression will be more functionally impaired

The prediction here is that patients with more vascular risk factors, evidence of heart disease¹ and depression as measured by the CSD, will obtain a higher score on the BADLS, indicating more functional impairment. Multiple regression analysis showed that BADLS was not significantly predicted by depression ($\beta = 0.04, p = 0.57$), vascular risk ($\beta = -0.06, p = 0.48$), or evidence of heart disease ($\beta = 0.12, p = 0.15$), neither was the overall model significant (adjusted $R^2 = -0.004, p = 0.50$). This analysis suggests that a combination of depression and vascular risk factors do not play a significant role in performance of activities of daily living.

Hypothesis 4: Patients with vascular risk and depression will show more impairment on tests of executive function.

The results of 5 separate multiple regression analyses are shown in Table 5. Each of these analyses is discussed in more detail below.

Table 5:

Multiple regression: influence of depression, vascular risk and heart disease on cognitive variables

	Depression		Vascular Risk		Heart Disease		Overall Model	
	B	<i>p</i>	β	<i>p</i>	B	<i>p</i>	R^2	<i>p</i>
Trails A (<i>N</i> =84)	-0.05	0.6	0.06	0.57	-0.09	0.44	-0.02	0.82
Trails B (<i>N</i> =76)	-0.06	0.6	0.10	0.42	-0.12	0.3	-0.02	0.68
CLOX1 (<i>N</i> =156)	-0.004	0.95	0.05	0.54	-0.26	0.002**	0.04	0.02*

¹ Heart disease was associated with age ($r = 0.23, p = 0.004$) and vascular risk ($r = 0.31, p = 0.001$)

IPSum ^a	-0.02	0.73	0.03	0.66	0.03	0.70	-0.01	0.9
(N=160)								
Category	-0.08	0.28	-0.019	0.82	0.06	0.44	-0.007	0.6
Fluency								
(N=152)								

* *Note:* for the above tests, a high score on Trails A and B indicate poor performance, whereas for the other three (Clox, IPSum and Category fluency) a high score indicates better performance; so for instance, the significant correlation between heart disease and CLOX1, is in the expected direction, i.e. more risk/disease correlates with worse performance.

^a IPSum indicates a composite initiation/perseveration variable

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

It was hypothesized that patients with depression and vascular risk factors would exhibit poorer completion times on the Trail Making Test part A, indicating greater psychomotor slowing. As Table 5 shows, multiple regression analysis showed that time to complete trails A was not significantly predicted by depression, vascular risk or evidence of heart disease; neither was the overall model significant. This analysis suggests that patients with depression and vascular risk factors do not display significantly slower processing speed.

It was hypothesized that patients with depression and vascular risk factors would take longer on Trails B, indicating impairment in cognitive flexibility. Multiple regression demonstrated that time to complete trails B was not significantly predicted by depression, vascular risk, or evidence of heart disease; neither was the overall model significant. This analysis suggests that patients with depression and vascular risk factors do not display significantly poorer cognitive flexibility. It should be noted that a strong floor effect was observed for Trails B; of the 76 patients that attempted trails B, only 28 were able to complete the task within the time limit of 4 minutes.

It was hypothesized that patients with depression and vascular risk factors would obtain poorer scores on the CLOX1, which provides a broad measure of executive control (Royall, Cordes & Polk, 2005). As shown in Table 5, multiple regression analysis showed that performance on the CLOX1 task was not significantly predicted by depression or vascular risk, however there was a significant effect for evidence of heart disease. The overall model was also significant. This analysis suggests that although vascular risk and depression are not sufficient to impact significantly on executive functioning, the presence of heart disease does play a role in executive functioning. Adding age to the model did not contribute significantly ($\beta = -0.14, p = 0.07$). However adding BADLS to the model made a highly significant contribution both individually ($\beta = -0.27, p = 0.0009$) and to the overall model ($R^2 = 0.12, p = 0.0002$). Evidence of heart disease still contributed significantly to the model after the inclusion of age and BADLS ($\beta = -0.21, p = 0.01$).

It was hypothesized that patients with depression and vascular risk factors would show poorer performance on category fluency tasks, suggesting poorer generativity and persistence and increased apathy. Multiple regression analysis showed that the number of generated words in the category fluency task was not significantly predicted by depression, vascular risk, or evidence of heart disease; neither was the overall model significant. This analysis suggests that patients with depression and vascular risk factors do not display significantly poorer functioning in the domains measured by this test.

The four tests that measure aspects of initiation and perseveration (Luria's motor sequencing tasks 1 and 2, and Luria's recursive figures tasks 1 and 2) were combined into a single outcome variable. It was hypothesized that patients with depression and vascular risk factors would exhibit more difficulty initiating and maintaining a sequence and a tendency to perseverate. Multiple regression analysis showed that scores on this composite variable were not significantly predicted by depression, vascular risk, or evidence of heart disease, neither was the overall model significant. This suggests that patients with depression and vascular risk factors do not display significantly worse on tasks measuring initiation and perseveration.

To summarise the results of the executive function tests, as depicted in Table 5, vascular risk factors and depression did not exert a significant influence on any of the executive function variables investigated. Physical evidence of heart disease had a significant influence on performance on only one of the tests, CLOX1. This hypothesis is therefore disconfirmed.

Additional analyses of interest

Relationships that have been assumed to underlie the data were tested using correlations. These are summarised in Table 6, and a comment on some of these relationships follows.

Table 6:

Correlations between key variables

	Age	BADLS	Vascular Risk	Heart Disease	MMSE
Age	-----				
BADLS	$r = 0.28$ $p < 0.001^{***}$	-----			
Vascular Risk	$r = 0.05$ $p = 0.4$	$r = -0.01$ $p = 0.9$	-----		
Heart Disease	$r = 0.23$ $p = 0.004^{**}$	$r = 0.12$ $p = 0.1$	$r = 0.31$ $p < 0.001^{***}$	-----	
MMSE	$r = -0.20$ $p = 0.01^*$	$r = -0.50$ $p < 0.0001^{****}$	$r = 0.15$ $p = 0.053$	$r = -0.07$ $p = 0.3$	-----
CSD	$r = -0.22$ $p = 0.006^{**}$	$r = 0.04$ $p = 0.6$	$r = 0.23$ $p = 0.003^{**}$	$r = 0.09$ $p = 0.23$	$r = 0.13$ $p = 0.09$

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$

As can be seen from Table 6, age is related in a linear manner with BADLS, MMSE, and evidence of heart disease, in line with expectations, and depression decreases with age, in line with the published literature (Alexopoulos, 2005). At first glance the relationship between age and vascular risk shows no relationship, which does not fit with expectations. An ANOVA was therefore used to examine relationships between all age bands (including those below 55) and vascular risk, which revealed a significant relationship, $F(4, 177) = 2.80, p = 0.02$. As depicted graphically in Figure 1, vascular risk sharply increases with age up to a point, and thereafter declines. It should be noted that the relationship between vascular risk and age only remains significant if all age bands are included; if one excludes the age band 30-60, there is no statistically significant relationship between vascular risk and age, $F(2, 143) = 0.48, p = 0.61$. In other words the decline post-age 60 is not statistically meaningful.

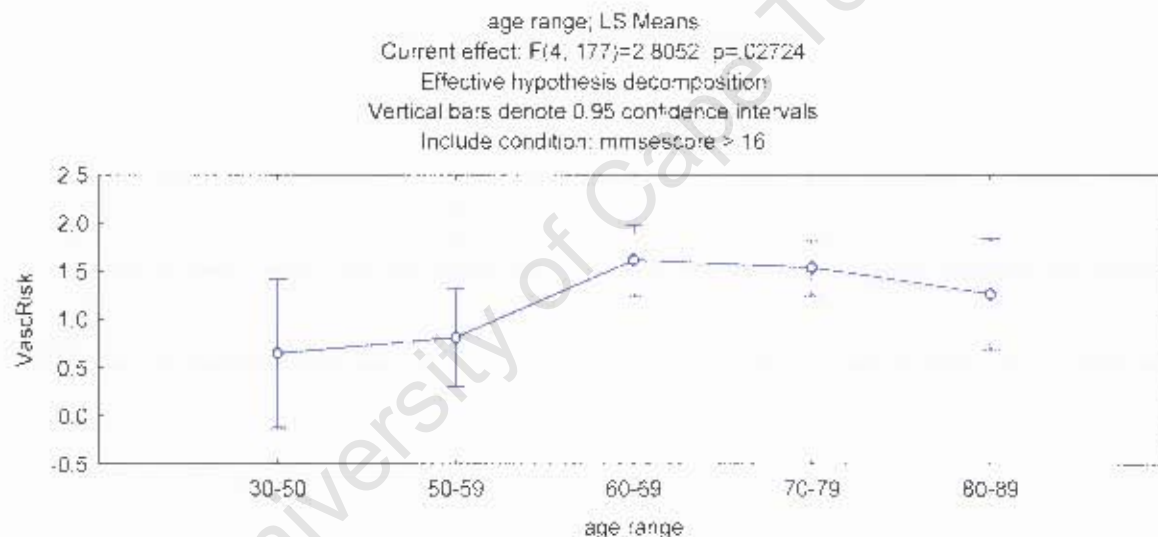
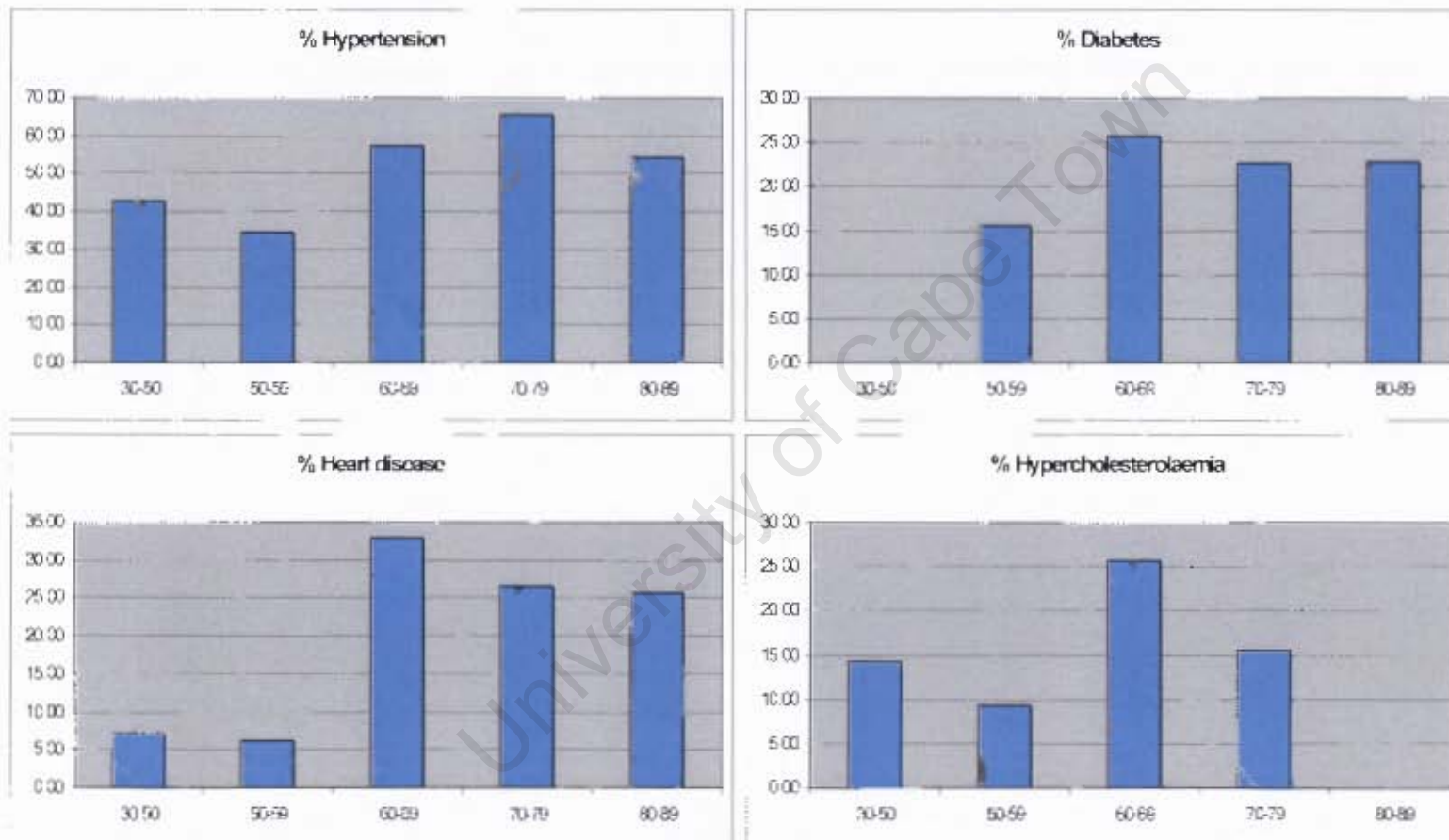


Figure 1: ANOVA age vs. Vascular Risk

It was nevertheless expected based on the extant literature that vascular risk factors would continue to increase through the age range 60 and above rather than experiencing a downward trend. For this reason, the relationship between age and vascular risk was interrogated further to see if any specific risk factors were responsible for this unusual pattern. To examine this, the number of patients with each risk factor within each age band, was converted to a percentage. As the graphs in Figure 2 illustrate, there is a tendency for increases up to a point, followed by slight declines in each of the risk factors at various points between the ages 60 and 90.

Figure 2: % Vascular risk factors within specified age bands



Relationships between functional impairment and other variables of interest

As expected, and shown in Table 6, there was a significant linear relationship between age and functional impairment as measured by the BADLS. A highly significant relationship was found between MMSE and BADLS scores. As an incidental finding, all of the above executive function tests were strongly correlated with ADL impairment; Pearson's correlations demonstrated relationships between BADLS score and trails A time ($r = 0.4, p < 0.001$), trails B time ($r = 0.35, p = 0.003$), CLOX1 ($r = -0.35, p < 0.001$), IPSum ($r = -0.4, p < 0.001$) and category fluency ($r = -0.24, p = 0.002$).

Primitive Reflexes

Other investigations of interest were that primitive reflexes were associated with MMSE score and with ADL score but not with depression or vascular risk.

DISCUSSION

The major focus of this thesis was to examine whether vascular risk factors and depression appear to confer greater functional and cognitive disability, and whether patients with vascular risk factors and depression present with a specific depression profile. If, as the vascular depression hypothesis proposes, we can identify patients at greater risk for treatment-resistant depression and vascular dementia on the basis of their clinical presentation, we can hopefully tailor treatment accordingly. The results obtained here suggest that although vascular risk and depression are related, a) vascular risk on its own does not appear to influence depression profile, and b) the combination of vascular risk and depression appear does not appear to have a significant influence on cognitive and functional ability.

A brief discussion follows exploring hypotheses supported, those not supported, and some other findings of interest to the field of late-life depression and vascular disease.

Hypotheses supported

Vascular risk and depression

The current data suggest that there is a relationship between vascular risk and depression, and that this relationship holds even after controlling for age and degree of functional impairment. This was a relatively strong finding given the fact that vascular risk factors included in this study do not include actual evidence of vascular disease (for example radiological evidence or history of vascular surgery). The current sample might thus include many patients at the milder end of the disease spectrum.

The current findings are in line with those reported in both longitudinal (Lyness et al., 2000; Mast et al., 2008; Zimmerman et al., 2008) and correlational studies (Kim et al., 2006; M. Krishnan et al., 2005; Sanders et al., 2006). Interestingly however, the current findings stand in contrast with a similar study with a UK-based Caribbean sample in which a relationship between vascular risk and depression was expected

based on high rates of vascular risk in that population, but none was found (Stewart et al., 2001).

In terms of the relationships between individual vascular risk factors and depression, statistically significant relationships were found between depression and a) diabetes and b) heart disease. A strong trend was shown for the relationship between depression and c) claudication and d) cholesterol. Depression was not however statistically significantly related to smoking, atrial fibrillation or hypertension. The sample size is too small to draw any conclusions regarding these separate relationships, nevertheless it was of interest to explore which of the individual vascular risk factors might be contributing to the positive relationship found between vascular risk and depression. The statistically significant relationship between depression and diabetes is in keeping with findings by Whyte (2004), Almeida et al. (2007) and Rajala et al. (1997), and the strong relationship between depression and heart disease is supported by the large cardiovascular health study (Steffens et al., 1999). Interestingly however, despite the fact that the self-reported vascular risk factor 'heart disease' was statistically significantly related to depression, the index measuring physical evidence of heart disease was not similarly related to depression. This is intriguing; at face value it suggests that the relationship between depression and heart disease may be at least partly mediated by the experience of being given a diagnosis of heart disease. This would be consistent with findings by Rajala et al. (1997), in which only diagnosed diabetes, as opposed to undiagnosed diabetes, was linked with depression.

With respect to the other individual risk factors examined, no previous studies in this field have specifically examined claudication as a vascular risk factor. The finding of no statistically significant relationship between depression and atrial fibrillation might be attributed to the fact that very few patients ($n=7$) in this sample presented with atrial fibrillation. On the other hand, the negative finding with respect to a relationship between depression and hypertension is in keeping with the results of a large longitudinal study by Cervilla et al. (2004), as well as studies by Whyte et al. (2004)

and Kim et al. (2006). Furthermore, although the relationship between smoking (as a vascular risk factor) and depression has not been specifically examined in many previous studies, the lack of statistical significant association found here is similar to that found by Almeida et al. (2007) and Whyte et al. (2004). The above pattern of relationships is therefore in keeping with the extant literature, and might be related to the fact that hypertension and smoking may be considered 'asymptomatic' vascular risk factors, whereas diabetes and heart disease might be expected to confer poorer quality of life, including significant depressive symptomatology.

Of relevance for the strength of the relationship between vascular risk and depression is the fact that both depression and vascular risk decrease after age 70 in this patient sample. As previously mentioned, the decrease in depression scores with age is consistent with the extant literature, but decline in vascular risk with age is not. In this regard, Nuyen et al. (2007) also documented a non-linear association between age, vascular risk factors and depression, with a strong link in the age group 50-69, but no relationship between vascular risk factors and depression after age 70. There is a possibility that in our sample of patients from a developing nation there is poor control of vascular risk factors, and that this poor control may have resulted in disproportionate attrition (due to mortality) of patients with a higher number of vascular risk factors.

Hypotheses not supported:

No specific depression profile

The current data suggest that a specific depression profile does not characterise those with vascular risk factors in late life. This study did show that there is more apathy and loss of energy in depression with vascular risk factors, as predicted, and in keeping with findings of Alexopoulos (1997) and Krishnan (2004). However, it also found more (rather than fewer) ideational features such as sadness and pessimism. Although this latter pattern has also been found in previous studies (Kim et al., 2006; Whyte et al., 2004), it is contrary to predictions derived from the vascular depression

hypothesis. Additionally, more cyclical sleep disturbance was reported. Because there were no CSD items endorsed less frequently in patients with vascular risk factors, but numerous items endorsed more frequently, the current findings are suggestive of a more severe depression where vascular risk is present, rather than any specific presentation of depression.

It was anticipated based on prior research (Mast, Yochim et al., 2004), that once a broader range of cognitive profile had been included there might be a specific profile of depression emerging. The reason for this was that in excluding patients with more cognitive impairment, it was felt it was possible that patients with less characteristic 'vascular' depression were being investigated. This in turn was on the basis of findings by Alexopoulos et al. (1997) that patients with vascular depression have more cognitive impairment. Because this study did not demonstrate a relationship between self-reported vascular risk factors and cognitive impairment, this hypothesis was unsupported. This obviously does not rule out the possibility that where there is evidence of cognitive impairment in the presence of vascular *disease*, there might be a specific depression profile. Vascular dementia in particular is reportedly associated with significant amotivational symptoms (Cummings et al., 1994; Kalaria, 2002; Li et al., 2001; Moretti et al., 2005; Schmidtke & Hull, 2005).

Vascular risk factors and depression are not associated with functional impairment

The current data suggest that vascular risk factors are not associated with significant impairment in activities of daily living (ADLs). The current study stands in contrast to that of Naarding et al. (2007), who found that patients with vascular risk factors were more impaired on Instrumental ADL's such as shopping and managing finances, but not basic ADL's such as feeding and transfers. In the same study, using a separate sample with slightly older patients, those with vascular risk factors were more impaired in both IADL and BADL functioning. It should be re-iterated here that it was not possible to examine the contributions of IADL and BADL separately in the current study. The findings also stand in contrast to those of Alexopoulos (1997) and Licht-Strunk et al. (2004); both of those studies documented a decline in ADL

associated with the presence of vascular risk factors. Importantly, however, those studies used a definition of vascular risk that included actual vascular disease (i.e., their patients are more likely than mine to have been drawn from a population at the severe end of the disease spectrum). In contrast with their findings, K. R. Krishnan et al. (2004) found no difference in ADL between patients with MRI-defined vascular depression (presence of subcortical infarcts) compared with patients with depression in the absence of vascular lesions. Their study excluded patients with MMSE < 24, and given our own findings demonstrating strong links between MMSE scores and ADL impairment, this perhaps explains why they obtained this pattern of data.

Vascular risk factors and depression are not associated with poorer executive functioning

This study provides no evidence to suggest that vascular risk factors and depression are associated with significant decline in executive functioning. This is in contrast to the findings of Smith et al. (2007), as well as Knopman et al. (2001) in which small but significant differences were found in executive functioning between depressed middle aged and older adults with and without vascular risk factors. A major difference is that the abovementioned studies are community-based, whereas the current study uses a memory clinic sample of older adults, in which there are high overall levels of cognitive impairment. The average MMSE of the current sample was 24, and the mean time to complete Trails A was 85 seconds, which falls around the 5th percentile, indicating abnormal functioning (Strauss et al., 2006). By way of contrast, the mean time to complete Trails A in the Smith et al. (2007) study was 28 seconds, which is in the normal range (90th percentile). Patients with other diagnoses such as stroke and dementia were not excluded from the current study because it was of interest whether vascular risk and depression confer any additional risk of cognitive impairment regardless of other diagnoses. The findings were that the combination of vascular risk and depression is insufficient to contribute significantly to variance in executive function. It is acknowledged that such effects would be more difficult to detect in the current sample.

The only statistically significant relationship between vascular risk factors and executive functioning was that between physical measures of heart disease and CLOX1 score. Scores on the CLOX1 have been shown to function as an indicator of overall executive functioning (Royall, Espino, Polk, Palmer, & Markides, 2004). This finding suggests that impairments in cognitive functioning may indeed arise when there is physical evidence of disease as opposed to just having risk factors for disease.

The current findings, then, suggest that vascular risk is not sufficient to cause clinically significant impairment in either executive functioning or activities of daily living; the contrast between these findings and those from previous work in the field suggest that vascular disease is required before deficits start to emerge. From this study, there is insufficient evidence to suggest concomitant impairment in either cognitive or ADL functioning at the 'risk' end of the spectrum.

Incidental Findings of Relevance/Interest

The finding that depression scores decrease with age is generally supported by the literature (Alexopoulos, 2005). It has been suggested however, that that late life depression may be under-recognised and under-treated due to reluctance on the part of this cohort to talk about depression, as well as time constraints on the part of general practitioners (Alexopoulos, 2005). Since all new patients at the GSH memory clinic undergo a standardised depression battery, it would appear that at least in this sample, the finding of decreased depression with age is not merely an artefact of under-reporting, as it might be in other samples.

Furthermore, because in the current sample the relationship between depression and age declined in a linear manner, this study did not support Alexopoulos' (2005) assertion that depression increases after age 75. A more pessimistic view might be that since depression has been prospectively associated with medical morbidity, particularly heart disease and stroke, that there are fewer depressed patients with advancing age due to disproportionate mortality amongst this group. Until follow-up

data becomes available within the Memory Clinic sample, this possibility remains open to question.

The current study also found very strong relationships between MMSE and ADL as well as between each of the measures of executive functioning and ADL. The MMSE was designed as an instrument to measure cognitive change over time, and to track the progression of dementia, specifically dementia of the Alzheimer's type. Since increased functional impairment is anticipated with progression of dementia, this relationship is therefore expected, but the strength of the relationship in the current data is quite striking. A PUBMED search of the literature yielded only one study specifically examining the relationship between MMSE and ADL (Ford, Haley, Thrower, West, & Harrell, 1996), and another comparing various dementia staging instruments including the MMSE and ADL scales (Juva et al., 1994). The paucity of research on this association is surprising given that the MMSE is such a well-used instrument.

The strong relationship between ADL functioning and executive impairment is consistent with findings that executive impairment is a strong predictor of functional impairment, regardless of etiology, and of overall cognitive status (Boyle, Paul, Moser, & Cohen, 2004; Chen, Sultzer, Hinkin, Mahler, & Cummings, 1998; Grigsby, Kaye, Baxter, Shetterly, & Hamman, 1998; Johnson, Lui, & Yaffe, 2007; Pereira, Yassuda, Oliveira, & Forlenza, 2008). If data had been available on IADL functioning in the current study it would have been interesting to examine whether any of the cognitive measures showed significant relationships with IADL, as certain executive function tests such as the CLOX1 have been shown to correlate with poor IADL functioning (Royall et al., 2004), independent of age and MMSE scores. The relationships between various cognitive measures and ADL scores point to the importance of controlling for ADL functioning when exploring relationships between cognitive impairment and variables such as depression.

Finally, the finding that primitive reflexes were not associated with either vascular risk or depression but were associated with both age and MMSE scores is consistent with the rest of the findings of this study, namely that the combination of depression and vascular risk is insufficient to assume an underlying disease process.

To summarise the above findings, it would appear that the combination of vascular risk and depression is insufficient to confer clinically significant impairment in cognitive and functional abilities, though the combination does appear to result in a more severe depression profile. The data do however demonstrate that heart disease is associated with poorer executive functioning, furthermore primitive reflexes, which is a marker of neurological disease, was associated with MMSE scores. Functional impairment is strongly linked with cognitive impairment in this model, but non-significant relationships between ADL and other variables of interest could be explained by lack of differentiation of basic and instrumental ADL's. The above findings suggest that there may be a threshold of severity of vascular burden before clinically significant symptoms become apparent. This is consistent with findings that the theoretical frameworks of 'Subcortical ischemic depression' (Taylor, Steffens, & Krishnan, 2006) or 'MRI-defined vascular depression' (K. R. Krishnan et al., 1997), i.e. radiological evidence of vascular disease, appear to delineate a group of patients with common clinical features more clearly than those using a vascular risk model. Similarly, a study by Sneed et al. (2008) demonstrated the ability to predict membership of a vascular depression group with near-perfect sensitivity and specificity on the basis of radiological findings. It would appear therefore that studies using patients with confirmed evidence of vascular disease appear to have produced more consistent findings than those using a vascular risk model.

Conclusions

This study provides no evidence to suggest that older adults with depression and vascular risk factors present differently in terms of depressive symptom profile, cognitive ability or functional status. It does provide evidence that vascular risk is associated with depression, as well as limited evidence that heart disease is associated

with cognitive impairment. As discussed above, one explanation is that these findings could be understood in terms of a spectrum of severity. Almeida (2008) points out that the majority of older adults in the general population have at least one vascular risk factor, particularly hypertension (In this sample 70% of participants had at least one vascular risk factor). This would mean that by far the majority of older adults presenting with depression and vascular risk factors would fit the 'vascular' depression label. This would give the diagnosis limited usefulness in terms of ability to predict prognosis and response to treatment.

A controversial possibility to consider is that there may be only a weak relationship between vascular risk factors and vascular disease. In this regard, Thomas et al. (2004) reported that they found more atheromatous disease and ischemic change in post-mortem depressed as compared with non-depressed patients but did not find any significant differences in vascular risk factors between these groups. Barnes et al. (2006) showed that despite the fact that MRI evidence of vascular disease increased the chance of developing MCI by 50-60%, the relationship between depression and cognitive impairment was independent of vascular disease. Furthermore, Salloway, Correia et al. (2002) found that the relationship between subcortical disease and depression was mostly explained by age (24% of variance explained), with vascular risk factors adding almost nothing to the model (0.2%). Finally, as discussed in the Introduction, it still cannot be stated with certainty whether white matter disease is related with vascular risk factors or what proportion of it is ischemic in nature.

The vascular depression hypothesis carries with it the theory that vascular disease may predispose, precipitate, or perpetuate depression in the elderly (Alexopoulos, 2003). This places vascular disease in a causal role with respect to late-life depression, with the underlying assumption that vascular disease results in damage to frontal-subcortical circuits responsible for mood regulation. There is at best mixed evidence for this proposition, as there are relatively few longitudinal studies examining baseline vascular risk factors and incident depression, and none that examine this relationship over a reasonably long time interval (10 years or greater). By comparison, there is a

large body of longitudinal evidence supporting a causal link between depression and later stroke, some with follow-up periods of as much as 29 years.

Despite the strength of some of these longitudinal findings, the mechanisms for the relationship between depression and vascular disease remain unknown. The relationships between depression and both cerebro- and cardiovascular disease have been shown to be stronger than those for other medical illness (Folstein et al., 1977; Taylor, McQuoid, & Krishnan, 2004), and the relationship between depression and vascular dementia stronger than that between depression and dementia of the Alzheimer's type (Li et al., 2001; Newman, 1999). Mosovich (2008) has postulated that there may be some common mechanism underlying both vascular disease and depression, possibilities being lifestyle factors (obesity, smoking, sedentary lifestyle); stress, which is linked to both depression and cardiovascular disease; a common genetic mechanism; or some kind of inflammatory process. These remain important avenues for longitudinal study.

Treatment implications

Although treatment outcome was not specifically addressed in this study, the results show negative findings with respect to the impact of vascular risk and depression on depression symptom profile, functional ability, and cognitive ability. The data does however suggest that depression may be more severe in the presence of vascular risk factors, and the fact that depression is more severe might be expected to influence response to treatment.

Literature reviews in the area of post-stroke and vascular depression often cite treatment studies as reporting poor outcome in patients with depression and vascular disease. It should be noted that this does not necessarily mean that the depression was unsuccessfully treated, but that greater medical morbidity and dementia may have resulted in patients with depression and vascular disease (Hickie, Scott, Wilhelm, & Brodaty, 1997; O'Brien et al., 1998). This is not always clear from the summaries of evidence provided but from the depressed patient's perspective, it remains an

important distinction, as depression is associated with significant reduction in quality of life (Firbank et al., 2005). According to Robinson (2003) both ADLs and cognitive functioning improve with antidepressant use post-stroke, and use of antidepressants is associated with increased survival at 5 years post-stroke. Steffens, Taylor, and Krishnan (2003) outlined the case of a 78-year-old woman with depression and vascular disease who went on to develop vascular dementia and congestive heart failure. The patient was initially treatment resistant, but with perseverance with a variety of different antidepressants, eventually obtained relief from her depressive symptoms despite worsening medical morbidity. This treatment regimen resulted in both improved quality of life and (together with donepezil) some improvement in cognitive functioning (MMSE increase from 16 to 21). Cases such as this provide useful insight into multiple perspectives on what constitutes 'successful' treatment.

What are the implications of findings in the vascular depression literature for clinical practice? The message that should be disseminated in general practice is that wherever there is severe depression, relief from depressive symptoms may take longer, may require augmentation with further treatment, or require shifts to alternative treatment. This should not lead to therapeutic nihilism, however, but rather to 'vigorous treatment and careful follow-up of such cases in clinical practice' (Baldwin & O'Brien, 2002, p. 159).

Limitations and directions for future research

This is the first study to examine vascular risk and depression in an elderly South African population. Although the current sample is not representative of the demographic of the country as a whole, it is a non-Western sample amongst whom vascular risk factors are thought poorly controlled. Furthermore, although the final sample size was relatively small ($N = 160$), it is comparable to the majority of studies in the field of vascular depression. Nonetheless, the small sample size limits the scope of data analysis, particularly with respect to the relationship between individual vascular risk factors and depression. The results of those analyses should be thus be treated with caution.

An important limitation of the study is that the data are retrospective and thus the way in which the data were captured and compiled was not designed to address any specific research question. Any conclusions are inevitably constrained by this fact. The characteristics of the database have therefore not permitted exploration of some of the hypotheses linked to the vascular depression model (e.g., the relationships between onset of depression and family history of depression, on the one hand, and vascular risk, on the other). The lack of information on co-morbid medical illness made it impossible to control for this important factor, as this would be expected to impact on quality of life.

The limitations of the way in which data were captured also made it impossible to examine relationships between separate components of ADLs, namely instrumental and basic ADL's, and their relationships with vascular risk factors and depression. The fact that this study has helped to identify these limitations in Memory Clinic data capturing and compilation means it has been exceptionally useful in terms of providing valuable information about the gaps in the research protocol used by the Clinic. A strong recommendation is that the research protocol be amended to address the identified limitations.

A further restriction provided by the research protocol is that the memory clinic neuropsychological battery began as a short assessment instrument, and has been gradually added to over time. For instance, measures such as the test of phonemic fluency and the Trail Making Test have only been added recently. As a result, data that may reflect subtle impairments in executive functions that are tapped by those tests (e.g., difficulties with cognitive flexibility and generativity) are not yet available in sufficient numbers. As this database grows, further possibilities for neuropsychological research on the Memory Clinic population will present themselves.

Given a) the strength of findings in prospective and longitudinal studies of depression and incident stroke, b) the very limited body of longitudinal data regarding vascular risk and incident depression, and c) outstanding questions regarding causality, it would follow that the gold standard for research in the field of vascular risk and depression should be prospective, longitudinal studies. As yet there are no follow-up data captured for Memory Clinic patients, so it is not possible to examine longitudinal relationships between vascular risk and incident depression, or between a combination of vascular risk and depression, and incident dementia. The examination of such relationships is an important direction for future research at the Memory Clinic.

Finally, the unavailability of radiological data to examine presence of subcortical ischemic vascular disease makes it difficult to draw conclusions regarding the relationship between vascular disease and depression. It would also be of interest to examine the strength of the relationship between vascular disease and vascular risk in a sample with poor control of vascular risk factors. Although unavailability of radiological data is a reality in a resource-poor environment such as the public health system in South Africa, it has been noted elsewhere that radiological investigation is unlikely to become a routine investigation in clinical practice in memory clinics (Licht-Strunk et al., 2004). Notwithstanding the above, in order to produce quality research in the area of geriatric psychiatry and dementia, resources need to be committed so that radiological investigations become a standard part of South African memory clinic protocol.

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Appendix 1: Cornell Scale for Depression

Unable to Evaluate	Absent	Mild or Intermittent	Severe
(U)	(0)	(1)	(2)

1. Mood related signs

1. Anxiety (anxious expression, ruminations, worrying)
2. Sadness (sad expression, sad voice, tearfulness)
3. Lack of reactivity to pleasant events
4. Irritability (easily annoyed, short-tempered)

2. Behavioural disturbances

5. Agitation (restlessness, hand-wringing, hair pulling)

6. Retardation (slow movements, slow speech, slow reaction)
7. Multiple physical complaints (score 0 of GI symptoms only)
8. Loss of interest (less involved in usual activities; score only if change occurred acutely, i.e. in less than one month)

3. Physical Signs

9. Appetite Loss (eating less than usual)
10. Weight loss (score 2 if greater than 2 kilos in one month)
11. Lack of energy (fatigues easily, unable to sustain activities; score only if change occurred acutely, i.e. in less than one month)

4. Cyclic functions

12. Diurnal variation of mood (symptoms worse in the morning)
13. Difficulty falling asleep (later than usual for this individual)
14. Multiple awakenings during sleep

15. Early morning awakening (earlier than usual for this individual)

5. Ideational disturbance

16. Suicide (feels life is not worth living, has suicidal wishes or makes suicide attempt)

17. Poor self esteem (self-blame, self deprecation, feelings of failure.

18. Pessimism (anticipation of the worst)

19. Mood-congruent delusions (delusions of poverty, illness or loss)

TOTAL SCORE (max 38)

Appendix 2: Bristol Activities of Daily Living Scale (modified)

Instructions: Encircle the response that best describes the patient's level of ability to perform that activity. Only one box should be marked for each activity. Where in doubt, choose the level of ability which represents the patient's average performance over the past two weeks

Scoring: Add encircled numbers for 17 activity domains (max score 51)

1) Food

- | | |
|---|---|
| a. Selects and prepares food | 0 |
| b. Able to prepare food only if ingredients are set out | 1 |
| c. Able to prepare food only if shown step by step | 2 |
| d. Unable to prepare food | 3 |
| e. Not applicable | 0 |

2) Eating

- | | |
|--|---|
| a. Eats as previously | 0 |
| b. Eats appropriately if food is made manageable and/or uses a spoon | 1 |
| c. Needs someone to help guide food to mouth | 2 |
| d. Needs to be fed | 3 |
| e. Not applicable | 0 |

3) Drink

- | | |
|--|---|
| a. Able to make tea/coffee as previously | 0 |
|--|---|

- | | |
|--|---|
| b. Able to make tea/coffee only if ingredients are set out | 1 |
| c. Able to make tea/coffee only if shown step by step | 2 |
| d. Unable to make tea/coffee | 3 |
| e. Not applicable | 0 |
| 4) Dressing | |
| a. Dresses as previously | 0 |
| b. Puts clothes on incorrectly or inappropriately | 1 |
| c. Unable to dress self but moves limbs to assist | 2 |
| d. Has to be dressed | 3 |
| e. Not applicable | 0 |
| 5) Hygiene | |
| a. Washes self as previously | 0 |
| b. Able to wash self if given soap, towel and water | 1 |
| c. Able to wash self but needs help | 2 |
| d. Has to be washed | 3 |
| e. Not applicable | 0 |
| 6) Teeth | |
| a. Cleans teeth as previously | 0 |
| b. Cleans teeth only if given water and toothpaste or gargle | 1 |
| c. Able to clean teeth but needs help | 2 |

- | | |
|---|---|
| d. Unable to clean teeth | 3 |
| e. Not applicable | 0 |
| 7) Toilet | |
| a. Uses toilet as previously | 0 |
| b. Able to use toilet (or bucket) if helped | 1 |
| c. Incontinent of urine | 2 |
| d. Incontinent of urine and faeces | 3 |
| e. Not applicable | 0 |
| 8) Transfers | |
| a. Able to get in/out of a chair as previously | 0 |
| b. Able to get in a chair but needs help to get out | 1 |
| c. Needs help getting in/out of a chair | 2 |
| d. Has to be lifted in/out a chair | 3 |
| e. Not applicable | 0 |
| 9) Mobility | |
| a. Walks independently | 0 |
| b. Walks with assistance, i.e. furniture, arm for support | 1 |
| c. Uses aid to walk, i.e. cane, frame | 2 |
| d. Unable to walk | 3 |
| 10) Orientation -- time | |

- a. Fully oriented to time/day/date etc. 0
 - b. Unaware of time/day/date but seems concerned 1
 - c. Repeatedly asks the time/day/date 2
 - d. Mixes up night and day 3
 - e. Not applicable 0
- 11) Orientation – space
- a. Fully oriented to surroundings 0
 - b. Orientated to familiar surroundings only 1
 - c. Gets lost in home, needs reminding where toilet is 2
 - d. Does not recognise own home 3
 - e. Not applicable 0
- 12) Communication
- a. Able to hold appropriate conversation 0
 - b. Understands others and tries to respond verbally with gestures 1
 - c. Can make self understood but has difficulty understanding others 2
 - d. Does not respond to or communicate with others 3
 - e. Not applicable 0
- 13) Telephone
- a. Uses telephone appropriately 0

- b. Uses telephone with help 1
- c. Answers telephone but does not make calls 2
- d. Unable/unwilling to use telephone 3
- e. Not applicable 0

14) Housework/gardening

- a. Able to do housework/gardening to previous standard 0
- b. Able to do housework/gardening but not to previous standard 1
- c. Limited participation in housework/gardening 2
- d. Unwilling/unable to participate in previous housework/gardening activities 3
- e. Not applicable 0

15) Shopping

- a. Shops to previous standard 0
- b. Only able to shop for 1 or 2 items without a list 1
- c. Unable to shop alone, but participates when accompanied 2
- d. Unable to participate in shopping even when accompanied 3
- e. Not applicable 0

16) Finances

- a. Manages own finances as previously 0
- b. Recognises money values and can sign name 1
- c. Does not recognise money values but can sign name 2

- d. Unable to sign name or recognise money values 3
- e. Not applicable 0

17) Transport

- a. Able to drive, cycle or use public transport independently 0
- b. Unable to drive but uses public transport, bike etc. 1
- c. Unable to use public transport alone 2
- d. Unable or unwilling to use public transport even when accompanied 3
- e. Not applicable 0

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