NUTRITIONAL FACTORS OF VASCULAR DEPRESSION

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MARTHA ELIZABETH PAYNE: Nutritional Factors of Vascular Depression
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Depression, the most common mental disorder, is the leading cause of years lived with disability and responsible for the majority of the more than 800,000 suicides annually. In addition, individuals with depression are more likely to have comorbid chronic diseases. Determination of dietary factors related to the incidence of late-life depression, presence of ischemic brain lesions, and depression outcomes is needed in order to characterize better the complex relationship between depression and vascular disease. Vascular nutritional factors (dietary attributes believed to either promote or prevent cardiovascular disease) were examined in three groups of elderly individuals: vascular depression, non-vascular depression, and comparison subjects. These same dietary factors were examined for their relationship to brain lesion volume in those with vascular depression. Dietary quality was assessed as a predictor of both depression outcome and lesion volume progression.

Nutrient intake was assessed in elderly depression and comparison subjects using a Block 1998 food frequency questionnaire. Brain lesion volumes were calculated from magnetic resonance imaging (MRI). Depression subtype (vascular or non-vascular) was determined by the extent of hyperintensities on brain MRI. All subjects received medical comorbidity assessments, and depression subjects received psychiatric assessment and treatment.

Vascular nutritional factors were found to differ between depression and comparison subjects but tended to be similar across the two depression groups, while most factors were unassociated with brain lesion volume. Depression subjects (both groups) consumed more cholesterol, trans-unsaturated fat, and high-fat dairy products, had higher body mass index (BMI) values and Keys scores, and consumed less fruit than comparison subjects. High-fat dairy and whole grain consumption were significantly and positively correlated with brain lesion volume, even after adjustment for age, sex, hypertension, diabetes, and total kilocalories. Dietary quality was not associated with longitudinal change in depression score or lesion volume.

These findings may indicate the influence of “vascular” nutrients on late-life depression, regardless of the presence of comorbid cerebrovascular disease. The less healthful diets of depression subjects may have important implications for management of comorbid chronic diseases that are commonly associated with depression.

In memory of Ruth Johnson

This dissertation is dedicated to the memory of Ruth Johnson who was my beloved teacher and science mentor at Walnut Hills High School in Cincinnati, Ohio. She taught me courses in human anatomy, physiology, and zoology, but more importantly she instilled in me the ideal always to strive for excellence in all academic and scientific endeavors. Her enthusiasm and dedication to excellence were infectious and served as a standard by which to measure my own accomplishments. Although nutrition was not her field, she always stressed the importance of a healthy diet to one's well-being and productivity. Despite her absence, Ms. Johnson has guided my educational pursuits and scientific career since high school. "Clarity, precision, and brevity" were her standards for high-quality scientific writing. I hope that I have achieved the first two of these qualities with my dissertation though it is likely not the third.

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5-HIAA	5-hydroxyindoleacetic Acid (metabolite of serotonin)
5-HT	5-hydroxytryptamine or serotonin (a neurotransmitter)
5HTT	Serotonin Transporter
µg	Micrograms
ώ-3FA	Omega-3 Fatty Acid
ADLs	Activities of Daily Living
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
apoE	Apolipoprotein E
ARIC	Atherosclerosis Risk in Communities
BDI	Beck Depression Inventory
BMI	Body Mass Index
CAD	Coronary Artery Disease
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CES-D	Center for Epidemiologic Studies – Depression Scale
CGI	Clinical Global Impressions
CHD	Coronary Heart Disease
CHOL	Cholesterol
CRF	Corticotrophin-Releasing Factor
CRP	C-Reactive Protein
CT	Computerized Tomography
CVD	Cardiovascular Disease

DALYs	Disability-Adjusted Life Years
DDES	Duke Depression Evaluation Schedule
DepGroup	Depression Group assignment (vascular depression, non-vascular depression, or control)
DHA	Docosahexaenoic Acid (a PUFA)
DWML	Deep White Matter Lesion
ECT	Electroconvulsive Treatment
EPA	Eicosapentaenoic Acid (a PUFA)
FLAIR	Fluid-Attenuated Inversion Recovery (type of MRI scan)
FFQ	Food Frequency Questionnaire
FSE	Fast Spin Echo (type of MRI scan)
g	Grams
HAM-D	Hamilton Depression Rating Scale
HDL	High Density Lipoprotein
HEI	Healthy Eating Index
HIPAA	Health Insurance Portability and Accountability Act
HPA	Hypothalamic Pituitary Adrenal
hTPH2	human Tryptophan Hydroxylase-2
IADLs	Instrumental Activities of Daily Living
ICC	Intraclass Correlation Coefficient
IF	Intra-abdominal Fat
IHD	Ischemic Heart Disease
IU	International Units
kcal	Kilocalorie

Keys score	Indicator of serum cholesterol-raising capacity of diet
LesionVol	Lesion Volume
logLESION	Natural logarithm of lesion volume
MADRS	Montgomery-Asberg Depression Rating Scale
MAOI	Monoamine Oxidase Inhibitor (a type of antidepressant)
MHCRC	Mental Health Clinical Research Center
MI	Myocardial Infarction
mg	Milligrams
mL	Milliliters
MMSE	Mini-Mental State Examination
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
MTHFR	Methyltetrahydrofolate Reductase
NF	Nutritional Factor
NHANES I	National Health and Nutrition Examination Survey I
NHEFS	National Health Examination Follow-up Study
NIMH	National Institute of Mental Health
NIRL	Neuropsychiatric Imaging Research Laboratory
OR	Odds Ratio
PA	Physical Activity
PctPUFA	Percentage of kcals from polyunsaturated fat
PctSatFat	Percentage of kcals from saturated fat
PD	Proton density (type of MRI scan)

PET	Positron Emission Tomography
PHI	Protected Health Information
PUFA	Polyunsaturated Fatty Acid
PVL	Periventricular lesion
RDA	Recommended Dietary Allowance
RR	Relative Risk
SES	Socioeconomic Status
SFA	Saturated Fatty Acid
SGML	Subcortical Gray Matter Lesion
SNS	Sympathetic Nervous System
SSRI	Selective Serotonin Reuptake Inhibitor (a type of antidepressant)
TBF	Total Body Fat
TCA	Tricyclic Antidepressant
Vitamin B_6	Pyridoxine
Vitamin B_{12}	Cobalamin
Vitamin E	Alpha-tocopherol
USDA	United States Department of Agriculture
WHI	Women's Health Initiative
WHO	World Health Organization
WHR	Waist to Hip Ratio
YLDs	Years Lived with Disability

CHAPTER I

INTRODUCTION

Depression in later life is a debilitating and costly affliction considered to be a leading cause of disability, cognitive decline, poor outcomes from comorbid vascular disease, and suicide. This mood disorder characterized by apathy, low mood, and vegetative symptoms, has a multifactorial etiology. As shown in Figure 1.1, risk factors for late-life depression range from sociodemographic factors to poor functional status to medical comorbidity. Cardiovascular conditions are especially common with depression, and individuals with both depression and chronic disease have poorer outcomes from both conditions. Comorbid cerebrovascular disease is considered to be indicative of a specific subtype of late-life depression, namely vascular depression.

Poor diet may have a role in the etiology and progression of depression, may interact with other risk factors such as diabetes, or may simply be the result of depression. Research into the relationship between nutrition and depression has been scant. Studies have suffered from poor psychiatric assessments, problematic dietary measures, and inadequate control for potential confounders. It is imperative to investigate factors such as diet that may affect the risk or outcome of depression, as well as factors that affect the outcome of medical conditions that co-exist with depression. Since diet is modifiable, there is the potential to lessen the occurrence of depression or to diminish the impact of both depression and comorbid vascular

disease. An important first step in evaluating the potential relationship between diet and late-life depression was a cross-sectional evaluation of certain dietary components in those with and without depression. In particular, nutritional factors needed to be assessed in those with vascular and non-vascular depression subtypes to determine if dietary factors differed based upon comorbid cerebrovascular disease. This subtype analysis was one of the three aims of this dissertation project. See CHAPTER II for Specific Aims. Dietary factors of interest for this project were those believed to affect the risk of vascular disease

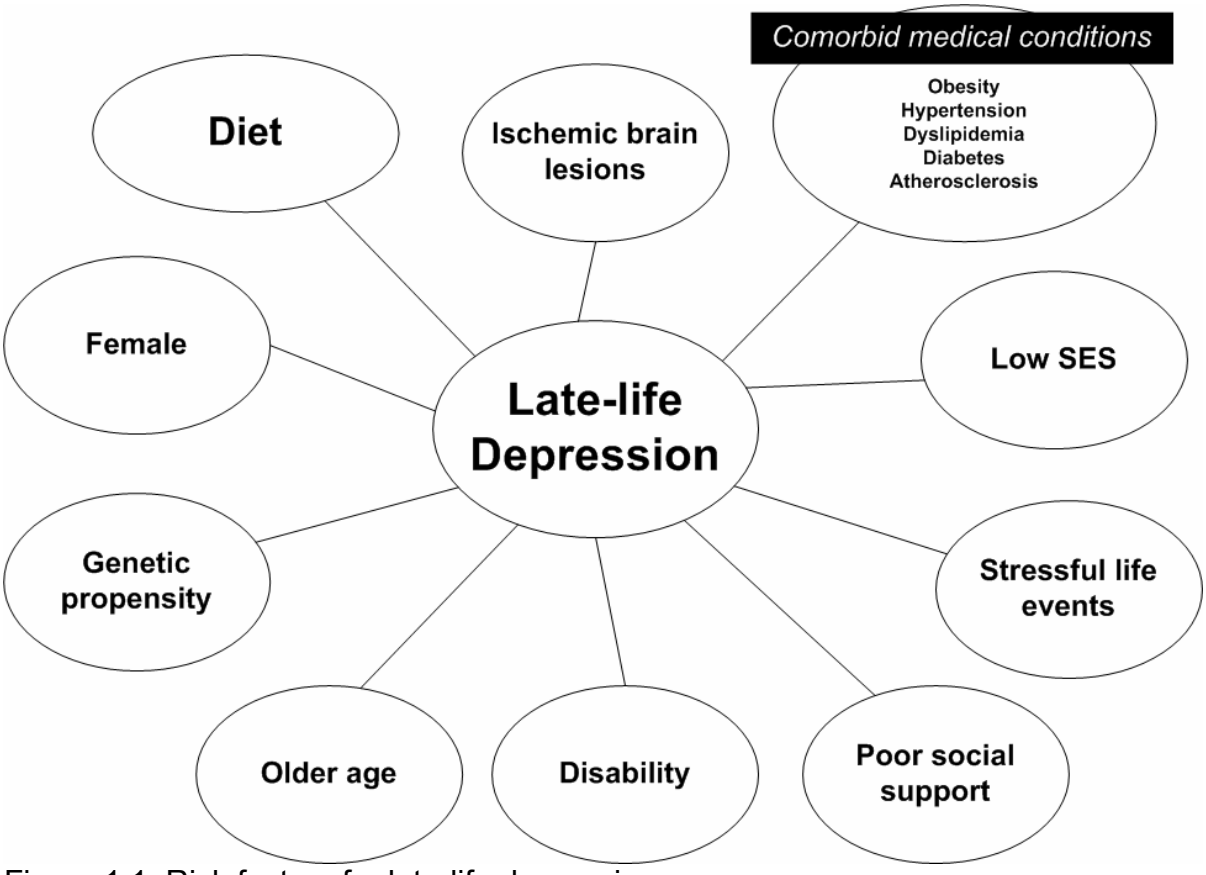

Figure 1.1. Risk factors for late-life depression

(vascular nutritional factors), including total energy, cholesterol, saturated and trans-unsaturated fats, ethanol, omega-3 fatty acids, fiber, vitamin E, and lycopene. In

addition, intakes of the following food groups were examined: fruits, vegetables, meats, high and low-fat dairy products, and whole grains. Atherogenic factors (saturated fat, trans fat, meats, high-fat dairy) were predicted to be positively associated, whereas preventative factors (ethanol, omega-3 fats, fiber, vitamin E, lycopene, fruits, vegetable, low-fat dairy, and whole grains) would be negatively associated with vascular depression as compared with non-vascular depression and comparison subjects.

Cerebrovascular disease of late-life depression is characterized by ischemic brain lesions which are seen on magnetic resonance imaging (MRI) scans as bright (or hyperintense) regions. These hyperintense lesions are more common in elderly individuals with depression than in either non-depressed elders or those with depression in early adulthood. Brain lesions are associated with age and hypertension in both depressed and non-depressed individuals. The presence of brain lesions is associated with negative outcomes including physical impairment, cognitive decline, dementia, and resistance to treatment for depressed individuals. Given their ischemic nature, lesions may be preventable with dietary changes or other lifestyle modifications. As with depression, little prior research had been done to assess the relationship between lesions and nutritional status, and a cross-sectional study was a necessary first step undertaken by this research project. The same vascular nutritional factors were examined for their relationship to brain lesion volume as those investigated for depression subtype. Dietary factors predicted to be positively or negatively associated with vascular depression subtype were hypothesized to be similarly related to brain lesion volume.

Although etiological factors for depression and brain lesions were of interest, they could not be investigated directly because subjects in the depression group had already been diagnosed with depression and most subjects had lesions when first enrolled in the project. It was, however, possible to investigate depression outcomes and progression of lesions in subjects with late-life depression. Given the often malignant course of late-life depression in those with brain pathology (resistance to treatment, cognitive decline, and depression recurrence), as well as adverse outcomes associated with progression in brain lesion volumes (physical disability and dementia), any factors that could be identified to predict such consequences might be helpful in terms of prevention strategies. Overall dietary quality as measured by the Healthy Eating Index (HEI) was evaluated as a potential predictor. A negative association was predicted between dietary quality and adverse outcomes of depression, including progression in lesion size and increases in depression ratings.

CHAPTER II

SPECIFIC AIMS

The goal of this study was to investigate the role of nutritional factors in the occurrence and progression of depression in later life. Depression is the most common mental disorder and a leading cause of disability among elderly people throughout the world. Recent research on the etiology of late-life depression indicates that neuroanatomical abnormalities may be as important as genetic or psychosocial factors. In fact, many researchers consider the category of late-life depression to include a unique syndrome known as vascular depression, which is characterized by multiple brain infarcts and a resistance to treatment. The brain lesions, commonly found in elderly depressed individuals, appear to be ischemic and develop from an atherogenic process. Nutritional factors are known to have important causative and preventive roles in vascular conditions such as heart disease and hypertension. However, the importance of dietary intake to late-life depression is unknown.

I planned to investigate the role of nutrition in vascular depression within an existing study of depression in the elderly. Located at Duke University Medical Center, the NIMH-sponsored Clinical Research Center and Longitudinal Study of Depression in Later Life is an ongoing study of more than 500 elderly depressed patients and controls. Measurements include psychiatric, psychosocial, medical,

genetic, nutrition and brain imaging assessments. A 1998 Block Food Frequency Questionnaire has been used for nutrition assessment in a subgroup of this cohort and will allow an investigation of the role of nutrients, food groups, and dietary quality in the occurrence and progression of vascular depression. If dietary intake is found to be associated with depression, brain lesions, and depression severity and outcomes, future prospective research may lead to methods of preventing vascular depression and to improving its prognosis.

Specific Objectives

AIM 1: Nutritional Correlates of Vascular Depression

Determine the differences in dietary intake between individuals with vascular depression as compared to those with non-vascular depression and control subjects.

Hypothesis 1: Higher values in nutritional factors that are associated with promoting atherosclerosis (including kilocalories, saturated fat, trans fat, cholesterol, meats, high-fat dairy products, body mass index, and Keys score) will be positively associated with vascular depression.

Hypothesis 2: Higher values in nutritional factors that are associated with prevention of atherosclerosis (including omega-3 fatty acids, fiber, vitamin E, fruits, vegetables, whole grains, and low-fat dairy products) will be negatively associated with vascular depression.

AIM 2: Association of Brain Lesion Size with Nutritional Factors

Among individuals with vascular depression, determine the association between dietary intake of specific nutrients and food groups, and other nutritional factors, with lesion severity (as defined by lesion volume).

Hypothesis 1: Higher values in atherogenic nutritional factors, such as kilocalories, saturated fat, trans fat, cholesterol, meats, high-fat dairy products, body mass index, and Keys score, will be positively associated with lesion severity.

Hypothesis 2: Higher values in nutritional factors which may decrease one's risk of atherogenesis, including omega-3 fatty acids, fiber, vitamin E, fruits, vegetables, whole grains, and low-fat dairy products, will be negatively associated with lesion severity.

AIM 3: Dietary Quality as a Predictor of Depression and Lesion Outcomes

Among individuals with depression, determine if the quality of the diet, as defined by the Healthy Eating Index, was predictive of the course of illness (as defined by changes in lesion volumes and depression scores).

Hypothesis 1: Higher baseline Healthy Eating Index scores will be associated with smaller changes in lesion volumes from baseline to follow-up.

Hypothesis 2: Higher baseline Healthy Eating Index scores will be associated with smaller changes in depression scores from baseline to follow-up.

CHAPTER III

BACKGROUND AND SIGNIFICANCE

Major depression is a serious mental disorder characterized by low mood, apathy, sleep and appetite disturbances, feelings of hopelessness, and suicidal thoughts and behaviors. It is the most common mental disorder and a leading cause of disability worldwide. Late-life depression is a common affliction in the elderly and its prevalence is expected to increase as the geriatric population swells in the next several decades. Recent evidence has pointed to a unique subtype of late-life depression that is related to vascular risk factors, and is characterized by ischemic brain lesions. Since nutrition is an important modifier of other vascular diseases, such as heart disease and stroke, it is logical to assume that diet may play an important role in the etiology and progression of late-life depression. One potential mechanism is shown in Figure 3.1. Dietary factors may promote or prevent the occurrence of numerous conditions that are associated with the metabolic syndrome. These conditions may lead to arterial occlusion, which in turn could lead to brain lesions affecting mood. This neuronal damage may result in the occurrence of vascular depression. If nutritional factors are determined to be associated with depression in the elderly, future research may lead to a means of preventing this disorder or to attenuating its impact. Given the increasing numbers of elderly individuals expected in the 21st century, it will be critical to develop methods of preventing and addressing afflictions of late life. The association of nutritional

factors with late-life depression and brain lesions, including whether dietary quality was predictive of such occurrences were investigated.

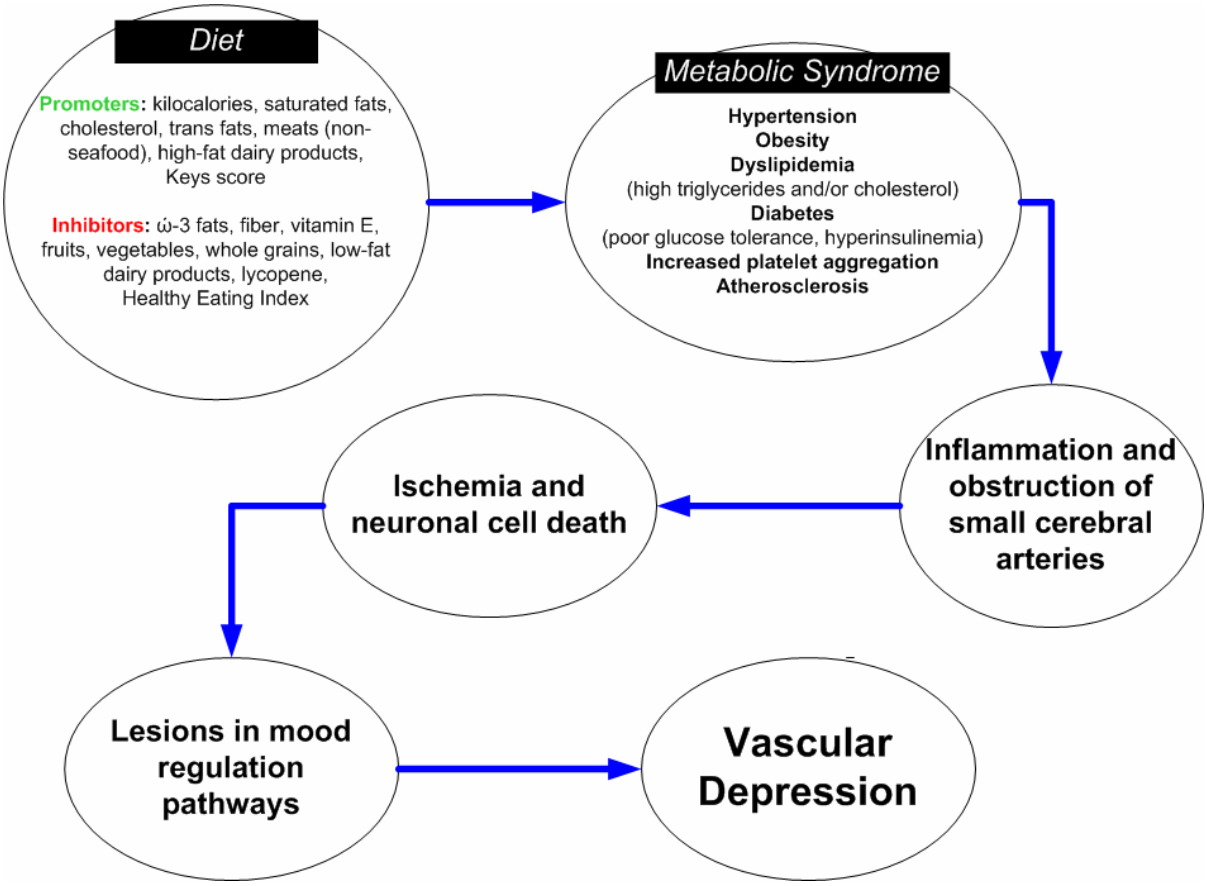

Figure 3.1. A proposed etiologic nutritional mechanism for vascular depression (Payne, 2006)

Depression

Major depression is one of a category of psychiatric illnesses known as mood disorders. Its hallmark symptoms are sadness, feeling down or blue, and being disinterested in usual activities. Low mood is a persistent phenomenon and distinguished from daily "ups and downs" that most people experience. In many cases this dysphoria does not seem to be associated with a particular event or

situation in the individual's life. However, mood disturbance is not the only effect of depression. Depressed individuals also have groups of symptoms known as vegetative and ideational. Vegetative symptoms include appetite and energy disturbances. Ideational symptoms encompass feelings of guilt and hopelessness, as well as suicidal thoughts.

According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (1994), a diagnosis of major depression requires that at least five of the following nine symptoms have persisted for at least two weeks: 1) feeling depressed, sad, or blue, 2) loss of interest or pleasure, 3) increased or decreased sleep, 4) increased or decreased appetite with weight change, 5) feeling agitated, restless, or slowed down, 6) feelings of worthlessness or excessive guilt, 7) low energy, 8) difficulty concentrating, and 9) feeling that life is not worth living. Major depression may be diagnosed by a psychiatrist, psychologist, general practitioner, or other health professional. However, in approximately 50% of cases, depression is undetected and untreated (Kessler et al 2003).

Prevalence and Significance

Worldwide prevalence of major depression is 10.4%, according to the World Health Organization (Murray 1996), which makes it the most prevalent psychiatric disorder. Prevalence of depression in the elderly ranges from 0.4% to 35% depending upon locality and definition (Beekman et al 1999). One U.S. study found a prevalence between 2.7% and 4.4% for those over age 65, although this was in a cohesive, predominantly Mormon community (Steffens et al 2000b). Prevalence of depression in other elderly populations has been between 6.6% and 10.1% (Roberts

et al 1997). Depression is even more common among those with poor health and those in nursing homes (WHO 2001). In addition to major depression, many individuals suffer from dysthymia (chronic minor depression), as well as clinically significant depressive symptoms that are below the threshold of diagnosis. Many depression studies have, in fact, included individuals with depressive symptoms rather than only those with a diagnosis of major depression.

In 1990 and 2000 the World Health Organization (WHO) reported on the Global Burden of Disease which assessed the causes of mortality, morbidity, and disability from physical and psychiatric ailments as well as accidents and injuries (Murray 1996; WHO 2001). In addition to determining estimates for 1990 and 2000, they projected trends up until the year 2020. The WHO calculated Disability-Adjusted Life Years (DALYs) which was a measure of disease burden that reflected not only years lost to premature death but also years lived with disability (YLDs). They determined that in both 1990 and 2000 depression was the leading cause of YLDs, as it accounted for one out of every ten years lived with a disability worldwide. Disability includes cognitive and functional impairment, and declines in physical functioning, all of which were associated with depression (Callahan et al 1998). In addition to disability burden, the WHO determined that depression accounted for the majority of the 800,000 suicides annually (Murray 1996). In 2000 the WHO ranked depression as the fourth leading cause of disease burden as defined by DALYs, behind respiratory infections, perinatal conditions, and HIV/AIDS (WHO 2001). It was projected that in 2020 depression would become the second leading cause, behind ischemic heart disease, and would be the leading cause of disease burden

among women (Murray 1996; WHO 2001). The proportionate increase in disease burden expected between 1990 and 2020 from psychiatric conditions was predicted to surpass that of cardiovascular disease (Murray 1996). The WHO concluded that mental disorders and especially depression were responsible for a significant and often unnoticed proportion of suffering, and that public health policy should shift attention away from infectious disease, as those conditions would be accounting for less of the disease burden, and towards a focus on chronic diseases and mental disorders (Murray 1996).

Disability and suicide are not the only costs associated with depression. Health care costs are higher for depressed individuals. Among 2,558 older adult members of a health maintenance organization, those with depression had 50% more health care costs than non-depressed individuals (Unutzer et al 1997). This increase in costs was not explained by increased utilization of mental health care (Unutzer et al 1997). Work productivity was diminished in individuals with depression as they experienced a loss of 5.6 productive work hours on average each week, both from absenteeism (1 hour) and inefficient performance while at work (4.6 hours) compared to 1.5 lost productive hours per week among non-depressed workers (Stewart et al 2003). The WHO defines two additional facets of the effect of depression on society, the undefined burden and the hidden burden (WHO 2001). The undefined burden relates to the impact of depression upon people connected with the depressed individual. Impaired psychosocial and cognitive functioning and other disabilities from depression can have a tremendous impact upon the emotional and socioeconomic well-being of relatives, caregivers, and the community. Lost

productivity, financial costs, and diminished quality of life for family members typically follow. The hidden burden is that associated with the stigma of mental illness, which may lead to humiliation, isolation, and unemployment. Finally, depression has been established to have a substantial negative impact upon a person's medical health (Vaillant 1998). In particular, depression can affect the course of cardiac disease and increase mortality rates.

Depression of Later Life

Late-life depression, that is, depression which occurs after age 60, is of considerable importance because of the increasing numbers of elderly and particularly because of its malignant course. Recent evidence indicates that late-life depression can be distinguished from depression in early adulthood by its symptoms, etiology, course, and neuropathology (Alexopoulos et al 1997a; Alexopoulos et al 1997b; Krishnan et al 1997). Symptomatology of late-life depression tends to involve more apathy, psychomotor slowing, cognitive impairment, flat affect rather than sadness, and a more profound loss of interest, as compared to early-life depression (Alexopoulos et al 1997a). As shown in Figure 1.1 there are many risk factors for late-life depression. Genetic and psychosocial factors are believed to be less important in the etiology of late-life depression, while biological and neurological changes figure more prominently (Baldwin and Tomenson 1995; Krishnan et al 1997). Risk factors likely interact with one another. For example, poor dietary quality may exacerbate diabetes management, leading to physical disability, which may in turn contribute to depression. The course of depression in later life tends to be more malignant with a higher rate of recurrence,

lower rate of remission, more treatment resistance, and an increased likelihood of death or progression into dementia (Baldwin and Tomenson 1995; Steffens et al 2000a; Steffens et al 1997). Vascular risk factors and vascular diseases, including hypertension, atherosclerosis, heart disease, cerebrovascular disease, stroke, diabetes mellitus, and ischemic brain lesions, are more common in those with late-life depression than in younger depressed subjects (Baldwin and Tomenson 1995; Conway and Steffens 1999; Krishnan and McDonald 1995). The presence of vascular risk factors and, in particular, ischemic brain lesions have led to the vascular depression hypothesis of late-life depression (Alexopoulos et al 1997a; Krishnan et al 1997).

Vascular depression

Although the concept of an association between vascular disease and depression was first mentioned in 1905 by Gaupp [as quoted by Post (Post 1968)] when he described 45 elderly patients with depression secondary to arteriosclerosis, only recently have investigators been able to assess vascular brain changes *in vivo* by the use of magnetic resonance imaging (MRI) and other brain scanning techniques. In 1995 Krishnan and McDonald proposed the term 'arteriosclerotic depression' to describe that blood vessel disease may underlie many cases of late-life depression (Krishnan and McDonald 1995). More recently, the 'vascular depression' hypothesis was proposed by Krishnan (Krishnan et al 1997; Steffens and Krishnan 1998) and Alexopoulos (Alexopoulos et al 1997a), which posits that cerebrovascular disease can predispose, precipitate, and perpetuate depression in the elderly. Brain lesions are known to be present in elderly depressed subjects at a

higher frequency than in either non-depressed elderly or younger depressed individuals (Conway and Steffens 1999; Steffens and Krishnan 1998). These lesions may accumulate to a threshold above which there is a predisposition to depression (Alexopoulos et al 1997a). In addition, the lesions may disrupt neuronal pathways that are critical for mood regulation, which could precipitate depression (Alexopoulos et al 1997a). A large body of evidence exists to support of the vascular depression hypothesis. Evidence includes studies of clinical populations with heart disease, obesity, and diabetes, investigations into cardiovascular risk factors among elderly depressed individuals, and extensive assessments of brain lesions.

Heart Disease

The relationship between depression and vascular disease is complex, multidirectional, and multifactorial. Individuals with depression are at greater risk for heart disease and diabetes, while these medical patient populations are at greater risk for depression (Aromaa et al 1994; Gonzalez et al 1996; Goodnick et al 1995). In addition, patients with both depression and an accompanying vascular medical disease are at greater risk for poor outcomes, including death. As mentioned above, Gaupp first noted depression that was secondary to arteriosclerosis. In the 1980's there was preliminary evidence that cardiac patients with coronary artery disease (CAD), and especially those with a history of myocardial infarction (MI), were more likely to have depression than the medically healthy (Dalack and Roose 1990; Schleifer et al 1989). Depression was a significant predictor of poor outcomes among heart patients, as they were very unlikely to have returned to work after three

months (Schleifer et al 1989), were more likely to require a coronary bypass or angioplasty (Carney et al 1988), and were more likely to experience a first or subsequent MI, myocardial arrest, or death, as compared to heart patients without depression (Carney et al 1988; Dalack and Roose 1990; Falger and Appels 1982; Schleifer et al 1989; Silverstone 1987). Some of these early studies failed to control for known cardiovascular risk factors, such as serum cholesterol and obesity, so that whether depression was an independent risk factor or whether depression was simply correlated with other risk factors could not be established.

Studies in the 1990s continued to demonstrate that heart patients were at increased risk of depression, and vice versa. In a study of 99 CAD inpatients, 23% were found to have a diagnosis of depression, an incidence much higher than that expected in the general population (Gonzalez et al 1996). In addition, the severity of medical illness was associated with increased risk for depression (Gonzalez et al 1996). Other research determined that individuals who were depressed but showed no evidence of cardiac disease at baseline were at increased risk for future MI, ischemic heart disease (IHD), and cardiac mortality (Aromaa et al 1994; Dinan 1999; Ford et al 1998; Pratt et al 1996). The Precursors Study followed 1190 men who had attended medical school between 1948 and 1964, and found that depression increased the risk of coronary heart disease (relative risk = 2.12) even after control for cardiovascular risk factors (Ford et al 1998). This increased risk remained for ten years after the depressive episode (Ford et al 1998). The Finland Population Survey followed 5,355 individuals for up to eight years. It showed that depression at baseline predicted an increased risk of cardiac and all-cause mortality among those

with and without cardiovascular disease (CVD) at baseline, while controlling for socioeconomic status and other CVD risk factors (Aromaa et al 1994). Depression and depression scores were also shown to be increased more in the CVD group than in the non-CVD group (Aromaa et al 1994). The Baltimore Epidemiologic Catchment Area cohort between 1981 and 1994 demonstrated that individuals with major depression at baseline were four and a half times more likely to have a non-fatal MI during the 13 year follow-up period than those without depression at baseline (Pratt et al 1996). A study of primary care patients in England found that men, but not women, with a diagnosis of depression were three times more likely to develop IHD than those without depression (Hippisley-Cox et al 1998). A Danish study following a cohort born in 1914 found that an increased depression score, among men and women, was associated with an increased risk of MI (Relative Risk (RR) = 1.71, $p < .005$) and all-cause mortality (RR = 1.59, $p < .001$) (Barefoot and Schroll 1996).

Analysis of the National Health and Nutrition Examination Survey I (NHANES I) and National Health Examination Follow-up Study (NHEFS) examined 2,832 individuals who were at baseline without serious medical illness and between 45 and 77 years of age (Anda et al 1993). Participants who had symptoms of depressed affect or hopelessness at baseline were found to be at increased risk for fatal and non-fatal IHD, while controlling for age, sex, marital status, smoking, total cholesterol, BMI, systolic blood pressure, education, race, alcohol use, and physical activity (PA) (RR range of 1.3 - 2.1). Another NHANES I study demonstrated that those with depression but no coronary heart disease (CHD) in 1982 had a relative

risk (RR) of 1.7 for CHD incidence, while controlling for the same risk factors as the Anda study, during ten year follow-up as compared with controls (Ferketich et al 2000). In addition, depressed men showed an increased risk of CHD mortality (RR = 2.34) (Ferketich et al 2000). NHANES I and NHEFS also showed that depressive symptoms among individuals without hypertension at baseline predicted later incidence of hypertension (Jonas et al 1997).

Heart disease and depression do not simply predict one another; they also affect the prognosis and outcomes of one another. Depressed outpatients with a history of MI tended to have a poor clinical course of their depression during a one to two year follow-up period (Wells et al 1993). Studies of MI inpatients found that those who had depression while in the hospital were more likely to die within the 6 or 18 months following the MI (Frasure-Smith et al 1995; Ladwig et al 1991). The six-month follow-up study of 560 men showed that depression ratings predicted cardiac death (Ladwig et al 1991). The second study followed 222 MI patients for 18 months and found that depression while in the hospital was a significant predictor of cardiac mortality, although the researchers did not control for important cardiac risk factors such as physical activity (PA), body mass index (BMI), or changes in treatment adherence (Frasure-Smith et al 1995). A study of elderly subjects with major depression showed that increased baseline depression scores were a major risk factor for mortality in men, while vascular comorbidity was a major risk factor in women (Steffens et al 2002c). A major factor in prognosis for heart disease patients is adherence to treatment, which is a factor known to be diminished in those with depression (Horwitz et al 1990). A study in 1980 showed that MI patients who

dropped out of prescribed exercise regimens were more likely to be depressed (Blumenthal et al 1982). Another study, reported in 1987, demonstrated that among men and women with angina or MI, depression predicted poor compliance to smoking cessation and exercise programs at one year follow-up (Guiry et al 1987). More recently depression and depression symptoms were shown to decrease adherence to lifestyle changes following MI not only for physical activity and smoking, but also for diet (Ziegelstein et al 2000). Medication adherence is also diminished by depression as shown by a study of CAD patients who were prescribed aspirin (Carney et al 1995). Adherence to treatment is a critical factor in determining outcomes for heart patients. MI patients who adhered poorly to treatment were 2.6 times more likely to die within one year even after controlling for other risk factors (Horwitz et al 1990). The Coronary Drug Project found increased mortality among 8,341 clinical trial patients who adhered poorly to medication treatment during 5 year follow-up (1980). Surprisingly, poor adherence predicted mortality even for those subjects who were assigned to the placebo group (1980). Some have hypothesized that the effect of depression upon heart treatment adherence is what mediates depression's effect upon heart disease outcomes (Carney 1995).

A variety of factors, including poor adherence to recommended exercise and dietary regimens during cardiac treatment, have been proposed to explain the adverse cardiac effects of depression. A simple explanation would be that depressed subjects have more severe heart disease, but this notion has not been supported by evidence (Carney et al 1988; Frasure-Smith et al 1995). Some investigators have speculated that the cardiotoxic effects of antidepressants are

responsible for depression's apparent influence on cardiac outcomes. This explanation is also unlikely because the depression and heart disease relationship was observed both before antidepressants were available (Fuller 1934) and after the advent of the selective serotonin reuptake inhibitors (SSRIs), a class of antidepressants which have minimal cardiotoxic effects (Carney et al 2002). Even with use of the more cardiotoxic tricyclic antidepressants, cardiac damage affected relatively few patients (Pary et al 1989; Warrington et al 1989). Finally, most heart patients with depression are not diagnosed or treated for depression (Freedland et al 1992; Kessler et al 2003). Another hypothesis is that the neuroendocrine changes observed in depression have adverse cardiac effects (Carney et al 2002; Siever and Davis 1985). These neuroendocrine changes include increased sympathetic nervous system (SNS) activity, decreased vagal tone, and altered activity of the hypothalamic pituitary adrenal (HPA) axis. These changes have even been observed in individuals experiencing a transient depressive emotional state (Forbes and Chaney 1980). Neuroendocrine alterations lead to increased heart rate, increased systolic and diastolic blood pressure, increased platelet activity, and decreased heart rate variability, all of which promote cardiac morbidity and mortality (Laghrissi-Thode et al 1997; Musselman et al 2000). Changes in neuroendocrine activity also alter circadian rhythms (Muller et al 1985). Depressed patients tend to have myocardial infarctions earlier in the morning than non-depressed individuals, and this parallels a phase shift in thrombogenic factors (Muller et al 1985). Lastly, researchers have speculated that an increased incidence of risk factors, such as hypertension and smoking, explain the cardiotoxic effects of depression. However,

studies that have controlled for these factors have still found an association between heart disease and depression (Anda et al 1993; Ferketich et al 2000). Depression may possibly potentiate the effects of risk factors upon heart disease (Carney 1995). Evidence exists of an increased effect of smoking upon carotid atherosclerosis in those with depression. To summarize, multiple mechanisms may explain the cardiotoxic effects of depression including decreased adherence to treatment, altered nervous system and endocrine activity, and increased incidence or potentiation of vascular risk factors.

Obesity

Obesity is another condition related to vascular risk which may be important in the etiology and progression of vascular depression. True obesity requires a 20% increase above the ideal in body fat; however, most researchers and clinicians do not measure body fat directly but use body weight, waist to hip ratio (WHR), or body mass index (BMI) to define adiposity indirectly. Unfortunately, it is difficult to evaluate the relationship between obesity and body weight, and depression. Depression itself is associated with an increased appetite and accompanying weight gain in some individuals while being associated with decreased appetite and weight loss in others. The likelihood of weight gain or loss with depression or in those who develop depression may be different for early and late-life depression. In addition, treatments for depression differ in their effects upon appetite and body weight (Levine et al 1987; Morley et al 1988; Tayek et al 1988). The majority of research on body weight and depression has been concerned with low body weight, decreased appetite, weight loss, and undernutrition. This focus is particularly true of geriatric

research because elderly individuals are already at increased risk for malnutrition due to chronic disease and inadequate food intake. Research has shown that depression is a risk factor for inadequate intake of calories and nutrients, but some of these studies have failed to properly diagnose depression or to include a control group (Christensen and Somers 1994; DiPietro et al 1992; Kolasa et al 1995; Pirlich and Lochs 2001). Reviewers have concluded that depression in the elderly often leads to malnutrition, anorexia, and weight loss (Cohen 1994; Gray and Gray 1989; Morley 1996; Reife 1995). This relationship does not exclude the possibility that obesity is an important etiological factor in depression nor that obesity may be associated with depression in certain individuals.

When studies have assessed weight and appetite change in both directions, depression has been associated with both increases and decreases in appetite and weight (Paykel 1977). Although most studies have found that declines in appetite and weight are more common than increases, these changes are likely to vary by age, other demographic variables, type of treatment, and subtype of depression (early versus late-life, and vascular versus non-vascular). Overeating is a symptom of depression and may also be a coping strategy for those who are depressed (1994; Lasslo-Meeks 1999). A syndrome known as “atypical depression” is characterized by excess food intake, hypersomnia, and anergy. Obesity may be associated with the risk of depression by increasing physical impairment or increasing the likelihood of dieting, characteristics which are independently associated with depression (Jorm et al 2003; Musante et al 1998; Ross 1994). Despite societal ideals of thinness, particularly for women, little evidence has been

produced that obesity itself promotes depression simply because of attitudes about body weight (Ross 1994). The influence of obesity upon depression may be exerted through obesity's effects upon vascular risk although little research has been done in this area. Prior work has demonstrated that individuals with late-life depression have higher BMI than elderly comparison subjects (Payne et al In press).

Three studies of depression and intra-abdominal fat have measured body fat directly through the use of computerized tomographic (CT) scanning, rather than relying upon weight or BMI as an indirect measure of adiposity (Thakore et al 1997; Weber-Hamann et al 2002; Weber-Hamann et al 2005). Increased intra-abdominal fat is a risk factor for vascular illnesses including hypertension and diabetes. This risk is most likely related to increased metabolic activity of intra-abdominal fat, as compared to that of subcutaneous fat. One study measured intra-abdominal fat (IF), total body fat (TBF), and waist-to-hip ratio (WHR) in a group of 7 depressed and 7 non-depressed women (Thakore et al 1997). The depressed women were found to have a two-fold higher IF when compared with controls (Thakore et al 1997). IF was found to be correlated with cortisol levels (a measure of HPA activity) which were also significantly higher, as expected, in the depressed group (Thakore et al 1997). IF was also positively associated with WHR, another risk factor for vascular illness, but not with TBF. Interestingly, all except two of the subjects (one in each group) were within 10% of ideal body weight (Thakore et al 1997). This finding would imply that the traditional BMI definition of obesity may not be adequate to identify those at risk for depression from increased adiposity in the absence of increased body weight. Thakore concluded that the abdominal fat distribution found in depressed

subjects may have been due to high cortisol exposure, and that this may be related to the association of major depression with certain physical illnesses (Thakore et al 1997).

A second abdominal fat study found that elderly depressed women with elevated cortisol levels had greater IF and lower glucose tolerance than age-matched controls (Weber-Hamann et al 2002). A longitudinal study of 46 individuals found that elderly depression subjects accumulated more visceral fat during one to two years of follow-up when compared to non-depressed subjects (Weber-Hamann et al 2005). These studies offer insight into the potential mechanisms that link depression and physical disease. However, the findings need to be replicated with larger samples, including individuals of varying body weights, ages, and both sexes. In addition, the studies do not demonstrate the temporal sequence of depression and altered abdominal fat distribution. Did depression cause IF changes or did increased IF raise the risk of depression? Alternatively, a common cause could have led to both conditions. If increased IF is found to be related to depression, then this could provide a critical clue to the mechanism connecting depression and vascular disease.

Three other studies support an association between increased body weight and depression or depressive symptoms. A subgroup of the NHANES I cohort demonstrated that BMI was positively correlated with depressive symptoms, after controlling for age, years of education, and smoking (Istvan et al 1992). Another national survey population showed that obesity (BMI $\geq$ 30) in women was associated with having had major depression in the past year (odds ratio = 1.37) (Carpenter et al 2000). Most intriguing and consistent with the notion of a vascular etiology to

depression is the prospective Alameda County Study which followed 1,886 individuals between ages 50 and 94 years for 5 years and evaluated both BMI and depressive symptomatology (Roberts et al 2003). Baseline obesity was associated with an increased risk of incident major depression over the follow-up period, even after adjustment for other significant predictors of depression including age, sex, education, marital status, financial strain, life events, social support, chronic medical conditions, and activities of daily living. Baseline depression was not associated with later development of obesity. Additional studies are needed to replicate this finding and further investigate the etiological role of obesity in depression.

Diabetes

Diabetes mellitus, a condition common in obese individuals and having vascular consequences, has been found to be associated with depression as well. Women with Type II diabetes were found to be more likely to have depression than controls, although it was not clear whether this was related to common etiology or to the emotional impact of being diabetic (Malacara et al 1997). The overall prevalence of depression among diabetics is between 8.5% and 27.3%, rates which are much higher than in the general population (Goodnick et al 1995). An increase in lifetime depression prevalence was also found in individuals with long-standing Type I diabetes as compared to the general population (Popkin et al 1988). This finding was not related to complications or to duration of diabetes (Popkin et al 1988). Another study failed to observe a higher likelihood of depression among mental health patients with fasting blood glucose greater than 45, although the generalizability of this finding to the non-mental health population is unknown

(Kymissis et al 1979). On the converse, depressed individuals demonstrated greater insulin resistance during a 5-hour oral glucose tolerance test (Winokur et al 1988). Depressives had greater basal glucose levels, and increased glycemic and insulin responses to the glucose tolerance test (Winokur et al 1988). As with heart disease, the coexistence of diabetes and depression has negative implications for the patient. Among primary care patients with diabetes and depression, depression severity was associated with poorer diet and decreased medication adherence, both of which led to increased functional impairment and health care costs (Ciechanowski et al 2000). Depressed diabetics were also more likely to drop out of weight management programs (Marcus et al 1992). Scores on the Beck Depression Inventory (BDI), a rating scale of depressive symptoms, were found to be correlated with hyperglycemia, diabetic complications, and poorer diabetic management as evidenced by hemoglobin A_{1c} (HbA_{1c}), a measure of long-term glycemic control (Leedom et al 1991). A study of diabetics with depression at baseline found that 79% of them experienced either depression or dysthymia during 5-year follow-up, indicating that the natural course of depression may be more malevolent in diabetic populations than in the medically well (Lustman et al 1988).

A variety of mechanisms have been proposed to explain the association of diabetes and depression. Some researchers argue that the emotional impact of having diabetes is responsible, although this explanation is unlikely to explain the association fully. Antidepressants have a variety of effects upon glycemic control and weight, and their use may explain some of the apparent effects of depression upon diabetes (Lustman et al 1988). Monoamine oxidase inhibitors (MAOIs) have

hypoglycemic effects, tricyclic antidepressants (TCAs) can cause weight gain, while Selective Serotonin Reuptake Inhibitors (SSRIs) may improve glycemic control by decreasing blood glucose, decreasing insulin requirements, and promoting weight maintenance or loss (Goodnick et al 1995; Lustman et al 1988). However, given that commonly prescribed SSRIs do not adversely affect glucose control and given that most depressed individuals do not receive any treatment, antidepressants are unlikely to explain fully the association of depression and diabetes. Both depression and diabetes exhibit dysregulation of the hypothalamic pituitary adrenal (HPA) axis and associated vascular changes (Cameron et al 1984; Lustman et al 1988). This neuroendocrine or another, not yet elucidated, mechanism may be responsible for the co-occurrence of these two conditions and their effects upon one another.

Brain lesions

Brain lesions on magnetic resonance imaging (MRI) are considered to be a defining feature of vascular depression as they provide evidence of cerebrovascular disease in individuals with late-life depression (Krishnan et al 1997). They have been associated with the presence, persistence, and worsening of depressive symptoms (Steffens et al 1999; Steffens et al 2002b). Advances in brain imaging technology, particularly in nuclear magnetic resonance techniques, have provided the first non-invasive *in vivo* assessments of the human brain. Lesions are often referred to as hyperintensities because they appear brighter than surrounding gray and white matter tissue on certain types of magnetic resonance imaging (MRI) scans, as seen in Figure 3.2.

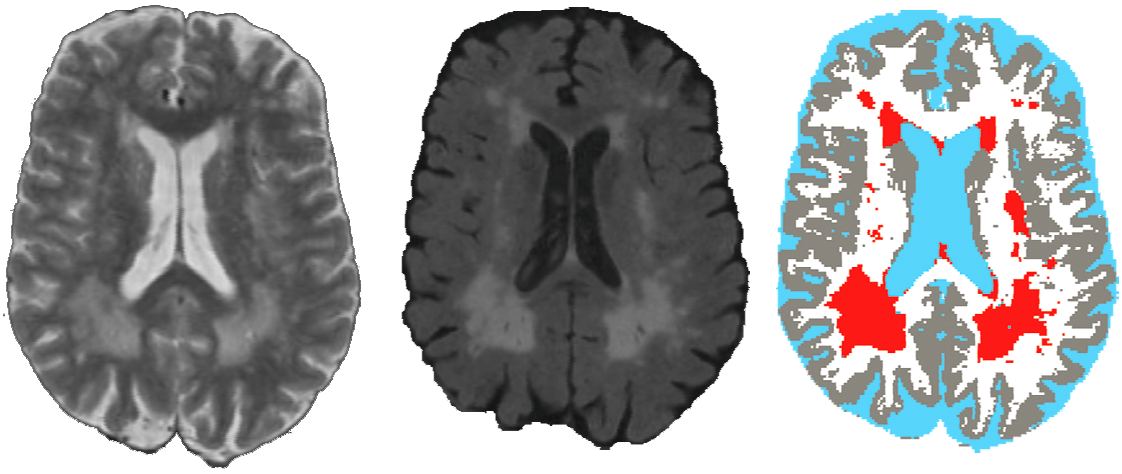

Figure 3.2. Hyperintense brain lesions seen on MRI.
Lesions visible on Proton Density (left), Fluid-Attenuated Inversion Recovery (center), and segmentation (right) images. Lesions are red on segmentation.

These lesions are sometimes called “silent cerebral infarcts” because their etiology and appearance are believed to be similar to those for ischemic stroke but without the overt neurological deficits (Fujikawa et al 1993). These lesions do not represent the neurofibrillary tangles or amyloid plaques found with Alzheimer’s Disease (AD), although they may be present in individuals with AD (O'Brien et al 1996). The amyloid plaques and intracellular neurofibrillary tangles of AD are not visible on MRI, but detection currently requires advanced radiolabeling techniques combined with Positron Emission Tomography (PET) or postmortem neurohistological staining. Lesions may be found in the white matter tracts (deep white matter lesions or DWMLs), which provide connections within the brain; in regions surrounding the fluid-filled lateral ventricles (periventricular lesions or PVLs); in gray matter nuclei deep within the brain (subcortical gray matter lesions or

SGMLs); or, rarely, in the gray matter of the cerebral cortex. The focus of depression research has been almost exclusively on DWMLs and SGMLs because these lesions are found in regions known to regulate mood and may be altered in depression. Hyperintensities have been found to be associated with depression, and individuals with late-life depression have them more frequently than younger depressed subjects (Conway and Steffens 1999; Steffens and Krishnan 1998). These brain lesions are more common with advancing age (Uehara et al 1999); however, those with late-life depression are more likely to have lesions than are age-matched controls (Firbank et al 2004; Krishnan et al 1997; Taylor et al 2005). In addition, white and gray matter lesions at baseline in non-depressed subjects have been found to predict the later development of depressive symptoms (Steffens et al 2002a), cognitive decline and dementia (Vermeer et al 2003b), decline in motor functioning, and physical disability (Rosano et al 2005). Lesions have consistently been associated with late-life depression, and there is some evidence that they may be causal (Steffens et al 2002c). Longitudinal studies of depressed individuals have found that the presence of white and gray matter lesions predict poorer outcomes of depression, including relapse, cognitive decline, higher depression scores, and functional impairment (O'Brien et al 1998; Steffens et al 2002a; Steffens et al 2005). In addition, progression in lesion volumes has been associated with relapse and worsening of depressive symptoms (Chen et al 2006; Taylor et al 2003b).

Lesions, hypertension, and ischemia

Research into the etiology of hyperintensities has indicated a vascular mechanism. Hypertension has been shown to be positively associated with brain

lesions. Numerous studies of lesion etiology have been conducted in the elderly, as well as with depression subjects. In the mid-1990s hypertension was shown to be associated with the presence of both periventricular (PVLs) and deep white matter lesions (DWMLs) (Fukuda and Kitani 1995; Liao et al 1996). Findings from a sample of over 1900 subjects in the population-based study of Atherosclerosis Risk in Communities (ARIC) showed odds ratios for lesions of between 2.3 and 3.4 for those with hypertension as compared with controls (Liao et al 1996). Both studies found that individuals with poorly treated hypertension were most at risk for brain lesions (Fukuda and Kitani 1995; Liao et al 1996), and in one study risk from treated hypertension was indistinguishable from that of normotensives (Fukuda and Kitani 1995).

Studies have demonstrated that baseline blood pressure predicted the presence of PVLs and DWMLs twenty years later and that progression in lesion size was associated with blood pressure and duration of prior hypertension (de Leeuw et al 1999; de Leeuw et al 2002; Schmidt et al 1999; Uehara et al 1999; Veldink et al 1998). Diastolic blood pressure was more consistently associated with lesion presence and progression than was systolic blood pressure (Schmidt et al 1999; Veldink et al 1998). Unfortunately, some of the studies which have linked hypertension and brain lesions suffered from small sample size, inadequate control of other vascular risk factors, and poor methodology for measuring lesions on MRI. In addition, the definition of what constitutes hypertension differed between studies, with minimum systolic blood pressure cutoffs ranging from 140 to 160. However, the results have been consistent across populations from various nations and ethnic

backgrounds, differences in definitions and measurement, and age ranges. Recently, a study of individuals with late-life depression demonstrated an association between hypertension and brain lesions (Taylor et al 2005).

In addition to hypertension, other vascular risk factors and conditions have been associated with brain hyperintensities in the elderly. These factors include arteriosclerosis, heart disease, diabetes, history and risk of ischemic cerebrovascular disease, history of MI, extracranial carotid artery disease and stenosis, smoking, homocysteine levels, number of carotid plaques, cerebral microvascular disease, and microcirculatory disturbances leading to decreased cerebral blood flow (Awad et al 1986a; Awad et al 1986b; Cook et al 2004; de Leeuw et al 2000; de Leeuw et al 1999; Fazekas et al 1988; Hatazawa et al 1997; Taylor et al 2003a; Uehara et al 1999; Vermeer et al 2003a; Vermeer et al 2002).

The most convincing evidence that brain lesions result from vascular disease and ischemia (inadequate oxygen to the tissues) comes from postmortem studies. Awad and colleagues found that gray matter and white matter lesions were associated with arteriosclerosis and dilated blood vessels (Awad et al 1986a). They also found histological changes that were associated with hypertension (Awad et al 1986a). In 2002 a critical study was reported that assessed DWML neuropathology in depressed and non-depressed subjects (Thomas et al 2002). Lesions on post-mortem *in vitro* MRI, confirmed to represent tissue damage upon histological examination, were assessed as being either ischemic or non-ischemic (Thomas et al 2002). Lesions were categorized as ischemic if there was evidence of increased macrophage or microglial activity, or evidence of astrogliosis. Although lesions were

present in depressed and non-depressed subjects, lesion etiology was not the same for both groups. All DWMLs in depressed subjects were ischemic, while less than one-third of lesions were ischemic in controls. This study provided conclusive evidence that lesions found on neuroimaging in depressed subjects are ischemic in nature. In summary, substantial evidence exists for a connection between depression and cardiovascular risk, as seen in the heart disease, hypertension, diabetes, obesity, and neuropathology literature.

Other factors in the etiology of late-life depression

Depression has for several decades been considered a disorder of neurotransmitter regulation. In particular, it has been held that diminished activity occurs in the serotonergic and noradrenergic neurotransmitter systems. Serotonin, or 5-hydroxytryptamine (5-HT), is believed to be important for diverse functions including feeding, emotional response, cognition, and motor behaviors. Noradrenalin, also known as norepinephrine, is involved in many of the same activities as serotonin and also has important roles in regulating blood pressure and in the body's response to external stimuli. Not surprisingly, all of these functions may be disturbed with depression. Numerous studies have attempted to deplete brain levels of serotonin and noradrenalin by decreasing the availability of precursor nutrients. These depletion studies have sometimes succeeded in triggering depressive symptoms or relapse (Delgado et al 1994). More recently, researchers have hypothesized that, rather than a simple downregulation, depression is characterized by an impairment of the homeostatic regulatory mechanisms for serotonin and noradrenalin (Gottfries 2001; Siever and Davis 1985). This

homeostatic dysregulation may confer vulnerability to unstable or erratic neurotransmitter outputs (Siever and Davis 1985). Diminished serotonergic and noradrenergic activity occurs in the aging brain which may establish a lower threshold for depression in the elderly (Gottfries 2001). Another factor which may further disrupt neurotransmitter activity is the presence of brain lesions that sever the pathways between brain regions (Taylor et al 2001) or damage the regions themselves (Steffens et al 2000a). As discussed previously, elderly depressed individuals are more likely to have brain lesions than either elderly controls or young depressives. A more recent mechanistic model contends that depression is associated with activation of the inflammatory response system (Danner et al 2003; de Beaurepaire 2002; Ford and Erlinger 2004; Maes et al 1999; Smith 1991; Tiemeier 2003). Stress is thought to induce an inflammatory response which includes the activation of cytokines and other inflammatory mediators. These mediators in turn influence neurotransmitter and neuroendocrine activity leading to a depressive condition (de Beaurepaire 2002; Maes et al 1999; Smith 1991). The inflammatory response may also increase oxidative stress (Widner et al 2001) and promote cerebrovascular damage leading to depression.

As with the relationship between cardiovascular disease and depression, the risk factors for depression are numerous and may interact with one another (see Figure 1.1). However, certain risk factors have been consistently associated with late-life depression, including being female, unmarried particularly if widowed, and of low socioeconomic status (SES) (Berkman et al 1986; Everson et al 2002; George 1996; Mitchell et al 1993). SES has been measured by income as well as years of

education; both were inversely associated with depression. Negative life events are also risk factors as they are thought to precipitate depressive episodes via a stress mechanism (George 1996; Hays et al 1998; Paykel 1994; Smith 1991). Similarly, functional disability is associated with depression, another example of a stress-inducer (Hays et al 1998; Jorm 1995). Functional disability is variously defined by scales of either basic activities of daily living (ADLs) or instrumental activities of daily living (IADLs), or a combinations of the two. As described earlier, physical illness is a risk factor for late-life depression, perhaps through a variety of pathways. Comorbid conditions may increase the likelihood of functional disability, may serve to promote vascular pathology, or may function through another mechanism, in promoting depression.

Low social support, particularly subjective social support, is believed to be a risk factor for depression, as social support is thought to buffer individuals from the effects of both internal and external stressors (Blazer et al 1992; George 1996; Hays et al 1998). In particular, individuals who have a confidant or who provide instrumental social support to others tend to have fewer depressive symptoms (Hays et al 1998). Family history is also considered to increase one's risk of depression, although this is thought to be less important in late-life depression than in early-life depression (Krishnan et al 1997; Mendlewicz 1976; Tiemeier 2003). Recently researchers have begun to investigate the importance of certain genotypes in the etiology of depression. In particular, there is interest in the serotonin transporter gene because of its relationship to serotonin activity, the apolipoprotein E gene which has been investigated for it role in dementia risk (Krishnan et al 1996), and the

tryptophan hydroxylase-2 gene which was recently linked to depression (Zhang et al 2005). However, the role of specific genes in late-life depression is unclear at this point. In summary, numerous biological, sociodemographic, and other factors are believed to affect the risk of depression.

Evidence for the role of nutritional factors in depression

General Nutritional Status

A limited number of studies have been conducted to investigate the relationship between depression and various dietary attributes including the B vitamins, antioxidants, fatty acids, and general nutritional status. Additionally, evidence that obesity may be causally related to depression was discussed previously. Unfortunately, poor methodologies including inadequate psychiatric assessment, vague or otherwise problematic dietary assessments, and failure to control for potential confounders, have plagued much research in the area of diet and depression. Also described earlier, concern has arisen about the relationship between poor nutritional status and depression, particularly among the elderly since they are already at increased nutritional risk. The general assumption has been that depression leads to malnutrition, anorexia, and weight loss (Cohen 1994; Gray and Gray 1989; Morley 1996), despite the fact that most research has been cross-sectional. One study found that currently depressed adults often consume less than the Recommended Dietary Allowances (RDAs) of kilocalories and nutrients, and individuals who consumed less than the RDA of energy were also not likely to meet the RDA for other nutrients (Christensen and Somers 1994). Forty-five percent of subjects did not meet the RDA for one or more nutrients. The researchers

concluded that it was the lack of food and not a deficient diet *per se* that was responsible for the failure to achieve RDA intake levels of specific nutrients. However, a number of problems existed with this study. The sample size was small (n = 29); no reporting of weight or weight history occurred, so it is difficult to evaluate if there had been weight loss or if the energy RDA was appropriate; subjects were moderately to severely depressed, so it is unclear if they were able to complete the detailed three-day food record used in the study; and there was no comparison group.

Studies which have focused on the elderly have also found poor nutritional status to be associated with depression (Arnold et al 2001; Mago et al 2000). Among 50 elderly individuals receiving home delivered meals, scores on the Beck Depression Inventory were negatively correlated with nutritional status as determined by the Mini-Nutritional Assessment (Arnold et al 2001). It is unclear whether these relationships would hold for a non-disadvantaged elderly population. In a study of 231 older adults living in nursing homes or congregate apartments, serum albumin was associated with depressive symptoms, as measured by the Geriatric Depression Scale (Mago et al 2000). Albumin was considered indicative of protein-energy malnutrition as well as for activation of acute phase factors, which might be related to inflammatory processes. Several studies have linked depression with weight loss in the elderly (Kolasa et al 1995; Morley 1996; Pirlich and Lochs 2001; Reife 1995), although it is difficult to ascertain if weight loss preceded the depressive episode or was the result of depression, treatment for depression, or comorbid disease. Depression was found to be a common explanation of geriatric

weight loss, accounting for weight loss in 18% of patients (Reife 1995). Another study of 2,178 community-living elderly individuals found that those who were underweight (body mass index < 21) were more likely to report depressive symptoms (Kolasa et al 1995).

The mechanism by which depression may lead to decreased appetite and weight loss and, in turn, malnutrition has not been elucidated. Although antidepressants have been blamed for causing the weight loss associated with depression (Morley 1996; Pirlich and Lochs 2001), the association of depression and weight loss preceded the invention of modern psychotropic medications. In addition, only the selective serotonin reuptake inhibitors (SSRIs) have been found to cause weight loss, and SSRIs have only been in use since the late 1980s (Levine et al 1987). Before that time, tricyclic antidepressants (TCAs) were widely prescribed, and they are known to cause weight gain. It seems clear that depression itself, not simply antidepressants, has effects upon body weight. One potential explanation is corticotrophin-releasing factor (CRF), a potent anorectic agent known to be elevated in people with depression (Morley 1996). Also possible is a role for brain lesions, particularly those in regions known to affect appetite.

In summary, evidence strongly supports the association between depression and weight loss. However, most researchers have neglected the possibility that weight status or weight change, including obesity and weight gain, could have a role in the etiology of depression, instead concluding that the relationship is unidirectional and leads only from depression to weight loss.

Macronutrients

Another focus of research has been the role of diet in affecting neurotransmitter levels. In particular, tryptophan, the amino acid precursor of serotonin, has received attention. Dietary tryptophan enters the bloodstream and competes with other large neutral amino acids for facilitated transport across the blood-brain barrier. Once in the brain tryptophan undergoes hydroxylation to 5-hydroxytryptophan, which, in turn, is decarboxylated to form serotonin (5-hydroxytryptamine or 5-HT) (Sandyk 1992). If increased tryptophan enters the brain and there are adequate coenzymes and cofactors, serotonin synthesis is upregulated (Sandyk 1992).

Three questions exist with regard to tryptophan: do depressed individuals have low levels of tryptophan or tryptophan-converting cofactors, does dietary manipulation affect serum and brain tryptophan levels, and do these dietary changes affect depression? Regarding the first question, whereas serotonin dysregulation does occur in depression, this dysregulation may not be related to serum tryptophan concentrations. Inadequate amounts of cofactor vitamins or enzymes or a general failure of homeostatic control of serotonin synthesis may be responsible. A longitudinal population study of over 29,000 elderly individuals who were not depressed at baseline found no association between intake of tryptophan or any other amino acid and low mood on follow-up (Hakkarainen et al 2003). Depressed individuals may experience food cravings aimed at increasing brain tryptophan levels. Since tryptophan uptake into the brain depends upon levels of other amino acids, including tyrosine, phenylalanine, leucine, isoleusine, and valine, increasing the ratio of tryptophan to other neutral amino acids in the blood will serve to increase

brain levels of tryptophan (Sandyk 1992). Increasing carbohydrates in a meal leads to increased insulin release, which may serve to decrease the availability of amino acid competitors (Benton and Donohoe 1999; Moller 2001; Sandyk 1992). Evidence exists that depressed individuals, including those with late-life depression, experience carbohydrate cravings, which may be aimed at increasing brain tryptophan levels (Kazes et al 1994; Wurtman et al 1988). One study demonstrated that people with untreated depression have a higher carbohydrate to protein ratio in their diet than controls and that this ratio decreases after antidepressant treatment (Kazes et al 1994). Other studies have shown that increased dietary carbohydrates are associated with improved mood, while protein-rich diets are associated with low mood states, which would appear consistent with the role of tryptophan (Benton and Donohoe 1999). However, this effect is not time- or meal-dependent, leading some to the conclusion that the carbohydrate effect upon mood is not mediated by tryptophan (Benton and Donohoe 1999). Carbohydrate consumption may be important for mood regulation, but its role has not yet been elucidated, particularly among those with clinical depression. Furthermore, an increased carbohydrate diet may be a coping strategy for adjusting tryptophan levels or may be a symptom or response to depression.

Ethanol and fat intake may also influence the risk of depression and comorbid brain lesions. Light to moderate alcohol intake may prevent late-life depression through a vascular mechanism similar or identical to that found for ischemic stroke (Berger et al 1999; Mukamal et al 2001). In a study of over 3,000 geriatric participants of the Cardiovascular Health Study, regular, light consumption of alcohol

(between 1 and 7 drinks per week) was found to be associated with decreased prevalence of white matter lesions as seen on brain MRI (Mukamal et al 2001). As brain lesions are thought to increase one's risk of late-life depression, it is reasonable to hypothesize that moderate alcohol intake may be protective. Alcohol may act through multiple mechanisms to decrease risk of ischemic lesions. Ethanol itself is known to raise levels of high density lipoprotein (HDL), a beneficial cholesterol scavenger. In addition, wines contain polyphenols, which may suppress platelet activation, as well as antioxidants (Rein et al 2000). This theory is supported by evidence that alcohol intake was lower in a study of elderly depression subjects when compared with non-depressed comparison subjects (Payne et al In press).

Omega-3 (ω-3) fatty acids have been the focus of recent investigations into the role of fats in depression. These polyunsaturated fatty acids (PUFAs), found primarily in seafood and flaxseed, are known to have numerous metabolic effects, including decreasing platelet aggregation and improving lipid profiles, which are conducive to lowering vascular risk (Connor and Connor 1997). Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the primary ω-3 fatty acids believed to be important to nervous system functioning. It should be noted that the majority of PUFAs in the American diet are ω-6 fatty acids found in vegetable oils. The ω-6 and ω-3 fatty acids differ in the location of their double bonds. An ecologic study found that the prevalence of major depression in different countries was negatively correlated with apparent fish consumption ($r = -0.8$, $p < 0.005$) (Hibbeln 1998). A sixty-fold variation in depression prevalence across nations existed, and

this pattern was similar to differences in coronary artery disease mortality, which may indicate that depression and heart disease are related to similar dietary factors.

A study of 1,767 Finnish adults found that frequent fish consumption (2 or more servings per week) was associated with a decreased risk of depressive symptoms (odds ratio = 0.63) as compared to infrequent consumption, while controlling for age, sex, marital status, education, employment status, disability, region, income, general health, smoking, alcohol and coffee consumption, and physical activity (Tanskanen et al 2001). Another study with 20 major depression patients found that blood measures of ω-3 fatty acids were negatively correlated with Hamilton depression scores (Adams et al 1996). In particular, erythrocyte levels of EPA were negatively associated, while the ω-6 to ω-3 ratio was positively associated with depression scores. Furthermore, these correlations were not explained by dietary intake, leading some researchers to conclude that there may be abnormal ω-3 fatty acid metabolism in depression (Adams et al 1996; Maes et al 1999). Another study found that low plasma levels of DHA predicted low levels of 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin (Hibbeln et al 1997). Low levels of 5-HIAA are associated with not only depression but also suicidal behavior (Lidberg et al 1985; Samuelsson et al 2006). DHA is concentrated in neural cells and synapses, and is likely to play a role in the synthesis, release, and reuptake of serotonin (Lombard 2000).

A study of 34 depressed patients and 14 controls found lower levels of ω-3 fatty acids in phospholipids and cholesterol esters of those with depression than in control subjects (Maes et al 1999). Along with other measures this result was considered

indicative of activation of the inflammatory response system (IRS), which might lead to increases in lipid peroxidation, neuronal membrane damage, and disturbed serotonin metabolism. A positive association was found between the ω-6 to ω-3 fatty acid ratio and both activation of inflammatory factors and depression. Some have speculated that the striking increases in depression prevalence over the past 100 years are related to changes in dietary ratios of ω-6 to ω-3 fatty acids which have increased significantly in the average American diet over the same period (Maes et al 1999). In addition to these preliminary studies showing that fish oils may lower risk of depression, ω-3 fatty acids may serve as therapeutic agents for depression (Nemets et al 2002; Peet and Horrobin 2002; Puri et al 2001). In summary, ω-3 fatty acid consumption and metabolism may be important in the etiology and treatment of major depression, which would be consistent with the effect that these fats have on vascular risk and disease.

Micronutrients

Micronutrients, particularly the B vitamins, have also been investigated their potential role in depression. In a double-blind placebo-controlled trial, a megadose vitamin combination was found to be associated with improvements in mood among 101 college students (Benton et al 1995). The megadose combination was administered for one year and included vitamins A, C, E, thiamin (B_1), riboflavin (B_2), niacin (B_3), pyridoxine (B_6), folate, and biotin. Unfortunately, no psychiatric evaluation of depression was performed, only an imprecise measure of self-rated mood. In addition, even if the vitamin complex were protective of depression, it is not known which vitamins may have played the most significant roles.

One of the early B vitamin studies found that a vitamin B_6 supplement decreased depressive symptoms in oral contraceptive users who were B_6-deficient (Adams et al 1973). Vitamin B_6 or pyridoxine has multiple functions in addition to its role in carbohydrate and protein metabolism. Of possible relevance to depression are its roles in tryptophan metabolism and myelin sheath formation. As mentioned earlier, tryptophan is the amino acid precursor of serotonin, which is thought to be one of the critical neurotransmitters in depression. The myelin sheath is a fat-containing covering of nerve cell projections which serves to insulate the neuron from electrical impulses and to increase the rate of signal conduction. Myelin gives the characteristic whitish appearance to white matter of the brain and peripheral nerves. If the myelin is damaged or inadequately synthesized, impaired neuronal conduction by the affected cells may result. The consequences of this damage would depend upon which brain regions were involved, although mood disturbances are possible.

Another study from the 1970s found that among psychiatric inpatients with a history of poor diet, those with depression were more likely to have low levels of vitamin B_6 (Carney et al 1979). A similar study by the same group found that psychiatric inpatients with vitamin B_6 deficiencies were more likely to have a mood disorder than non-deficient patients (Carney et al 1982). A study of 101 depressed outpatients found that 21% had abnormally low pyridoxine levels prior to antidepressant treatment (Stewart et al 1984). Low vitamin B_6 was also found to be associated with neurological symptoms, which would be consistent with its role in myelin sheath formation. Pyridoxine deficiency has also been confirmed in a sample of geriatric depression subjects (Bell et al 1991). A study in Europe estimated that

25% of Finnish and Dutch elderly individuals were B_6-deficient (Tolonen et al 1988). If pyridoxine is related to depression, then a high prevalence of deficiency in the elderly would put a large portion of the population at risk. However, none of the vitamin B_6 studies has shown more than a correlation between current depression and low vitamin levels. Also, no evidence exists that pyridoxine deficiency causes an increased risk of depression. Depression itself may cause low B_6 levels, or there may be no causal pathway between the two conditions.

Cobalamin or vitamin B_{12} has also been investigated for its role in nervous system disorders including depression, although the main focus of research has been dementia. Vitamin B_{12} functions in folate metabolism, serotonin synthesis, DNA synthesis, myelin sheath formation, and as a coenzyme for fatty acid and amino acid oxidation (Penninx et al 2000). Cobalamin is particularly important for nerve health; a deficiency can lead to permanent neurological damage. Neuropsychiatric disorders may be present with cobalamin deficiency even in the absence of anemia or macrocytosis, the classic signs of B_{12} deficiency (Lindenbaum et al 1988). One study found that B_{12}-deficient patients had lower levels of 5-HIAA, the serotonin metabolite, as compared with control subjects (Botez et al 1982). None of these low 5-HIAA subjects exhibited depression; however, there were only six subjects.

Several recent large-scale studies, mostly done in Europe, have had conflicting results with regards to depression and cobalamin status. A Baltimore study of 700 geriatric women with physical disabilities showed that those with B12 deficiency were twice as likely to be severely depressed, according to the Geriatric Depression

Scale, as were non-deficient participants (Penninx et al 2000). The prevalence of depression (31.7%) was high in this sample as might be expected among those with functional disabilities. Another study assessed vitamin status in 806 elderly individuals living in Rotterdam and also found that B_{12} deficiency was associated with depression, after controlling for cardiovascular disease and functional disability (Tiemeier et al 2002). The European SENECA project population study assessed cobalamin status and longitudinal depressive symptoms, as measured with the Geriatric Depression Scale, in a group of 586 elderly subjects (Eussen et al 2002). Baseline vitamin B_{12} status was not associated with depressive symptoms during follow-up. A Norwegian study of 5,948 middle-aged and elderly subjects also found no association between depression and cobalamin levels. Finally, a community study in Australia measured vitamin B_{12} status in 412 elderly individuals and found no correlation with depressive symptoms (Sachdev et al 2005). No satisfactory explanation for the contradictory findings in these studies exists although sampling may have had a role. At this time compelling evidence does not exist that low cobalamin levels promote depression.

Folate has received more attention than the other B vitamins for its purported role in the etiology of depression. This B vitamin functions in myelin formation, serotonin synthesis, and in the methylation reactions of phospholipids (critical to cell membrane functioning) and homocysteine (for the conversion to methionine). As early as the 1960s, there were reports of low serum folate levels in psychiatric patients (Hunter et al 1967). One study of 150 psychiatric inpatients found that 50% had low folate levels; however, many of these subjects were alcoholics or had used

medications which were known to diminish folate status (Hunter et al 1967). Another study of inpatients found that depressed patients had significantly lower folate levels than either non-depressed psychiatric patients or non-psychiatric patients (Ghadirian et al 1980). In addition, folate levels were inversely associated with Hamilton Depression (HAM-D) scores. Other clinical studies have found that low folate status among depressed individuals, including those with late-life depression, was negatively associated with duration of depressive episode, length of hospitalization, and resistance to antidepressant treatment and electroconvulsive treatment (ECT), and positively correlated with 5-HIAA levels (Abou-Saleh and Coppen 1986; Bell et al 1990; Botez et al 1982; Bottiglieri et al 1990; Levitt and Joffe 1989).

Unfortunately, these studies failed to control for comorbid disease as well as many other risk factors for depression. Researchers have speculated that folate deficiency is secondary to depression (Abou-Saleh and Coppen 1986; Morris et al 2003), perhaps because increased utilization of folate occurs during a depressive episode (Levitt and Joffe 1989). However, since these studies had no dietary, longitudinal folate, or other biochemical measures, it is not known if there was increased utilization of folate. In addition, of six population and community studies, one found a correlation between low blood folate levels and depressive symptoms (Sachdev et al 2005), one found a negative association between dietary folate intake and later depression diagnosis (Tolmunen et al 2004), and four failed to find any association between folate status and depression (Bjelland et al 2003; Eussen et al 2002; Lindeman et al 2000; Penninx et al 2000). Recently evidence of a genetic polymorphism for MTHFR (methyltetrahydrofolate reductase) related to depression

has arisen (Bjelland et al 2003; Kelly et al 2004; Lewis et al 2006). Genetic factors related to folate metabolism may mediate the relationship between folate intake and depression and may help explain the contradictory findings from population folate studies.

Increased homocysteine has recently gained attention as a potential risk factor for both depression and heart disease (Alfthan et al 1997; Bjelland et al 2003). Since folate is necessary for the methylation of homocysteine to methionine, one may hypothesize that some of the detected associations between folate and depression may actually be explained by homocysteine. Also logical is the notion that homocysteine may be related to vascular depression risk. Two elderly population studies have found hyperhomocysteinemia to be related to depression, although in one study this association did not remain after controlling for functional disability and cardiovascular disease (Bjelland et al 2003; Tiemeier et al 2002). It is premature to conclude that either folate or homocysteine are related to depression. Longitudinal studies, which include diet assessment, biochemical measures, and psychiatric evaluations, are needed in order to determine the association of depression with homocysteine and folate, as well as the other B vitamins.

Nutrients Related to Cardiovascular Disease

With the exception of folate and omega-3 fatty acids, few studies have investigated the role of cardiovascular nutrients in depression. It is reasonable to speculate that many nutrients could impact the risk of depression, particularly late-life depression of vascular origin. One study which examined diet in 196 elderly subjects found that those with late-life depression had higher intakes of saturated fat

and cholesterol, lower alcohol intake, and higher BMI when compared to non-depressed elderly subjects (Payne et al In press). Oxidative stress has been proposed as the underlying cause of neurotransmitter dysregulation, increased homocysteine levels, and low folate levels, in depression (Widner et al 2001). In support of this hypothesis, a few studies have found an association between antioxidant vitamins and mood. A one year double-blind trial of an antioxidant "cocktail" was found to promote improved mood and cerebral blood flow in nursing home residents (Clausen et al 1989). This antioxidant mixture included 300 μg selenium, 45 mg zinc, 270 mg vitamin C, 2.7 mg β-carotene, 6 mg pyridoxine, 465 mg vitamin E (α-tocopherol), and 250 mg γ-linolenic acid. Since these nutrients are known to have functions in addition to their antioxidant properties, it is possible that their effect upon mood and cerebral blood flow was not related to reductions in oxidative stress. A study of 880 individuals between 74 and 79 years of age included measurement of plasma micronutrients and found that antioxidant levels were negatively correlated with depression scores (Haller et al 1996). Another study found that supplementation of selenium, another antioxidant, led to improved mood in a 5 week double-blind, cross-over design (Benton and Cook 1991).

More recently, a study found lower levels of serum vitamin E in patients with major depression, as compared with controls, suggesting that depressed individuals may have decreased antioxidant defenses (Maes et al 2000). Serum vitamin E (or α-tocopherol) and lycopene, an antioxidant carotenoid, were found to be negatively associated with white matter hyperintensities on MRI in 355 elderly participants of the Austrian Stroke Prevention Study (Schmidt et al 1996). The association

remained for α-tocopherol even after controlling for coronary heart disease risk factors. Although this study did not involve depression subjects, since hyperintensities are associated with late-life depression, it is possible that vitamin E may be protective.

Also in support of antioxidants being protective, a study of 418 adults found that women with high fruit and vegetable consumption were less likely to be depressed, as compared with low consumers (Cook and Benton 1993). This finding is consistent with large cohort studies which have shown that fruits and vegetables are protective for ischemic stroke, and heart disease mortality (Joshipura et al 1999; Rissanen et al 2003). Overall, studies have begun to show that antioxidants may be related to depression. Longitudinal studies are needed, particularly ones which include subjects with diagnosis of major depression. Dietary assessment will be critical in determining whether antioxidant intake is low in depressives or whether increased turnover of antioxidants exists in the presence of normal intake levels.

While few studies assessing the role of cardiovascular nutrients in depression exist, the literature indicates the importance of these nutrients to other vascular conditions; so it is reasonable to hypothesize that they play a role in late-life depression. Considered of paramount importance are the quantity and type of dietary fats (Ascherio 2002; Hu and Willett 2002). Although the role of total fat has recently been questioned in regards to cardiovascular disease risk (Howard et al 2006), much work continues into the specific roles of fat types. Saturated fats are believed to increase serum concentrations of total and low-density lipoprotein cholesterols, both of which increase vascular risk, while polyunsaturated fats have

opposite effects (Ascherio 2002; Hu and Willett 2002; Nordoy et al 1993). A higher Keys score (Keys et al 1965a; Keys et al 1965b), an estimate of the cholesterol-raising capacity of a diet and primarily determined by dietary saturated and polyunsaturated fats, has been found to increase the risk of CHD (relative risk = 1.60, $p < 0.05$) among 1,001 middle-aged men (Kushi et al 1985). Trans-unsaturated fats have been found to have detrimental effects upon serum lipids, similar to those from saturated fat, and to increase risk of CHD as reported in the Nurses' Health Study (relative risk = 1.5, $p < 0.001$) (Willett et al 1993). The effects and benefits of omega-3 fats have been described earlier. Fiber is another dietary component believed to decrease risk of heart disease, although the mechanisms by which it acts are not fully understood. Certain subtypes of fiber have been found to decrease levels of serum cholesterol. Two large cohort studies found that fiber intake was associated with decreased risk of CHD (Kushi et al 1985; Wolk et al 1999). Whole grains contain fiber and polyunsaturated fats, as well as other beneficial nutrients including antioxidant vitamins, and have been found to decrease the risk of ischemic stroke and heart disease (Jacobs et al 1998; Liu et al 2000; Liu et al 1999).

In addition to these nutrients and foods, dietary quality, an aggregate measure of compliance with dietary guidelines, has been associated with all-cause mortality and chronic disease in three large cohort studies (Kant and Graubard 1999; McCullough et al 2002). As substantial evidence exists linking late-life depression with vascular disease, and linking vascular disease with dietary intake, investigations of the relationship between cardiovascular nutrients and depression are clearly needed.

CHAPTER IV

NUTRITIONAL FACTORS OF LATE-LIFE DEPRESSION SUBTYPE

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Abstract

Objective-Vascular nutritional factors (dietary attributes believed to either promote or prevent cardiovascular disease) were examined in three groups of elderly individuals, those with vascular depression, non-vascular depression, and comparison subjects.

Method-Nutrient intake was assessed in 250 elderly subjects (58 vascular, 53 non-vascular, 139 comparison) using a Block 1998 food frequency questionnaire. Nutrient and food intake, body mass index, and Keys score (a measure of the serum cholesterol-raising capacity of the diet), were determined. Subjects were age 60 or over, and were participants in a longitudinal study of major depression. All subjects received medical comorbidity assessments, and depression subjects received psychiatric assessment and treatment. Depression subjects were categorized as having vascular depression if they had ratings of 2 or greater on either subcortical gray matter or deep white matter hyperintensities on MRI; otherwise, they were categorized as having non-vascular depression.

Results-Nutritional factors differed between groups. Depression subjects (both groups) consumed more cholesterol, trans-unsaturated fat, and high-fat dairy products, had higher BMI and Keys scores, and consumed less fruit, than comparison subjects. Vascular depression subjects consumed fewer low-fat dairy products, while non-vascular depression subjects consumed less alcohol than comparison subjects. After controlling for age, sex, race, education, hypertension, diabetes, social support, stress, and total kilocalories, both depression groups consumed fewer whole grains than comparison, while vascular subjects consumed

less lycopene than comparison subjects. Omega-3 fatty acids were not found to be associated with group in any analysis.

Conclusions-Vascular nutritional factors differed between depression and comparison subjects but tended to be similar across the two depression groups (vascular and non-vascular). This may indicate the importance of vascular nutrients to late-life depression, regardless of comorbid cerebrovascular disease.

Introduction

Major depression is one of most common mental disorders and the leading cause of disability worldwide (WHO 2001). Depression is a common affliction in individuals over age 60 with a prevalence between 2.7 and 12 percent in the general population but significantly higher among elderly medically ill and those in nursing homes (Papadopoulos et al 2005; Steffens et al 2000). Recently a distinction has been made between vascular and non-vascular depression among older individuals, based upon evidence of comorbid hypertension or other vascular risk factors in the context of cerebrovascular pathology (Alexopoulos et al 1997; Krishnan et al 1997). In particular, subjects with significant brain hyperintensities, also known as lesions, have been categorized as having vascular depression (Krishnan et al 1997). These vascular conditions are believed to be related to both the etiology and course of depression in these individuals (Taylor et al 2003) The course of vascular depression is characterized by a higher rate of recurrence, lower rate of remission, more treatment resistance, and an increased likelihood of progression into dementia, as compared with non-vascular depression (Baldwin and Tomenson 1995; Taylor et al 2003). In comparison, non-vascular depression is characterized by younger age, earlier age of onset, greater depressed mood, and a family history of mental disorder and suicidality (Alexopoulos et al 1997; Krishnan et al 1997). Research into the correlates and causes of these two types of depression is critical to understanding the occurrence, course, and outcomes of late-life depression.

Given the prominence of vascular conditions, it may be important to consider whether specific dietary factors are associated with vascular depression. There is

evidence of an association between vascular nutritional factors (dietary attributes believed to either promote or prevent cardiovascular disease) and depression; however, researchers have not investigated these factors in subsets of vascular and non-vascular depression subjects. Cross-sectional clinical and population studies indicate that depression is negatively associated with both fish consumption (Hibbeln 1998; Tanskanen et al 2001) and plasma levels of omega-3 fatty acids, a type of fat found in fish and believed to improve blood vessel health and reduce clotting (Adams et al 1996; Maes et al 1999; Tiemeier et al 2003). Both cross-sectional and longitudinal studies have shown that high body mass index (BMI), an indirect measure of adiposity, is associated with current and future depression (Payne et al In press; Roberts et al 2003; Roberts et al 1997). A previous study by our group found that elderly individuals with depression were more likely than comparison subjects to consume a diet high in saturated fat and cholesterol, and lower in alcohol, while having a higher BMI (Payne et al In press). In addition to preliminary evidence of an association between vascular dietary factors and depression, two studies have been supportive of a relationship between diet and brain lesions, although they did not involve depressed individuals. In a study of over 3,000 geriatric participants of the Cardiovascular Health Study, regular, light consumption of alcohol (between 1 and 7 drinks per week) was found to be associated with decreased prevalence of white matter lesions as seen on brain MRI, while controlling for potential confounders (Mukamal et al 2001). Serum vitamin E (or α-tocopherol) and lycopene, an antioxidant carotenoid, were found to be negatively correlated with white matter hyperintensities on MRI in 355 elderly participants of the

Austrian Stroke Prevention Study (Schmidt et al 1996). The association remained for α-tocopherol even after controlling for coronary heart disease risk factors. In summary, although there is some evidence of an association between vascular dietary factors and both depression and late-life brain lesions, it is unknown whether elderly individuals with specific subtypes of depression (vascular or non-vascular) differ in terms of nutritional factors.

We conducted this study with a group of older adults who were identified as having vascular or non-vascular depression (current or prior), or no history of depression. Vascular depression subtype was defined by qualitative assessment of brain lesions on MRI. We sought to determine whether certain nutritional factors were associated with depression subgroup. We hypothesized that the reported intakes of total fat, saturated fat, meats, high-fat dairy products, and cholesterol, would be higher in the vascular depression group, as compared with the non-vascular and comparison groups. Similarly, we predicted that body mass index (BMI) would be higher in the vascular depression group. We also predicted that protective nutritional factors, such as intake of omega-3 fatty acids, vitamin E, fiber, lycopene, alcohol, fruits, vegetables, whole grains, and low-fat dairy products, would be lower in the vascular depression group, as compared with the non-vascular and comparison groups.

Method

Design

This cross-sectional project occurred within a larger longitudinal clinical study of depression in older adults which began in 1994. Located at Duke University Medical

Center, the NIMH Mental Health Clinical Research Center (MHCRC), the Longitudinal Study of Depression in Later Life, and the Conte Center for the Neuroscience of Depression are coordinated, ongoing studies of elderly depression and comparison subjects. Nutrition assessments were added in March 1999, after which time all comparison subjects, and depression subjects who were deemed clinically suitable based upon acceptable depression management and cognitive functioning, received a nutrition questionnaire. Going forward from March 1999 controls received a nutrition assessment at study baseline, and depression subjects received them when deemed clinically suitable.

Sample

This sample included patients of the Duke University Psychiatric Service with a primary diagnosis of major depression at study baseline and comparison subjects recruited from the Aging Center Subject Registry at Duke University. Enrollment was restricted to those 60 years or older who could speak and write English. Only subjects who received a nutrition questionnaire were included in analyses for this paper.

Exclusion criteria included a concurrent diagnosis of a major psychiatric or neurological illness. Subjects were also excluded if they exhibited significant cognitive impairment, as indicated by their Mini-Mental State Examination (MMSE) (Folstein et al 1975) score of less than 26 (out of 30). In addition, those with severe depression symptomatology were excluded because of concerns that the lengthy (8 page) Block 1998 food frequency questionnaire would present an undue burden to those individuals. This criterion did not require a specific depression rating cut-off

but was instead determined by the treating psychiatrist on a case-by-case basis. This allowed for flexibility based upon symptomatology and clinical stability. Subjects were also excluded if they had metal in the body which was a contraindication for MRI. Subjects were not excluded for following special dietary regimens.

Comparison subjects were required to have a non-focal neurological examination, no self-report of neurological or depressive illness, and no evidence of a depression diagnosis based on the Diagnostic Interview Schedule portion of the Duke Depression Evaluation Schedule (Robins et al 1981).

After complete description of the study to the subjects, written informed consent was obtained. This research protocol has been reviewed and approved by the Duke University Medical Center Institutional Review Board. In addition, data analyses for this project were approved by the Public Health Institutional Review Board at the University of North Carolina at Chapel Hill (as part of a doctoral dissertation research project).

Treatment

Depression patients received individualized treatment from a psychiatrist, who followed them throughout the study. Most received antidepressant medication; some received electroconvulsive treatment or psychotherapy.

Measures

Assessments included psychiatric, medical, nutrition, and imaging measures. At baseline and yearly thereafter a trained interviewer administered the Duke Depression Evaluation Schedule (DDES) in-person to each subject. The DDES, a

composite diagnostic interview instrument, included sections of the NIMH Diagnostic Interview Schedule which assesses depression, items on self-reported physical health including diabetes mellitus and hypertension (Robins et al 1981), four subscales of the Duke Social Support Index (George et al 1989; Landerman et al 1989), and a scale that assessed the frequency and severity of stressful life events during the six months preceding the interview (Landerman et al 1989). A composite subjective social support variable (scale between 1 and 30) was used for these analyses and was created from ten individual questions about one's satisfaction with personal relationships (George et al 1989; Hays et al 2001). Self-report of one's average degree of stress was used to control for stress level (scale between 1 and 10). Body mass index or BMI ([weight in kg]/[height in m]^2) was calculated from self-report.

Clinical assessments for depression subjects, including the Montgomery-Asberg Depression Rating (MADRS), were performed at study baseline and quarterly thereafter (Montgomery and Asberg 1979). Nutrition assessments were administered annually, based upon the time of a subject's initial food frequency questionnaire completion date. Follow-up questionnaires were only used if the initial one was unacceptable (greater than 15 questions unanswered). Brain MRI was performed every two years, starting at study baseline. See below for details on nutrition and MRI assessments.

Nutrition Protocol

The 1998 Block Food Frequency Questionnaire (FFQ) was used for nutrition assessment. This tool is an updated version of the FFQ developed by Gladys Block

at the National Cancer Institute. The Block FFQ was designed to estimate the components of a person's total dietary intake over the preceding year (Block 1992). It has been validated against and shows moderate correlation with other nutrition assessment instruments, including the Willett FFQ and multiple-day dietary records (Block et al 1992; Subar et al 2001). The Block FFQ is frequently used for longitudinal studies, allows for dietary comparisons between groups, necessitates no time-intensive interviews, requires less data management relative to other diet assessment methods, and provides for timely data analysis. The Block FFQ is a semi-quantitative assessment in that the respondent is asked to estimate both the frequency of consumption of listed food items (never, a few times per year, once per month, 2-3 times per month, once per week, 2 times per week, 3-4 times per week, 5-6 times per week, or everyday), and the typical serving size of that food. The 1998 Block questionnaire (Block Dietary Data Systems; Berkeley, CA) is a revision that includes standardized portion sizes, a wider variety of low-fat foods, questions on dietary supplements, and an updated database to reflect folate fortification in the food supply.

Returned questionnaires were checked for completeness and rejected if more than 15 food items were skipped (n=7) and then sent to Block Dietary Data Systems for scanning and nutrient analysis by comparison of responses to a nutrient database. In this way, responses such as servings of oranges, strawberries, and broccoli were converted to nutrient intake estimates for vitamin C, folate, and fiber. Output files containing both raw and nutrient estimate data were returned to the investigators.

Automated FFQ results included the following dietary variables: energy, total fat, saturated fat (SFA), polyunsaturated fat (PUFA), trans-unsaturated (trans) fat, omega-3 fatty acids (ώ-3FAs), fiber, vitamin E (total from foods and dietary supplements), alcohol, cholesterol (CHOL), and servings per day of fruits, vegetables, and whole grains. The Keys score, an estimate of the serum cholesterol-raising capacity of diet, was calculated from dietary data using the formula: [2(% of energy as SFA) – 1.35(% energy as PUFA) + 1.5(CHOL per 1000 kcal)$^{1/2}$] (Keys et al 1965). In addition, servings per day of high and low-fat dairy products, and meats, were calculated from individual food items on the FFQ. High-fat dairy products were estimated by summing intake of whole and 2% milk, cheese (except for individuals who reported regular consumption of low-fat cheeses), ice cream, butter, and pizza. Similarly, low-fat dairy products were estimated from intake of skim and 1% milks, low-fat cheese, and low-fat ice cream. Both categories of dairy products were underestimated since some dairy items on the FFQ were excluded from consideration. This was because of an inability to determine the fat content of certain food products, such as yogurt, or because a questionnaire item included both dairy and non-dairy foods (such as the item on hamburgers and cheeseburgers). Meat servings were calculated by total intake reported for the following food items: bacon, breakfast sausage, hamburgers/cheeseburgers/meat loaf, meat tacos/burritos/enchiladas/tamales, steaks/roasts, pork/ham, veal/lamb/venison, ribs, liver, gizzard/chitlins, mixed dishes with meat or chicken, fried chicken, non-fried chicken/turkey, hot dogs, and lunch meats. This measure of meat consumption differs from that typically estimated from the FFQ, which uses the

1996 U.S. Department of Agriculture Food Guide Pyramid definition of meat. The pyramid group definition includes, in addition to true meats, other non-dairy concentrated protein sources, such as eggs, peanut butter, beans, and seafood.

Magnetic resonance imaging (MRI)

Depression subtype, vascular versus non-vascular, was defined by qualitative assessment of the baseline brain MRI scan (Krishnan et al 1997; Krishnan et al 2004). Subjects were imaged under an IRB-approved protocol, with a 1.5 Tesla whole-body MRI system (Signa, GE Medical Systems, Milwaukee, WI) using the standard head (volumetric) radiofrequency coil. Padding was used to immobilize the head without causing discomfort. The scanner alignment light was used to adjust the head tilt and rotation so that the axial plane lights passed across the cantho-meatal line and the sagittal lights were aligned with the center of the nose. A rapid sagittal localizer scan was acquired to confirm the alignment.

The first set of images was obtained with an axial (horizontal) plane, multi-section, T1-weighted pulse sequence (TR = 500 ms, TE = 15 ms) with a 256 x 192 data acquisition matrix, 5 mm section thickness, a 20 cm field-of-view (FOV), 1 excitation per phase-encoding increment (1 Nex) and a 32 KHz (±16KHz) full imaging bandwidth. This was followed by a long TR (2500 msec), double-echo (TE = 30 and 80 msec) spin-echo data-acquisition sequence using the same FOV, section thickness, bandwidth and spacing, 256 x 192 data acquisition matrix, and 1 Nex. Saturation of spins outside the imaging volume (standard gap 15 mm) and flow compensation (gradient moment nulling) were employed to eliminate artifacts due to flowing blood and cerebrospinal fluid. These images were obtained in two separate

acquisitions with a 5 mm gap between sections for each acquisition. The second acquisition was offset by 5 mm from the first so that the resulting data set consisted of contiguous sections.

An additional set of images was obtained for subjects who enrolled after October 2001. This FLAIR (fluid-attenuated inversion recovery) series is used primarily for detection of hyperintensities. Sequence parameters were TR = 9000 ms, TI = 2250, TE = 100 ms, with a 256 x 256 data acquisition matrix, 2 mm section thickness, a 25 cm field-of-view (FOV), and a 32 KHz (±16KHz) full imaging bandwidth. These images were obtained in two separate acquisitions with a 4 mm gap between sections for each acquisition. The second acquisition was offset by 2 mm from the first so that the resulting data set consisted of contiguous sections.

The MR images were qualitatively assessed for the presence of lesions by a neuroradiologist. For scans with FLAIR sequence, evaluation began on the FLAIR and was then confirmed on T1-weighted sequence. Lesion ratings performed for this study have been described previously (Payne et al 2002). Ratings included the following Coffey scale items:

Deep white matter hyperintensity (lesion-intense regions within the white matter tracts of cerebrum): 0 - absent; 1 - punctate foci; 2 - beginning confluence of foci; 3 - large confluent areas

Subcortical gray matter hyperintensity (lesion-intense regions within the basal ganglia and other subcortical gray matter structures): 0 - absent; 1 - punctate; 2 - multi-punctate; 3 – diffuse

Depression subjects who received a rating of 2 or higher on either subcortical gray or deep white lesions were categorized as having vascular depression (Krishnan et al 1997); otherwise, they were categorized as having non-vascular depression. Depression subtype was defined by baseline MRI; for subjects without a baseline MRI or for whom the baseline MRI was not assessed for lesions, the Year 2 MRI was used for depression group categorization purposes.

Analyses

Statistical analyses were run using two software programs: JMP and SAS Enterprise Guide (SAS Institute, Cary, NC).

Data on hypertension, diabetes, social support, and stress were obtained from the closest annual DDES instrument. Analyses first assessed the potential for responder bias. Bivariate comparisons were made between individuals with acceptable FFQs ("responders") and those who either did not return a questionnaire or who returned an unacceptable one (together categorized as "nonresponders"). Variables of interest included age, sex, race, social support, average stress, years of education, depression subgroup, hypertension, and diabetes.

Bivariate analyses were performed to examine the characteristics of the sample (responders only) by group status (vascular depression, non-vascular depression, or comparison). Analyses of variance (ANOVA) were used for continuous variables, including age, stress, social support, years of education, and all nutritional variables. Chi-square tests were used for categorical variables, including sex, race (white versus non-white), hypertension, and diabetes. To look at group status by nutritional characteristics, controlling for potential confounders, we ran seventeen separate

analyses of covariance (ANCOVA) using indicator variables for group status. The dependent variables of interest were total energy (kcal), dietary cholesterol (mg), saturated fat (g), trans-unsaturated fat (g), omega-3 fatty acids (mg), fiber (g), lycopene (µg), alcohol (percentage of total energy), total vitamin E (IU), body mass index (kg/m^2), Keys score, and servings per day of vegetables, fruits, whole grains, meats, and high and low-fat dairy products. To control for potential confounding, each model contained a set of covariates. All models included age, sex, race, education, social support, average stress, hypertension, and diabetes as control variables. Finally, total energy (kcals) was included as a covariate in all food and nutrient models except alcohol (since this variable is alcohol as a percentage of total kilocalories). A typical model was as follows: saturated fat = β_0 + $\beta_1$dummy1 (vascular depression vs. not) + $\beta_2$dummy2 (non-vascular depression vs. not) + β_3Age + β_4Sex+ β_5Race + β_6Education+ β_7Hypertension+ β_8Diabetes + β_9Social Support + β_{10}Stress + β_{11}Calories + ε

Adjusted mean values were calculated from ANCOVA models using LSMEANS.

Results

A total of 250 subjects completed the FFQ, out of 312 who were given a questionnaire (58 of 86 vascular depression subjects; 53 of 74 non-vascular depression subjects; 139 of 152 comparison subjects). Nonrespondents did not differ from respondents in terms of age, sex, race, hypertension, diabetes or education, but they were more likely to have been in one of the depression groups than in the comparison group, and were more likely to report poorer social support

and higher stress levels than respondents. Eleven subjects were dropped from the multivariate analyses due to missing data on the DDES.

The sample characteristics are shown in Tables 4.1 and 4.2. Bivariate analyses between group status (vascular, non-vascular, and comparison) and demographic, medical comorbidity, social support, stress, and nutritional variables were performed. Age, education, hypertension, social support, and stress were significantly associated with group. Subjects in the vascular depression and comparison groups were typically older than non-vascular depression subjects. Being in either depression group was associated with fewer years of education, poorer social support, and higher stress when compared with non-depressed subjects. Of the nutritional variables, 8 were significant on ANOVA: cholesterol, Keys score, trans fat, high-fat dairy, low-fat dairy, fruit, alcohol, and BMI. Subjects in both depression groups consumed more cholesterol, trans fat, and high-fat dairy products, had higher BMI and Keys scores, and consumed less fruit, when compared to non-depressed subjects. Vascular depression subjects consumed less low-fat dairy products than comparison subjects, while non-vascular depression subjects consumed less alcohol than comparison subjects.

Multivariable models examined the association between group status and each of the seventeen nutritional variables, while controlling for age, sex, race, education, hypertension, diabetes, social support, and stress. Total caloric intake was included in all models except alcohol and BMI. Three models were significant for group status: Keys score ($F_{2, 238}$ =3.41; $p < 0.03$), whole grains ($F_{2, 238}$ =3.58; $p < 0.03$), and lycopene ($F_{2, 238}$ =3.42; $p < 0.03$). Non-vascular depression subjects had higher

Keys score and lower whole grain intake than comparison subjects. Vascular depression subjects consumed fewer whole grains and less lycopene than comparison subjects. Adjusted means, calculated from multivariable (ANCOVA) models, are presented in Table 4.3. Overall there were minimal differences in dietary intake between vascular and non-vascular subjects.

Discussion

To our knowledge, this study is the first to investigate vascular nutritional factors by MRI-based depression subtype in late-life depression. The major findings of this study were that vascular nutritional factors differed between depression and comparison subjects but tended to be similar across the two depression groups (vascular and non-vascular as rated on MRI). Overall, depression subjects, regardless of depression subtype, reported diets that are believed to promote vascular disease. This may indicate that vascular nutrients and foods are related to depression in subjects with and without comorbid vascular disease. In addition, this may have important implications for depressed individuals who are already at increased risk of cardiovascular chronic diseases. An atherogenic diet may promote both the development and exacerbation of comorbid vascular disease in individuals with depression. Comparing depression subjects to controls, dietary cholesterol, trans fat, high-fat dairy products, and Keys score and BMI were higher, while fruit intake was lower. Low-fat dairy consumption was lower among vascular depression subjects and alcohol intake was lower among non-vascular depression subjects than among comparison subjects. In multivariable analyses, lower whole grain and lycopene intake, and higher Keys score were associated with one or both of the

depression groups. Omega-3 fatty acids (ώ-3FAs), recently investigated for their potential role in mood disorder etiology and treatment, were not associated with depression group in either bivariate or multivariable analyses. Lycopene was the only nutrient found in multivariable analyses to differ only between vascular depression and comparison subjects, but not between non-vascular and comparison subjects.

The findings of this study are consistent with prior work showing a relationship between vascular nutritional factors and late-life depression. Payne and colleagues (Payne et al In press) also found higher Keys score, BMI, and dietary cholesterol, and lower alcohol intake in elderly depression subjects when compared to never-depressed subjects. The Keys score and cholesterol associations remained after controlling for covariates. Cross-sectional as well as longitudinal studies have been supportive of a relationship between increased BMI and intra-abdominal fat, and the occurrence of depression (Roberts et al 2003; Thakore et al 1997), as was found in bivariate analyses for our study. Whole grains, recently investigated for their cardioprotective properties, have not been investigated previously in depression but our finding of lower intake among both depression groups is consistent with other studies showing an association between vascular nutrients and depression. Finally, plasma levels of lycopene have been negatively associated with white matter hyperintensities in elderly subjects (Schmidt et al 1997). Our finding of an association between lycopene intake and vascular depression is consistent with this finding, particularly given that depression subtype in our study was determined by the presence of MRI lesions.

Given the recent interest in fish consumption and omega-3 fatty acids (ώ-3FAs) among psychiatric researchers, it is noteworthy that no relationship was found between ώ-3FA intake and either depression subgroup. Although the Block 1998 FFQ is not optimal for estimating ώ-3FAs, given the lack of specificity of fish types, the finding of no association is consistent with previous depression studies that have assessed dietary intake of ώ-3FAs. Ecologic and cohort studies which promoted interest in ώ-3FAs showed negative correlations between fish consumption and depression, depressive symptoms, and general mental health (Hibbeln 1998; Silvers and Scott 2002; Tanskanen et al 2001). Clinical and population studies have shown diminished ώ-3FA levels in serum phospholipids and erythrocytes, as well as elevated ratios of plasma omega-6 to omega-3 polyunsaturates, among depressed subjects (Adams et al 1996; Maes et al 1999; Tiemeier et al 2003). In addition, these alterations have been associated with depression severity (Adams et al 1996). A different picture emerges when looking at dietary intake of ώ-3FAs. Population studies in Australia (n=755) and Finland (n=29,133) found no association between dietary ώ-3FAs and depression or depressed mood (Hakkarainen et al 2004; Jacka et al 2004). The one study which measured both dietary and plasma levels of ώ-3FAs found that dietary differences did not explain plasma levels (Adams et al 1996). Some researchers have concluded that fatty acid metabolism is altered in subjects with depression and that this abnormality may influence both the etiology and course of depression (Maes et al 1999; Tiemeier et al 2003). Although dietary deficiencies likely exacerbate ώ-3FA plasma abnormalities, ώ-3FA intake itself may not be the most critical factor for depression. It is also interesting to note that fish

consumption but not ώ-3FAs has been associated with depression. Perhaps a component of fish other than ώ-3FAs is protective for depression.

The present study has a number of limitations including the modest sample sizes, especially for the depression subgroups, and the large number of statistical comparisons made. In addition, since diet was not assessed until after diagnosis of depression, it was not possible to distinguish dietary factors that may have been the result of depression from possible etiological factors. A further complication is the changing nature of depression over time combined with the nutrition assessment period of one year. Not only were both currently and recently depressed individuals included in the depression group, but some individuals were depressed part of the year and remitted for the remainder. Self-report of diet has limitations including selective underreporting by obese individuals. Given that over 10% of our sample was obese (BMI $\geq$ 30) and that obesity was more common among the depression subjects, this underreporting may have impaired our ability to detect true differences in diet between the depression and comparison groups. In addition, the Block 1998 FFQ is not optimal for some measures including ώ-3FAs and whole grains given the lack of specificity about food items. It should also be noted that antidepressants and other medications may affect appetite and weight. We did not have necessary medication intake data to evaluate these relationships. Finally, we recognize that our results may be generalizable only to geriatric individuals with depression who have received psychiatric treatment.

The similarity of diets across the two depression groups may be a real effect and indicate the importance of vascular nutritional factors to depression even in subjects

who lack comorbid vascular disease. Alternatively, the lack of differences found may be due to the small sample size or to the high intra-individual to inter-individual variation of human diets. It is also possible that subjects in the vascular depression group may have changed their diets in response to a vascular medical condition such as hypertension, a condition found to be more common in the vascular depression subgroup. This may have resulted in diminished differences between the two depression groups on vascular nutrients and foods, such as saturated fats and high-fat dairy products. As mentioned above, psychotropic and other medications may have affected food and nutrient intake among subjects in our study. Also, genomic factors related to both vascular disease and depression may mediate the relationship between diet and late-life depression subtype.

In conclusion, there is evidence that vascular nutritional factors differ between depression and comparison subjects but tend to be similar across depression subgroups. This may underscore the importance of vascular nutrients to late-life depression regardless of the presence of comorbid cerebrovascular disease. In addition, the atherogenic diets found in depression subjects may indicate the need for intervention to prevent the development and progression of comorbid vascular diseases. Further research is needed to confirm these findings and to distinguish dietary factors which affect the etiology of depression from those which are a result of depression, as well as to identify dietary factors which may affect the course and treatment of late-life depression and comorbid disease.

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Tables

Table 4.1. Sample characteristics – Demographics, medical comorbidity, and psychosocial measures[‡]

	Vascular depression[†] n=58	Non-vascular depression[†] n=53	Comparison[†] n=139	p-value[*]
Age in years	71.5 (0.8)	67.4 (0.8)	71.3 (0.5)	<0.0001
Sex (% female)	32 (55.2%)	31 (58.5%)	98 (70.5%)	0.074
Race (% white)	51 (92.7%)	48 (92.3%)	116 (84.1%)	0.122
Years of education	14.2 (0.3)	14.4 (0.3)	15.3 (0.2)	0.0024
Hypertension (%)	30 (51.7%)	21 (39.6%)	37 (26.6%)	0.003
Diabetes (%)	8 (13.8%)	8 (15.1%)	8 (5.8%)	0.068
Subjective social support	25.3 (0.3)	25.2 (0.3)	27.1 (0.2)	<0.0001
Average stress	4.5 (0.2)	4.7 (0.3)	2.8 (0.2)	<0.0001

[‡]sample size (n=250) except for race (n=245), social support (n=244), and stress (n=249); [†]mean (SE) for continuous variables, total # (%) for categorical variables; [*]p-value for difference between groups (Chi-square test used to compare proportions; ANOVA used to compare means).

Table 4.2. Sample characteristics – Nutritional factors[‡]

Characteristic	Vascular depression[†] n=58	Non-vascular depression[†] n=53	Comparison[†] n=139	p-value[*]
Total Energy (kcal)	1789.6 (90.9)	1743.2 (95.0)	1663.8 (58.7)	0.47
Dietary cholesterol (mg)	200.5 (12.7)	194.2 (13.3)	154.8 (8.2)	0.0026
Saturated fat (g)	20.5 (1.3)	20.3 (1.4)	17.4 (0.9)	0.0626
Trans-unsaturated fat (g)	6.8 (0.5)	6.6 (0.5)	5.5 (0.3)	0.0234
Alcohol (percentage of energy)	3.4 (0.7)	1.7 (0.7)	4.0 (0.4)	0.029
Omega-3 fatty acids (mg)	1.6 (0.1)	1.6 (0.1)	1.5 (0.1)	0.54
Fiber (g)	16.9 (1.2)	16.8 (1.2)	18.4 (0.8)	0.38
Vitamin E (IU)	159.6 (22.5)	153.8 (23.6)	168.3 (14.5)	0.86
Lycopene (µg)	4201.9 (685.1)	4880.3 (716.7)	4607.5 (442.5)	0.79

Characteristic	Vascular depression[†] n=58	Non-vascular depression[†] n=53	Comparison[†] n=139	p-value[*]
Meats (servings per day)	1.1 (0.1)	1.0 (0.1)	0.8 (0.1)	0.09
High-fat dairy (servings per day)	1.1 (0.1)	1.0 (0.1)	0.7 (0.1)	0.0198
Low-fat dairy (servings per day)	0.4 (0.1)	0.6 (0.1)	0.8 (0.1)	0.006
Vegetables (servings per day)	2.8 (0.2)	3.1 (0.3)	3.5 (0.2)	0.074
Fruits (servings per day)	1.7 (0.2)	1.8 (0.2)	2.2 (0.1)	0.0076
Whole grains (servings per day)	1.7 (0.2)	1.4 (0.2)	1.7 (0.1)	0.39
Keys score	29.9 (1.0)	31.6 (1.1)	27.4 (0.7)	0.0021
Body mass index	27.3 (0.6)	27.4 (0.6)	25.4 (0.4)	0.003

Characteristic	Vascular depression[†] n=58	Non-vascular depression[†] n=53	Comparison[†] n=139	p-value[*]
(kg/m^2)				

[‡]sample size (n=250) except for BMI (n=244); [†]mean (SE), [*]p-value for difference between groups (ANOVA used to compare means).

Table 4.3. Nutritional factors - Adjusted means[†]

Characteristic	Vascular depression	Non-vascular depression	Comparison
Total Energy (kcal)	1773.8	1734.8	1675.6
Dietary cholesterol (mg)[*]	185.0	183.2	160.6
Saturated fat (g)[*]	19.5	19.7	17.8
Trans-unsaturated fat (g)[*]	6.1	6.3	5.8
Alcohol (percentage of energy)	4.0	1.8	3.8
Omega-3 fatty acids (mg)[*]	1.6	1.6	1.5
Fiber (g)[*]	16.4	16.5	18.9
Vitamin E (IU)[*]	175.0	154.5	163.8
Lycopene (µg)[*]	3168.7[‡]	3873.0	5525.1
Meats (servings per day)[*]	1.0	0.8	1.0
High-fat dairy (servings per day)[*]	0.9	1.0	0.7
Low-fat dairy (servings	0.4	0.6	0.8

Characteristic	Vascular depression	Non-vascular depression	Comparison
per day)*			
Vegetables (servings per day)*	2.9	3.1	3.5
Fruits (servings per day)*	1.9	2.1	2.0
Whole grains (servings per day)*	1.4‡	1.3‡	1.9
Keys score*	29.8	31.0‡	27.2
Body mass index (kg/m^2)	27.0	26.9	25.6

†controlling for covariates (age, sex, race, education, hypertension, diabetes, social support, and stress), sample size (n=239); *also controlled for total kilocalories, ‡significant difference ($p<0.05$) from comparison group (ANCOVA used to compare means).

CHAPTER V

NUTRITIONAL CORRELATES OF BRAIN LESIONS IN LATE-LIFE VASCULAR DEPRESSION

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Abstract

Objective-The association between nutritional factors (dietary attributes believed to either promote or prevent cardiovascular disease) and brain lesion volumes in late-life depression was examined in an elderly cohort of individuals with current or prior depression.

Method-Nutrient intake was assessed in 54 elderly vascular depression subjects (vascular depression defined by presence of hyperintensities on brain MRI) using a Block 1998 food frequency questionnaire. Nutrient and food intake, body mass index, and Keys score (a measure of the serum cholesterol-raising capacity of the diet), were determined. Brain lesion volumes were calculated from MRI. Subjects were age 60 or over, and were participants in a longitudinal study of major depression. All subjects received psychiatric assessment and treatment, and medical comorbidity assessments. *Results*-High-fat dairy and whole grain consumption were significantly positively correlated with brain lesion volume, while other vascular nutritional factors were not significantly associated with lesion volume. In multivariable analyses, controlling for age, sex, hypertension, diabetes, and total kilocalories, the positive association with lesion volume remained significant for both high-fat dairy and whole grains. *Conclusions*-High fat dairy and whole grain consumption may be associated with brain lesions in elderly depression subjects.

Introduction

Major depression is a serious mental disorder characterized by low mood, apathy, sleep and appetite disturbances, feelings of hopelessness, and suicidal thoughts and behaviors. It is a common mental disorder and the leading cause of disability worldwide (WHO 2001). Depression is a common affliction in individuals over age 60 with a prevalence between 2.7 and 12 percent in the general population but significantly higher among elderly medically ill and those in nursing homes (Papadopoulos et al 2005; Steffens et al 2000). Biological and neurological changes figure as prominently or more so than genetic and psychosocial factors in the etiology of late-life depression, as compared with early-life depression (Baldwin and Tomenson 1995; Krishnan et al 1997). Late-life depression is distinguished from depression of early adulthood by both its course and neuropathology (Alexopoulos et al 1997a; Alexopoulos et al 1997b; Krishnan et al 1997). The course of late-life depression is characterized by a higher rate of recurrence, lower rate of remission, more treatment resistance, and an increased likelihood of progression into dementia, as compared with depression in earlier adulthood (Baldwin and Tomenson 1995; Taylor et al 2003). Brain lesions, seen on brain MRI (magnetic resonance imaging) are indicative of damage to gray and white matter and are more common among those with late-life depression as compared with early-life depression (Baldwin and Tomenson 1995). Some researchers have used the term vascular or subcortical ischemic depression to describe a sub-type of late-life depression that is characterized by these brain lesions or hyperintensities (Alexopoulos et al 1997a; Alexopoulos et al 1997b; Krishnan et al 1997; Krishnan et al 2004). Lesions are

considered to be an important element of depression in the elderly, being associated with both the persistence and worsening of depressive symptoms (Steffens et al 1999; Steffens et al 2002). Research into the causes of these brain lesions is critical to understanding the occurrence, course, and outcomes of late-life depression.

Cardiovascular and neuropathological research on the etiology of brain lesions has indicated an ischemic mechanism. Vascular risk factors and conditions, including hypertension, arteriosclerosis, heart disease, hypercholesterolemia, diabetes, history and risk of ischemic cerebrovascular disease, history of myocardial infarction, cerebral microvascular disease, and microcirculatory disturbances leading to decreased cerebral blood flow have been associated with brain lesions (Awad et al 1986a; Awad et al 1986b; de Leeuw et al 2000; de Leeuw et al 1999; Fazekas et al 1988; Hatazawa et al 1997; Liao et al 1996; Schmidt et al 1999; Schmidt et al 1997; Uehara et al 1999; Veldink et al 1998). Longitudinal studies have demonstrated that baseline blood pressure predicts the presence of brain lesions twenty years later, and that progression in lesion size is associated with blood pressure and duration of prior hypertension (de Leeuw et al 1999; de Leeuw et al 2002; Schmidt et al 1999; Uehara et al 1999; Veldink et al 1998). In addition, postmortem histopathological studies of depressed subjects have found that white matter lesions are ischemic based upon evidence of increased macrophage and microglial activity, and astrogliosis (Thomas et al 2002). Since both vascular disease and risk factors for vascular disease are related to brain lesions, it is reasonable to hypothesize that diet may have a role in their etiology and progression. Intake of food and nutrients known to affect vascular disease would

likely be associated with these lesions. Two studies support a possible relationship between diet and brain lesions, although they were not done with depressed individuals. In a study of over 3,000 geriatric participants of the Cardiovascular Health Study, regular, moderate consumption of alcohol (between 1 and 7 drinks per week) was found to be associated with decreased prevalence of white matter lesions as seen on brain MRI (Mukamal et al 2001). Serum vitamin E (or α-tocopherol) and lycopene, an antioxidant carotenoid which has been shown to prevent lipid peroxidation by scavenging free radicals (Klebanov et al 1998), were found to be negatively correlated with white matter hyperintensities on MRI in 355 elderly participants of the Austrian Stroke Prevention Study (Schmidt et al 1996). The association remained for α-tocopherol even after controlling for coronary heart disease risk factors.

Although studies have not assessed the role of vascular nutrients (dietary attributes believed to either promote or prevent cardiovascular disease) in brain lesions of depressed individuals, the literature indicates the importance of these nutrients to other vascular conditions (Connor et al 1993; Kushi et al 1985; Nordoy et al 1993; Willett et al 1993), so that it is reasonable to hypothesize that they play a role in late-life depression. Numerous studies have investigated the relationship between nutritional factors and mood; however, few have examined depression in the elderly and almost none of the depression studies have focused on factors known to affect vascular disease. In a previous study, we reported that elderly depressed individuals were more likely than never-depressed comparison subjects to consume a diet high in saturated fat and cholesterol, and lower in alcohol, while

having a higher body mass index (BMI) (Payne et al In press). In addition, follow-up work by our group determined that individuals categorized as having vascular depression consumed less lycopene and fewer whole grains and low-fat dairy products than comparison subjects (unpublished data). We conducted the present study with a group of geriatric individuals who were identified as having current or prior vascular depression. We sought to determine whether certain nutritional factors were associated with the size of brain lesions among these subjects. We hypothesized that the reported intakes of total fat, saturated fat, meats, high-fat dairy products, and cholesterol, would be positively correlated with brain lesion volume. Similarly, we predicted that BMI, an indirect measure of adiposity, would be positively associated with brain lesions. Protective dietary factors, such as intake of omega-3 fatty acids, vitamin E, fiber, lycopene, alcohol, fruits, vegetables, whole grains, and low-fat dairy products, were predicted to be negatively associated with brain lesion volume.

Method

Design

This cross-sectional project occurred within a larger longitudinal clinical study of depression in older adults which began in 1994. Located at Duke University Medical Center, the NIMH Mental Health Clinical Research Center (MHCRC), the Longitudinal Study of Depression in Later Life, and the Conte Center for the Neuroscience of Depression, are coordinated, ongoing studies of elderly depressed patients and controls. Nutrition assessments were added in March 1999, after which time all depression subjects who were deemed clinically suitable, based upon

acceptable depression management and cognitive functioning, received a nutrition questionnaire.

Sample

The sample included patients of the Duke University Psychiatric Service with a primary diagnosis of major depression at study baseline. Enrollment was restricted to those 60 years or older, and those who could speak and write English. Only vascular depression subjects (defined by MRI, see below) who received a nutrition questionnaire were included in analyses for this paper.

Exclusion criteria included a concurrent diagnosis of a major psychiatric or neurological illness. Subjects were also excluded if they exhibited significant cognitive impairment, as indicated by their Mini-Mental State Examination (MMSE) (Folstein et al 1975) score of less than 26 (out of 30). In addition, those with severe depression symptomatology were excluded because of concerns that the lengthy (8 page) Block 1998 food frequency questionnaire would present an undue burden to those individuals. This criterion did not require a specific depression rating cut-off but was instead determined by the treating psychiatrist on a case-by-case basis. This allowed for flexibility based upon symptomatology and clinical stability. Subjects were also excluded if they had metal in the body which was a contraindication for MRI. Subjects were not excluded for following special dietary regimens.

After complete description of the study to the subjects, written informed consent was obtained. This research protocol has been reviewed and approved by the Duke University Medical Center Institutional Review Board. In addition, data analyses for

this project were approved by the Public Health Institutional Review Board at the University of North Carolina at Chapel Hill (as part of a doctoral dissertation research project).

Treatment

Depression subjects received individualized treatment from a psychiatrist. Most received antidepressant medication; some received electroconvulsive treatment (ECT) or psychotherapy.

Measures

Assessments included psychiatric, medical, nutrition, and imaging measures. At baseline and yearly thereafter a trained interviewer administered the Duke Depression Evaluation Schedule (DDES) (Landerman et al 1989) in-person to each subject. The DDES, a composite diagnostic interview instrument, included sections of the NIMH Diagnostic Interview Schedule which assesses depression, and was enriched with items on physical health (Robins et al 1981). These included self-report of diabetes mellitus and hypertension. Body mass index or BMI ([weight in kg]/[height in m]^2) was determined from self-report. Clinical assessments, including the Montgomery-Asberg Depression Rating (MADRS), were performed at study baseline and quarterly thereafter (Montgomery and Asberg 1979). Nutrition assessments were administered annually, based upon the time of a subject's initial food frequency questionnaire completion date. Brain MRI was performed every two years, starting at study baseline. See below for details on nutrition and MRI assessments.

Nutrition Protocol

The 1998 Block Food Frequency Questionnaire (FFQ) was used for nutrition assessment. This tool is an updated version of the FFQ developed by Gladys Block at the National Cancer Institute. The Block FFQ was designed to estimate the components of a person's total dietary intake over the preceding year (Block 1992). It has been validated against and shows moderate correlation with other nutrition assessment instruments, including the Willett FFQ and multiple-day dietary records (Block et al 1992; Subar et al 2001). The Block FFQ is frequently used for longitudinal studies, allows for dietary comparisons between groups, necessitates no time-intensive interviews, requires less data management relative to other diet assessment methods, and provides for timely data analysis. The Block FFQ is a semi-quantitative assessment in that the respondent is asked to estimate both the frequency of consumption of listed food items (never, a few times per year, once per month, 2-3 times per month, once per week, 2 times per week, 3-4 times per week, 5-6 times per week, or everyday), and the typical serving size of that food. The 1998 Block questionnaire (Block Dietary Data Systems; Berkeley, CA) is a revision that includes standardized portion sizes, a wider variety of low-fat foods, questions on dietary supplements, and an updated database to reflect folate fortification in the food supply.

Returned questionnaires were checked for completeness and rejected if more than 15 food items were skipped, and then sent to Block Dietary Data Systems for scanning and nutrient analysis by comparison of responses to a nutrient database. In this way, responses such as servings of oranges, strawberries, and broccoli were converted to nutrient intake estimates for vitamin C, folate, and fiber. Output files

containing both raw (food-level) and nutrient estimate data were returned to the investigators.

Automated FFQ results included the following dietary variables: energy, total fat, saturated fat (SFA), polyunsaturated fat (PUFA), trans-unsaturated fat, omega-3 fatty acids, fiber, vitamin E (total from foods and dietary supplements), lycopene (food sources only), alcohol, cholesterol (CHOL), and servings per day of fruits, vegetables, and whole grains. The Keys score, an estimate of the serum cholesterol-raising capacity of diet, was calculated from FFQ dietary data using the formula: [2(% of energy as SFA) – 1.35(% energy as PUFA) + 1.5(CHOL per 1000 kcal)$^{1/2}$] (Keys et al 1965). In addition, servings per day of high and low-fat dairy products, and meats, were calculated from individual food items on the FFQ. High-fat dairy products were estimated by summing intake of whole and 2% milk, cheese (except for individuals who reported regular consumption of low-fat cheeses), ice cream, butter, and pizza. Similarly, low-fat dairy products were estimated from intake of skim and 1% milks, low-fat cheese, and low-fat ice cream. Both categories of dairy products were underestimated since some dairy items on the FFQ were excluded from consideration. This was because of an inability to determine the fat content of certain food products, such as yogurt, or because a questionnaire item included both dairy and non-dairy foods (such as the item on hamburgers and cheeseburgers). Meat servings were calculated by total intake reported for the following food items: bacon, breakfast sausage, hamburgers/cheeseburgers/meat loaf, meat tacos/burritos/enchiladas/tamales, steaks/roasts, pork/ham, veal/lamb/deer, ribs, liver, gizzard/chitlins, mixed dishes with meat or chicken, fried

chicken, non-fried chicken/turkey, hot dogs, and lunch meats. This measure of meat consumption differs from that typically estimated from the FFQ, which uses the 1996 U.S. Department of Agriculture Food Guide Pyramid definition of meat. The pyramid group definition includes, in addition to true meats, other non-dairy concentrated protein sources, such as eggs, peanut butter, beans, and seafood.

Magnetic resonance imaging (MRI)

Subjects were imaged under an IRB-approved protocol, with a 1.5 Tesla whole-body MRI system (Signa, GE Medical Systems, Milwaukee, WI) using the standard head (volumetric) radiofrequency coil. Padding was used to immobilize the head without causing discomfort. The scanner alignment light was used to adjust the head tilt and rotation so that the axial plane lights passed across the cantho-meatal line and the sagittal lights were aligned with the center of the nose. A rapid sagittal localizer scan was acquired to confirm the alignment. The MR images were then transferred to the Neuropsychiatric Imaging Research Laboratory (NIRL), located at Duke University Medical Center, for volumetric processing on SUN workstations, and secondary archive. In addition, the scans were qualitatively assessed for the presence of lesions by a neuroradiologist.

Lesion assessment (qualitative).

The first set of images were obtained with an axial (horizontal) plane, multisection, T1-weighted pulse sequence (TR = 500 ms, TE = 15 ms) with a 256 x 192 data acquisition matrix, 5 mm section thickness, a 20 cm field-of-view (FOV), 1 excitation per phase-encoding increment (1 Nex) and a 32 KHz (±16KHz) full imaging bandwidth. This was followed by a long TR (2500 msec), double-echo (TE

= 30 and 80 msec) spin-echo data-acquisition sequence using the same FOV, section thickness, bandwidth and spacing, 256 x 192 data acquisition matrix, and 1 Nex. Saturation of spins outside the imaging volume (standard gap 15 mm) and flow compensation (gradient moment nulling) was employed to eliminate artifacts due to flowing blood and cerebrospinal fluid. These images were obtained in two separate acquisitions with a 5 mm gap between sections for each acquisition. The second acquisition was offset by 5 mm from the first so that the resulting data set consisted of contiguous sections.

The studies were visually examined for incidental findings and lesion ratings. Lesion ratings performed for this study have been described previously (Payne et al 2002). Ratings included the following Coffey scale items:

Deep white matter hyperintensity (lesion-intense regions within the white matter tracts of cerebrum): 0 - absent; 1 - punctate foci; 2 - beginning confluence of foci; 3 - large confluent areas

Subcortical gray matter hyperintensity (lesion-intense regions within the basal ganglia and other subcortical gray matter structures): 0 - absent; 1 - punctate; 2 - multi-punctate; 3 – diffuse

Subjects who received a rating of 2 or higher on either subcortical gray or deep white lesions were categorized as having vascular depression (Krishnan et al 1997); otherwise, they were categorized as having non-vascular depression and excluded from analyses for this paper. Depression subtype was defined by baseline MRI; for subjects without a baseline MRI or for whom the baseline MRI was not assessed for lesions, the Year 2 MRI was used for depression group categorization purposes.

Quantitative brain assessments (including lesion volumes)

A dual-echo fast spin-echo (FSE) acquisition was obtained in the axial plane for morphometry (volumetric measurement) of brain structures, including gray and white matter lesions. The pulse sequence parameters were TR = 4000 ms, TE = 30, 135 ms, 32 KHz (±16KHz) full imaging bandwidth, echo train length = 16, a 256 x 256 matrix, 3 mm section thickness, 1 Nex and a 20 cm FOV. The images were acquired in two separate acquisitions with a 3 mm gap between sections for each acquisition. The second acquisition was offset by 3 mm from the first so that the resulting data set consisted of contiguous sections.

The NIRL image processing procedures have been described previously (Payne et al 2002). Volume measurements used a NIRL-modified version of MrX Software, which was created by GE Corporate Research and Development (Schenectady, NY) and originally modified by Brigham and Women's Hospital for image segmentation (Boston, MA). The method is a supervised, semi-automated method that uses the multiple MR contrasts available to identify different tissue classifications through a 'seeding' process wherein a trained analyst manually selects pixels in each tissue type that are to be identified (such as gray matter, white matter, cerebrospinal fluid, lesions, background). Lesion regions were manually segregated into gray and white matter lesions. Lesion areas were selected based upon a set of explicit rules. These rules were developed from neuroanatomical guidelines, consultation with a neuroradiologist, and knowledge of the neuropathology of lesions. These rules allowed trained analysts to reliably select lesion regions. Periventricular lesions were defined as regions that were contiguous with lateral ventricle and did not extend into

the white matter tracts. They were classified as white matter lesions on the processed image. Deep white matter lesions were located in the white matter tracts and may or may not have adjoined periventricular lesions. Subcortical gray matter lesions were defined as lesions within the basal ganglia or thalamus.

Once the brain was segmented into tissue types (gray matter, white matter, cerebrospinal fluid, gray matter lesions, and white matter lesions) and the non-brain tissue (meninges, eyes, subcutaneous fat, muscle and skull) stripped away through a masking procedure, specific regions of interest were assessed using tracing and connectivity functions. The final step was to run a summarizing program that calculated the total volume of each tissue type within the specific region defined by the analyst. Lesion volumes were calculated by multiplying the area of lesion on each slice by the slice thickness of 3 mm and then summing the volumes from all slices. Output volumes are given in milliliters (mL). Total lesion volumes were comprised of both gray matter lesions and white matter lesions, although white matter lesions were predominant.

All image analysis technicians received extensive training by experienced analysts. Inter-rater reliability was established by repeated measurements on multiple MR scans before raters were approved to process study data. Intraclass correlation coefficients (ICC's) between two raters were 0.99 for both lesion volumes.

Statistical analyses for this paper used lesion volumes from the MRI closest to the time of the nutrition assessment. This meant that for most subjects the MRI and nutrition assessments were separated by no more than one year.

Analyses

All statistical analyses were run using JMP software (Cary, NC) (SAS Institute 2001).

Depression subtype (vascular or non-vascular) was determined from baseline MRI lesion ratings, or Year 2 MRI if baseline ratings unavailable. Lesion volumes from the closest (in time to FFQ) available MRI were used in these analyses. Self-report of hypertension and diabetes was obtained from the closest annual DDES instrument. Analyses first assessed the potential for responder bias. Bivariate comparisons were made between individuals with acceptable FFQs ("responders") and those who either did not return a questionnaire or who returned an unacceptable one (together categorized as "nonresponders"). Variables of interest included sex, age, baseline depression score, lesion volume, and reported hypertension and diabetes.

Bivariate analyses were performed to examine the characteristics of the sample by total lesion volume. T-tests were used for categorical independent variables, including sex, hypertension, and diabetes. Simple regression models were used for continuous independent variables, including age and all nutritional variables. To examine lesion volume by nutritional characteristics, controlling for potential confounders, we ran seventeen separate multivariable regression models with total energy (kcal), dietary cholesterol (mg), saturated fat (g), trans-unsaturated fat (g), omega-3 fatty acids (mg), fiber (g), lycopene (µg), alcohol (percentage of total energy), total vitamin E (IU), body mass index (kg/m^2), Keys score, and servings of vegetables, fruits, whole grains, meats, and high and low-fat dairy products, as

independent variables. To control for potential confounding, each model contained a set of covariates. All models included age, sex, hypertension (yes/no), and diabetes (yes/no) as control variables. Finally, total energy (kcals) was included as a covariate in all models except that for which total energy was either the primary independent variable or was a component of the primary independent variable (alcohol).

Results

A total of 160 depression subjects were deemed eligible to receive an FFQ questionnaire. Seventy-nine subjects (of 160) were classified as having vascular depression, based upon the lesion rating criteria, of whom 54 successfully completed the FFQ (68%). The first FFQ assessment was used for all except three subjects (6%). For those three subjects who had returned an unacceptable initial questionnaire (greater than 15 food items missing), the second FFQ was used. Nonrespondents (those who did not return an FFQ or returned an unacceptable one) did not differ from respondents in terms of age, sex, baseline MADRS depression score, lesion volume, or self-reported hypertension or diabetes. All subjects had complete data except one, who was missing weight and height values. This subject was omitted from the BMI analyses.

Sample characteristics for the vascular depression group (n=54) are shown in Tables 5.1 and 5.2. Mean lesion volume (mL) was 9.76 ($\pm$10.68), with a range of 1.45 to 61.31. A Shapiro-Wilks test for normality was performed for total lesion volume. It indicated that lesion volume was not normally distributed ($W = 0.69$, $p < 0.0001$). A new variable for the logarithmic transformation (natural log) of lesion

volume (logLESION) was created, for which we could not reject the null hypothesis of normality ($W = 0.96$, $p < 0.2055$). Geometric mean for lesion volume was included in Table 5.1 as a measure of central tendency that is less prone to distortion from outliers. In addition, geometric means may be easier to interpret than logarithmic values given that they have the same units as the original variable (lesion volume). Bivariate analyses between logLESION and demographic, medical comorbidity, and nutritional variables were performed. Age ($\beta = 0.059$, $SE = 0.016$, $t = 3.70$, $p = 0.0005$) and intake of high-fat dairy ($\beta = 0.329$, $SE = 0.108$, $t = 3.04$, $p = 0.004$) and whole grains ($\beta = 0.137$, $SE = 0.066$, $t = 2.07$, $p = 0.044$) were significantly (at $p < 0.05$) positively associated with logLESION.

Multivariable models examined the association between logLESION and each of the seventeen nutritional variables, while controlling for age, sex, hypertension, diabetes, and total caloric intake. A typical model was as follows: $\text{logLESION} = \beta_0 + \beta_1\text{Fiber} + \beta_2\text{Age} + \beta_3\text{Sex} + \beta_4\text{Hypertension} + \beta_5\text{Diabetes} + \beta_6\text{Calories} + \varepsilon$. Servings of high-fat dairy ($\beta = 0.283$, $SE = 0.125$, $t = 2.26$, $p = 0.028$) and whole grains ($\beta = 0.197$, $SE = 0.079$, $t = 2.49$, $p = 0.016$) retained significance in multivariable models for their positive association with lesion volumes. No other nutritional variables were identified as statistically significant ($p < 0.05$). Age retained statistical significance in all models ($0.0004 < p < 0.0017$). Table 5.3 shows lesion volume (predicted geometric mean) ratios between the 75^{th} and 25^{th} percentile of intake for each nutritional factor, based upon multivariable analyses. For example, individuals consuming 1.8 servings per day of high-fat dairy products (75^{th} percentile of intake) had 1.5 times greater lesion volume than those consuming 0.3 servings (25^{th}

percentile). The 25th and 75th percentiles were chosen to represent "high" and "low" intake levels for this sample.

Discussion

To our knowledge, this is the first report on the relationship between diet and brain lesion volume in depression subjects. The major findings of this exploratory study are that high-fat dairy product consumption and whole grain consumption were significantly positively associated with brain lesion volume among individuals with current or prior vascular depression, while there was no significant association for other nutritional factors (total energy, dietary cholesterol, saturated fat, trans-unsaturated fat, omega-3 fatty acids, fiber, lycopene, alcohol, vitamin E, body mass index, Keys score, or servings of vegetables, fruits, meats, and low-fat dairy products) and brain lesion volume. After controlling for potential confounders, including age, sex, total energy, diabetes, and hypertension, high-fat dairy and whole grain intakes remained significantly associated with lesion volume. The finding of a possible association between high-fat dairy products and brain lesions is consistent with the ischemic nature of brain lesions seen in late-life depression, given that saturated fat, a prominent component of fatty dairy foods, is known to be a cardiovascular risk factor (Hu et al 1997). It is interesting to note that some saturated fatty acids, including those found in dairy products, may be more atherogenic than other saturated fatty acids (Kris-Etherton and Yu 1997). This may help explain why high-fat dairy consumption but not total saturated fat was associated with brain lesion volume.

The association found between brain lesions and whole grain consumption is in

the opposite direction of that predicted. The known beneficial effects of whole grains on cardiovascular morbidity and mortality would seem to indicate their possible protective qualities for ischemic brain lesions (Jacobs et al 1998; Liu et al 2000; Liu et al 1999). However, there are components in whole grain products that may have negative health consequences, including phytate, a compound found in the outer husk of grains, and certain dietary fibers which may impair the intestinal absorption of minerals including iron and zinc, potentially leading to deficiencies of those minerals (Hurrell et al 1992). Low iron levels have been associated with neuropsychological impairment and alterations on electroencephalography (Tucker et al 1990; Tucker et al 1984), while zinc levels have been negatively associated with senile and diffuse plaques on postmortem brain studies of elderly women (Tully et al 1995). It is possible that whole grains are correlated with brain lesions because of their association with inadequate mineral status. However, this is purely speculative given that we do not know if whole grain consumption was related to mineral status in this study (zinc and iron levels were not measured), nor whether there exists any relationship between minerals and brain lesions.

The paucity of research into the association between nutritional factors and brain lesions, especially in depression, provides little framework with which to interpret the current results. As mentioned previously, two studies have demonstrated associations between nutritional factors and the occurrence of brain lesions. Plasma concentrations of α-tocopherol and lycopene were negatively associated with brain lesions in the Austrian Stroke Prevention Study (Schmidt et al 1996). Moderate alcohol consumption was negatively associated with white matter lesions in the

Cardiovascular Health Study, after controlling for covariates (Mukamal et al 2001). Neither of these findings was supported by the present study. The failure to detect these associations may have been due to the focus on depression subjects, the small sample, the quantitative lesion methodology of the current study, or differing nutrition assessment methodologies, or to a combination of factors. Previous work with a sample that included the current vascular depression subjects, as well as individuals with non-vascular depression and comparison subjects, demonstrated higher intake of saturated fat and cholesterol, and lower intake of alcohol among the depression subjects as compared to elderly comparison subjects (Payne et al In preparation; Payne et al In press). If these nutrients are confirmed to be associated with late-life depression but not with brain lesions, this may indicate that the relationship between atherogenic nutrients and depression is not mediated by ischemic brain lesions. Or, a cross-sectional study may be unlikely to detect an association between nutritional factors and lesions because individuals with known vascular disease have already changed their diets. Alternatively, lesions in certain brain regions such as the basal ganglia and hypothalamus may lead to changes in dietary behavior.

The present study has a number of limitations, including the modest sample size. The cross-sectional design precludes confirmation of an etiological effect of diet on brain lesions. Many models were fitted and tested in this exploratory study, so results should be interpreted with caution. The Block FFQ may be insufficient to detect dietary differences in individuals across the spectrum of brain lesion volumes, due to problems associated with self-report and the inherently high intra-individual to

inter-individual variation of human diets. In addition, the whole grain findings should be interpreted with caution given that the Block 1998 FFQ is not optimal for measuring whole grain consumption because of lack of specificity about food items. This study did not have access to biochemical measures related to vascular dietary risk, including serum cholesterol, triglycerides, and homocysteine. Finally, we recognize that our results may be generalizable only to geriatric individuals with depression who have received psychiatric treatment.

In conclusion, we found evidence of a positive association between brain lesion volume and consumption of both high-fat dairy and whole grains among individuals with vascular depression. No significant associations were found between other nutritional factors and brain lesion volume. Our findings need to be confirmed in a larger sample, particularly the positive association for whole grains and brain lesion volume given the limitations of the Block 1998 FFQ. The dairy finding may indicate an association between saturated fat and lesions. If the nutrient intake differences observed in this study reflect long-term dietary patterns, then it is reasonable that a greater high-fat dairy consumption may have contributed to an increased volume of lesions. However, a longitudinal study will be needed before any etiological conclusions can be drawn between diet and brain lesions in depression. Finally, the authors speculate that an atherogenic diet may be related to late-life depression via mechanisms other than the development of brain lesions.

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Tables

Table 5.1. Sample characteristics – Demographics, medical comorbidity, and lesions*

Characteristic	Mean (±SD)
Age	71.5 (±6.6)
Sex	53.7% Female
Race	92.1% White
Hypertension	50.0%
Diabetes	14.8%
Body mass index	27.5 (±4.2)
Lesion volume (mL)	9.8 (±10.7)
Log† lesion volume	1.9 (±0.9)
Geometric mean of lesion volume (mL)‡	6.6 (±2.3)

*Vascular depression sample (n=54 for all except BMI, where n=53); †Natural logarithm (ln); ‡Geometric mean = $e^{(\text{mean of loglesion})}$, and has same units (mL) as lesion volume

Table 5.2. Sample characteristics – Nutritional variables*

Intake variable	Mean (±SD)
Total Energy (kcal)	1837.3 (±858.5)
Dietary cholesterol (mg)	206.5 (±121.3)
Saturated fat (g)	21.1 (±12.5)
Trans-unsaturated fat (g)	7.0 (±4.3)
Alcohol (percentage of energy)	2.6 (±5.1)
Omega-3 fatty acids (mg)	1.7 (±0.9)
Fiber (g)	17.6 (±9.9)
Vitamin E (IU)	159.7 (±179.4)
Lycopene (µg)	4197.9 (±6541.0)
Meats (servings per day)	1.1 (±1.1)
High-fat dairy (servings per day)	1.1 (±1.0)
Low-fat dairy (servings per day)	0.4 (±0.7)
Vegetables (servings per day)	2.9 (±1.9)
Fruits (servings per day)	1.8 (±1.2)
Whole grains (servings per day)	1.8 (±1.7)
Keys score	29.7 (±6.8)

*Vascular depression sample (n=54)

Table 5.3. Predicted ratio of lesion volumes (geometric means) by intake level

Intake variable	25th Percentile	75th Percentile	Ratio of geometric means of lesion volume (75th:25th)†
Total Energy (kcal)	1270.1	2201.4	1.2
Dietary cholesterol (mg)	128.7	248.9	1.1
Saturated fat (g)	12.1	27.4	1.2
Trans-unsaturated fat (g)	3.9	8.8	0.8
Alcohol (percentage of energy)	0	1.9	1.0
Omega-3 fatty acids (mg)	1.1	2.0	0.7
Fiber (g)	11.4	21.7	1.0
Vitamin E (IU)	15.8	291.8	1.1
Lycopene (µg)	1232	4796	1.0
Meats (servings per day)	0.5	1.6	1.0
High-fat dairy (servings per day)*	0.3*	1.8*	1.5*
Low-fat dairy (servings per day)	0	0.2	1.0
Vegetables (servings per day)	1.6	3.7	1.2
Fruits (servings per day)	0.7	2.8	1.0
Whole grains (servings per day)*	0.5*	2.4*	1.5*

*Factor was significant in multivariable model ($p<0.05$)

†Ratio = $e^{(\beta*intake75)}/e^{(\beta*intake25)}$ where β=parameter estimate from logLESION model for that intake variable, intake75=amount consumed at 75 percentile of intake, intake25=amount consumed at 25 percentile of intake

CHAPTER VI

EXPANDED METHODS

This nutrition project was part of a longitudinal clinical study of depression in older adults. Located at Duke University Medical Center, the NIMH Mental Health Clinical Research Center (MHCRC), the Longitudinal Study of Depression in Later Life, and the Conte Center for the Neuroscience of Depression are coordinated, ongoing studies of elderly depression and comparison subjects. To date, more than 550 subjects have been enrolled since the study began in 1994. The term "depressed patients" refers to individuals who were diagnosed with depression at study enrollment. Subjects may not have continued to be depressed but were always categorized as being in the depression group for the purposes of this study. Measurements for this project included psychiatric, neuropsychological, medical, psychosocial, genetic, brain imaging, and nutrition assessments.

Depressed and comparison individuals have been followed for up to twelve years. Depressed patients had clinic visits at three month intervals, or more often if necessary for management of their depression. Comparison subjects had annual visits during which they received many of the same assessments as the patient group. In addition, some assessments were mailed out to subjects at various intervals.

Depression Study

Sample

This study operated in a naturalistic treatment environment and screened for both single and recurrent cases of major depression. Inpatients and outpatients of the Duke University Psychiatric Service presenting with clinically significant depressive symptoms or a previous diagnosis of mood disorder were screened with the Center for Epidemiologic Studies-Depression Scale (Radloff 1977). Eligibility was limited to patients with CES-D scores greater than or equal to fifteen and a primary diagnosis of major depression, single or recurrent, which was made by a psychiatrist. Enrollment was restricted to patients who were 60 years or older, and could speak and write English.

Exclusion criteria for patients included a concurrent diagnosis of a major psychiatric or neurological illness, such as bipolar disorder, schizophrenia, alcohol or drug dependence, dementia, stroke, Parkinson's disease, seizure disorder or multiple sclerosis. People with physical disabilities that may have impaired cognitive testing and those with metal in the body (contraindicated for MRI) were also excluded.

Controls were recruited from the Aging Center Subject Registry at Duke University. The Registry included a listing of over nineteen hundred (1,900) community-dwelling elders in the Durham, Chapel Hill, and Raleigh areas, who had expressed a willingness to participate in Duke Aging Center research. Registry subjects may have been selected by race, gender, age or socioeconomic status. Eligible controls had a non-focal neurological examination, no self-report of

neurological or depressive illness, and no evidence of a depression diagnosis based on the Diagnostic Interview Schedule portion of the Duke Depression Evaluation Schedule (Robins et al 1981).

The purpose of the study and its procedures were explained to each potential subject, and those who provided written informed consent were enrolled. This research protocol was reviewed and approved by the Duke University Medical Center Institutional Review Board (IRB).

As of 31 December 2005, a total of 410 depressed and 160 control subjects had been enrolled in the depression study. Recruitment began in 1994 and is ongoing.

Treatment for Depression

Depressed patients received individualized treatment from psychiatrists and, in some cases, psychologists. The majority of patients received pharmacological treatment in the form of antidepressants; some received electroconvulsive treatment (ECT) or psychotherapy. Subjects in the depression group were followed by a psychiatrist.

Depression Study Assessments

Assessments were varied and extensive. They included psychiatric, medical, imaging, psychosocial, genetic, neuropsychological, and nutrition measures. Within 30 days of the MRI (see next section), a trained interviewer administered the Duke Depression Evaluation Schedule (DDES) to each subject. The DDES, a composite diagnostic interview instrument, included sections of the NIMH Diagnostic Interview Schedule which assesses depression, and was enriched with items that assessed sleep problems and the clinical features of melancholia and psychosis, dysthymia,

mania, and alcohol abuse or dependence (Robins et al 1981). The DDES also included the Montgomery-Asberg Depression Rating (MADRS) (Montgomery and Asberg 1979); the Mini-Mental State Examination (MMSE) (Folstein et al 1975) which assesses basic cognitive functions; the Global Assessment Scale (Endicott et al 1976); items on self-reported physical health; four subscales of the Duke Social Support Index (George et al 1989; Landerman et al 1989); and a scale that assessed the frequency and severity of stressful life events during the year preceding the interview (Landerman et al 1989).

Baseline clinical assessments included the Carroll Rating Scale for Depression (Carroll et al 1981); Hamilton Rating Scale for Depression (Hamilton 1960); Consortium to Establish a Registry for Alzheimer's Disease (CERAD) clinical and neuropsychological test battery (Morris et al 1988); Clinical Global Impressions (CGI) scale (Guy 1976); Hachinski Ischemia Scale (Hachinski et al 1975); and Cumulative Illness Rating Scale (CIRS) (Conwell et al 1993). In addition, genotypic data on the apolipoprotein E (ApoE) allele and the serotonin transporter (5HTT) were determined by blood sample from each subject.

Magnetic Resonance Imaging

MRI acquisition and assessments have been described in detail in CHAPTERS IV and V.

Longitudinal Assessments

Depression study subjects have been assessed on the parameters described above for up to twelve years, depending upon their enrollment date and continued participation. MRI was repeated every two years, and the DDES was repeated

yearly. Clinical assessment and treatment variables were repeated at regular intervals and may have occurred at extra intervals for relapsed subjects.

Nutrition Assessment

The nutrition assessment has been described in detail in CHAPTERS IV and V. See the next section for additional details on the variables for this project.

Data and Statistical Considerations

Variables

Primary Dietary Variables

The focus was on the following dietary intake variables: kilocalories, saturated and trans-unsaturated fats, omega-3 fatty acids, dietary cholesterol, fiber, lycopene, vitamin E, as well as intake of the following food categories: whole grains, vegetables, fruits, high and low-fat dairy products, and meats. All of these measures, except high and low-fat dairy products and meats (see separate section for details), were available as an output from scanning of the FFQ (by Block Dietary Data Systems, Berkeley, CA). Intake of food and nutrients was presented in quantity per day. Intake of vitamin E was calculated from both food and vitamin supplement sources.

In addition to specific food and nutrient intake variables, body mass index or BMI ([weight in kg]/[height in m^2]), Keys score, and Healthy Eating Index, were examined. BMI was calculated from self-reported weight and height. The Keys score is based upon metabolic ward experiments and estimates the cholesterol-raising capacity of the diet (Keys et al 1965a; Keys et al 1965b). It combines percentage of energy from saturated and polyunsaturated fatty acids (PctSatFat and PctPUFA,

respectively), and dietary cholesterol per 1000 kcals (CHOL), into the formula [2(PctSatFat) – 1•35(PctPUFA) + 1•5($CHOL^{1/2}$)]. The Healthy Eating Index (HEI) is an indicator of overall dietary quality (Kennedy et al 1995) and was available as an output variable from scanning. The HEI score ranges from 0 (worst) to 100 (best), and incorporates ten components which are each worth up to ten points. The components are servings of grains, vegetables, fruits, dairy, and meats, intake of total and saturated fats, cholesterol, and sodium, as well as a measure of dietary variety. Specific criteria have been established for scoring a zero or ten in each category. For example, the criterion for a ten on saturated fat is consumption of less than 10% energy from saturated fat; intake of greater than 15% energy from saturated fat is scored as zero; an intake between 10% and 15% is given a proportionate score. The HEI has been used by the United States Department of Agriculture (USDA) to monitor changes in dietary intake and as a basis for nutrition promotion activities for the population (Kennedy et al 1995). The HEI has been found to correlate with dietary vascular risk factors including fats and antioxidants (Chung et al 1996; Hann et al 2001).

All nutritional variables were obtained from the earliest FFQ assessment which was analyzable for any given subject. In other words, if the first FFQ was rejected for any reason, the second FFQ was used. This was only necessary for three subjects.

New Food Group Variables

Three food group variables were created to augment the 1992 U.S. Food Guide Pyramid-defined food groups (grains, vegetables, fruits, meats/protein, dairy, and

fats/sweets) available from scanning of the FFQ, namely high-fat and low-fat dairy, and meat variables. Five steps were required in creating each of the three new food group variables:

1) Determination of food items on FFQ that should be included in food group (see below for details).

2) Determination of standard serving size per food item. This valuation was guided by serving size guidelines from the Food Pyramid, typical serving size, and nutrient equivalents, in that order of priority. For example, the Food Pyramid lists 2 ½ to 3 ounces (cooked weight) as a serving of meat. While this sample size works for many meats, very lightweight items like bacon would yield a serving size of 15 pieces when using the weight guideline. In this case a more-typical standard serving size was used, namely 3 pieces. Standard serving sizes for each food item are identified below in BLUE.

3) Conversion of reported serving size of each food item into # of standard servings. For example, if a subject reported consumption of 2 pieces of bacon, their standard # of servings would be ⅔ (given the 3 slice standard serving size). For subjects who failed to report a serving size, the second option (out of four) was used.

4) Conversion of frequency data into # servings per day. For example, a frequency of 3-4 times per week would be converted to ½ serving per day (3.5 times per week divided by 7 days).

5) Calculating the product: (# of standard servings)*(# of servings per day).

An additional step was required for the dairy calculations, namely to categorize milk,

cheese, and ice cream into either high or low-fat categories based upon the type reported to be consumed. For example, if a subject reported usual consumption of low-fat cheese, then their cheese intake would be added to the low-fat dairy product total, otherwise cheese would be categorized as a high-fat dairy food.

High-fat dairy products were estimated by summing intake of whole and 2% milk (1 cup), cheese (1 ½ ounces), mixed cheese dishes (2 cups = 1 ½ ounces of cheese), ice cream (3/4 cup), butter (2 pats), and pizza (2 slices = 1 ½ ounces of cheese). Similarly, low-fat dairy products were estimated from intake of skim and 1% milks (1 cup), low-fat ice cream (3/4 cup), and low-fat cheese (1 ½ ounces). Both categories of dairy products were underestimated since some dairy items on the FFQ were excluded from consideration. This underestimation was because of an inability to determine the fat content of certain food products, such as yogurt, or because a questionnaire item included both dairy and non-dairy foods (such as the item on hamburgers and cheeseburgers). Meat servings were calculated by total intake reported for the following food items: bacon (3 pieces), breakfast sausage (2 pieces), hamburgers/cheeseburgers (1/4 pound), meat tacos/burritos/enchiladas/tamales (1 cup) , steaks/roasts (1/2 cup), pork/ham (1/2 cup), veal/lamb/deer (1/2 cup), ribs (5-6), liver (1/4 cup), gizzard/chitlins/miscellaneous pig parts (1/4 cup), mixed dishes with meat or chicken (1 cup), fried chicken (2 medium pieces), non-fried chicken/turkey (1/2 cup), hot dogs (1), and lunch meats (2 slices). This measure of meat consumption differs from that estimated for the meat “group” of the Food Guide Pyramid. The Pyramid group definition includes, in addition to true meats, other non-dairy concentrated

protein sources, such as eggs, peanut butter, beans, and seafood.

Depression Group Assignment

The depression group, defined by the inclusion and exclusion criteria described earlier, was divided into vascular and non-vascular subtypes. This division created three subject groups: vascular depression, non-vascular depression, and never-depressed comparison. Vascular depression is typically classified by the presence of brain lesions, as measured by a hyperintensity rating of the MRI films (Krishnan et al 1997). If a depression subject has a score of 2 or higher on either deep white matter or subcortical gray matter hyperintensities, then he or she was classified as having vascular depression. Otherwise, the subject was categorized as having non-vascular depression.

Covariate nutrition variables

Total daily caloric intake was included as a covariate in all models except those where kilocalories was the primary independent variable or a component of the primary independent variable. Caloric intake was included in nutrient models as a way of standardizing nutrient intake across different levels of energy consumption, and because it is positively associated with vascular risk.

Depression and lesion covariates

All depression models included the following covariates: age, sex, race, and socioeconomic status, hypertension, diabetes, subjective social support, and stress. Age was that at the time of FFQ assessment, which was calculated from completion date and birth date. For non-responders to the FFQ, the date that the FFQ was given to the subject was used in lieu of completion date. Because of the limited

number of minority subjects, race was categorized as white or non-white. Race data were obtained from the FFQ except for those who either did not return an FFQ or failed to complete the race question, in which case race data from the depression project were used. Socioeconomic status was defined by the proxy variable "years of education." Comorbid medical conditions including hypertension and diabetes were determined from self-report. Other covariates, including stressful life events, functional disability, and social support were determined from specific sections of the DDES. The stressful life events variable was the average stress level reported over the previous six month period (on a 10-point continuous scale). Disability was determined from the instrumental activities of daily living (IADLs) scale (9 items, summed and used as a continuous variable).

Subjective social support was determined from 10 items on the Duke Social Support Index scale (Hays et al 2001). The following questions were included:

When you are with family, how often do you feel lonely?

Does it seem that your family and friends understand you?

Is there at least one person with whom you have a close, lasting relationship?

Do you feel useful to your family and friends?

Do you know what is going on with your family and friends?

When you are talking with your family and friends, do you feel that you are being listened to?

Do you feel you have a definite role in your family and among your friends?

In a time of trouble, can you count on at least some of your family and friends?

Can you talk about your deepest problems with at least some of your family and

friends?

How satisfied are you with the kinds of relationships you have with your family and friends?

Data Management

A centralized data management system was utilized for the depression study. Data from standardized interviews, subject self-report, clinical interviews, neuroimaging, and laboratory testing, were sent to the data administrator for storage and management. Data were checked for accuracy and completeness. Data were managed on UNIX-based computers housed in the Duke Center for Aging and Human Development. The nutrition data and records for this project were held under secure storage by the nutrition study principal investigator. FFQ and other data were kept in SAS, Excel, and JMP files, on a password-protected Windows XP machine which resided behind a firewall. There was strict adherence to all requirements of the Health Insurance Portability and Accountability Act (HIPAA), enacted in April 2002. All protected health information (PHI), including that held in computer files, was stored in secure locations with data access limited to only those individuals who required such information for their research or clinical responsibilities.

Statistical Analyses

The statistical packages JMP (version 4) and SAS Enterprise Guide (version 2) (SAS Institute, Cary, NC) were used for all analyses. Both programs were run on a Windows XP platform. Analyses for depression subtype and lesion volume have been described in their respective chapters (CHAPTERS IV and V).

Longitudinal Analyses: Dietary Quality as a Predictor of Depression and Lesion Outcomes

Outcomes including changes in lesion volumes and depression scores were examined among the depression subjects. Critical to these longitudinal analyses was establishing the proper time sequence between predictor and outcome variables. Outcomes of interest were change from TIME 1 to TIME 2 in lesion volumes and depression scores. Depression score was that from the Montgomery-Asberg depression rating scale (MADRS)(Montgomery and Asberg 1979). MADRS scores range from 0 to 60 with a higher score indicating more severe symptomatology. The predictor variable for all hypotheses was HEI score (Kennedy et al 1995) calculated from the FFQ. HEI scores range from 0 to 100. This baseline HEI score always preceded TIME 2 (for assessing change in lesion volume and depression score). Since nutrition assessments were not done during a clinic visit, the baseline HEI and TIME 1 (for assessing change in lesion volume and depression score) were not the same date. For assessing change in lesion volumes, TIME 1 was the MRI date prior to FFQ if the MRI date is not more than six months before FFQ. Otherwise TIME 1 was the first MRI date after FFQ. TIME 2 was the MRI date for the first MRI done after TIME 1, usually performed approximately two years after TIME 1. For depression score changes, TIME 1 was the clinic visit date immediately prior to the FFQ. TIME 2 was the visit date after TIME 1 that was closest to one year after TIME 1. Since TIME 1 and TIME 2 were not separated by a fixed interval for depression score and lesion volume assessments, follow-up time was included in both models by using a rate variable for the dependent variable. For both the lesion and depression score analyses, non-nutrition covariates were determined from the TIME 1 clinic visit, if

possible. Covariates for depression change model included age, sex, race, educational level, functioning (from instrumental activities of daily living), subjective social support, average stress, hypertension (yes/no), diabetes (yes/no), baseline MADRS, and BMI. Covariates for lesion volume change model included age, sex, race, educational level, hypertension (yes/no), and diabetes (yes/no).

In addition to change from TIME 1 to TIME 2, depression score analyses also included evaluation of rate of change for all available follow-up assessments. Using all follow-up assessments that occurred after TIME 1, a MADRS slope (or rate of change) was calculated for each subject. This slope was used as the dependent variable for both bivariate and multivariable models, for which HEI score was the primary independent variable. Covariates were same as in the depression change (TIME 1 to TIME 2) model.

Separate bivariate analyses evaluated the association between baseline HEI and the following variables: rate of change in depression scores (over 1 year), rate of change in depression score (over entire follow-up period), and rate of change in lesion volumes (over 2 years). Multiple linear regression models were used to examine rates of change in lesion volumes and depression scores from TIME 1 to TIME 2 (dependent variable, $Y = \Delta\text{LesionVol}/\Delta\text{Time}$ or $\Delta\text{DepScore}/\Delta\text{Time}$) as a function of HEI (primary independent variable, X_1), among depression subjects. In addition, the association between HEI and rate of depression score change over entire follow-up period was examined. Potential confounders were included as covariates in the multiple regression models. A coefficient (β_1) was calculated for HEI (X_1) using the following linear regression model:

$Y = \beta_0 + \beta_1 HEI + \beta_2 X_2 + \beta_3 X_3 \ldots \beta_n X_n + \varepsilon$

Where **Y** and model-specific covariates (X_2, X_3, etc.) were,

Lesion 2-Year Change Model: Y= ΔLesionVol/ΔTime; covariates include age, sex, race, educational level, hypertension (yes/no), and diabetes (yes/no)

Depression 1-Year Change Model: Y= ΔDepScore/ΔTime; covariates included age, sex, race, educational level, functioning, subjective social support, average stress, hypertension (yes/no), diabetes (yes/no), baseline MADRS, and BMI

Depression Rate Model: Y=Rate of change (Change in MADRS per year); covariates included age, sex, race, educational level, functioning, subjective social support, average stress, hypertension (yes/no), diabetes (yes/no), baseline MADRS, and BMI

Human Subjects

This project has been approved by the Duke University Medical Center Institutional Review Board. All subjects provided written informed consent prior to participation. In addition, the UNC Public Health Institutional Review Board has approved this research

CHAPTER VII

LONGITUDINAL RESULTS

A total of 98 subjects had longitudinal depression and/or MRI assessments which meant they could be included in one or more of the longitudinal analyses for Aim 3 (see CHAPTER II for Specific Aims); 98 were included in the rate of change in all depression scores analyses, 92 were included in 1-year depression score rate of change analyses, and 45 were included in the 2-year lesion volume rate of change analyses. Sample size differences were due to the varied availability of follow-up assessments. Mean HEI score was 65 (range 37-94) for the depression group as a whole. Significance level used for all analyses was $p < 0.05$.

Change in Depression Scores (1-year rate)

Bivariate analyses between depression change (difference in MADRS scores) and Healthy Eating Index (HEI), as well as demographic, medical comorbidity, social support, and stress variables were performed. No significant associations were found.

Multivariable models examined the association between rate of depression change and HEI, while controlling for age, sex, race, education, functioning, hypertension, diabetes, BMI, social support, stress, and baseline MADRS score. The parameter estimate for HEI was not significant ($\beta = 0.0001$, $p < 0.57$), nor was the overall model ($F_{12, 92} = 1.03$; $p < 0.43$).

Rate of Change in Depression Scores (per year)

Rates of change were calculated for each subject based upon the MADRS closest in time to FFQ through all available follow-up depression ratings. These rates ranged from -13.9 to 6.2 per year, with a median of -1.6. Negative rates indicate improvement in depression symptomatology.

Bivariate analyses between rate of change (slope of MADRS scores) and Healthy Eating Index (HEI), as well as demographic, medical comorbidity, social support, and stress variables were performed. No significant associations were found.

Multivariable models examined the association between rate of depression change and HEI, while controlling for age, sex, race, education, functioning, hypertension, diabetes, BMI, social support, stress, and baseline MADRS score. The parameter estimate for HEI was not significant ($\beta = 0.03$, $p < 0.38$), nor was the overall model ($F_{13, 97} = 0.74$; $p < 0.72$).

Change in Lesion Volumes (2-year rate)

Bivariate analyses between lesion change (difference in lesion volumes from TIME 1 to TIME 2) and Healthy Eating Index (HEI), as well as demographic and medical comorbidity variables, were performed. Age and sex were significantly associated with lesion change. Age was positively associated with change in lesion volume ($\beta = 0.19$, $p < 0.002$), whereas women had greater increases in lesion volume than men ($F_{1, 46} = 5.43$; $p < 0.02$). No other significant associations were found.

Multivariable models examined the association between rate of lesion change and HEI, while controlling for age, sex, race, education, hypertension, and diabetes. The parameter estimate for HEI was not significant ($\beta = -0.00003$, $p < 0.47$); sex ($\beta = -0.001$, $p < 0.02$) and age ($\beta = 0.0003$, $p < 0.0015$) retained significance in the multivariable model.

CHAPTER VIII

SYNTHESIS

Overview of Findings

This late-life depression project was the first known to investigate the relationship between vascular dietary factors believed to either promote or prevent cardiovascular disease and MRI-based depression subtype, brain lesion volumes, and longitudinal depression outcomes. Vascular nutritional factors were found to differ significantly between depression and comparison subjects but tended to be similar across the two depression groups (vascular and non-vascular). Depression subjects, regardless of depression subtype, reported diets that may promote vascular disease, including higher dietary cholesterol, trans-unsaturated fat, high-fat dairy products, and Keys score, and lower fruit intake than comparison subjects. Low-fat dairy consumption was found to be lower in the vascular depression group as compared to the non-depressed group. In multivariable models, lower whole grain and lycopene intake and higher Keys score were associated with depression. Omega-3 fatty acids were not associated with depression group in either bivariate or multivariable analyses. Lesion volumes were found to be significantly and positively associated with high-fat dairy product and whole grain consumption in both bivariate and multivariable models among individuals with current or prior vascular depression. No other nutritional factors investigated in this study were found to be related to lesion volume. No associations were found between dietary quality as

measured by the Healthy Eating Index (HEI) and longitudinal changes in depression scores or lesion volumes. HEI failed to predict either 1-year change in Montgomery-Asberg Depression Rating Scale (MADRS) scores or 2-year change in brain lesion volumes. In addition, HEI was unassociated with rate of change in MADRS scores across all available follow-up depression evaluations.

Covariates

Older age was associated with being in either the vascular depression or comparison groups as compared with the non-vascular depression group. In multivariable analyses examining nutritional factors and group, age was not a significant covariate in most models. In both bivariate and multivariable lesion analyses, age was positively associated with lesion volume and was the only covariate found to be significantly associated with lesions.

Covariates other than age were similar to nutritional factors in that any differences found were for both depression groups as compared to the non-depressed group. Reported stress level was higher, subjective social support and years of education were lower among both depression groups as compared to the control group. Education was significantly associated with several nutritional factors in multivariable models. Lower education was consistently associated with less healthy eating behaviors. Social support was positively associated with fruit consumption in multivariable models. Stress was positively associated with whole grain and meat consumption. Sex was not associated with group but females reported healthier diets including higher consumption of omega-3 fats, fiber, low-fat dairy products, fruits, and vegetables, and lower consumption of trans fats.

Individuals with hypertension but not diabetes were more likely to be in one of the depression groups than in the control group. Diabetes was significantly associated with less healthy dietary attributes, including higher intake of cholesterol and trans fats, and higher BMI. Hypertension was associated only with higher BMI.

Significance

The devastating impact of depression upon health and quality of life cannot be overstated. Affected are individuals, their families and their communities. Depression is the most common mental disorder, is the leading cause of years lived with disability, and responsible for the majority of over 800,000 suicides annually (Murray 1996; WHO 2001). In addition, individuals with depression are more likely to have comorbid chronic diseases and to have poorer outcomes from those diseases than are individuals without depression (Aromaa et al 1994; Egede et al 2005; Gonzalez et al 1996; Goodnick et al 1995; Katon et al 2004; Schleifer et al 1989). This project adds important new knowledge to the field of late-life depression research. The characterization of food and nutrient intake among individuals with depression is critical to understanding the interrelationships between depression, cardiovascular disease, diabetes, hypertension, and brain pathology. The less healthful diets of depression subjects are likely an important component in the negative consequences seen of depression upon morbidity and mortality. The finding of significant nutritional differences between depression and comparison subjects but fewer differences between the two depression groups, combined with a lack of association between most nutritional factors and lesion volume, may indicate that vascular nutrients and foods are related to depression in subjects with and

without comorbid cerebrovascular disease and that diet may exert a vascular influence on depression primarily via other mechanisms than ischemic brain lesions. However, a few foods, such as high-fat dairy products, were found to be associated with brain lesions. Whether reducing the intake of these foods would affect the risk of developing lesions in the long-term needs to be determined. Given the detrimental effects of brain lesions upon cognition, mood, and quality of life in older adults (Kuo and Lipsitz 2004), factors related to such lesions, especially those which are modifiable, need to be identified.

The inability to detect a relationship between dietary quality and longitudinal outcomes may be indicative of an inadequate sample size. No association may have been found between HEI and outcomes because specific dietary factors are more important than overall dietary quality. However, even if no relationship exists between dietary quality and depression or lesion outcomes, the differences in diet found among depression subjects may have important implications for health. Poor diet may be one reason that depressed individuals not only have more cardiovascular disease, diabetes, and hypertension than non-depressed individuals, but also may help explain why depressed individuals have worse outcomes from those conditions (Egede et al 2005; Simonsick et al 1995). Prior research has indicated that depressed individuals have poorer diets and other lifestyle characteristics than non-depressed (Bonnet et al 2005). In addition, there is evidence that depressed individuals are less likely than non-depressed individuals to adhere to lifestyle recommendations, including dietary modification, following a myocardial infarction (Ziegelstein et al 2000). The current project was an important

first step and may guide research into the nutritional etiology and progression of late-life depression, comorbid vascular disease, and brain lesions.

The Context

This dissertation project found depression subjects to have higher intake of trans-unsaturated fat, cholesterol, and high-fat dairy products, lower intake of whole grains, fruit, and lycopene, and depression subjects had higher BMI and Keys score when compared with non-depressed subjects. The finding of an association between diet and the two depression groups was consistent with prior work showing a relationship between vascular nutritional factors and late-life depression when both subtypes were examined together (Payne et al In press). The author and colleagues previously found higher Keys score, BMI, and dietary cholesterol, and lower alcohol intake in elderly depression subjects when compared to never-depressed subjects (Payne et al In press). The Keys score, cholesterol, and alcohol associations remained after controlling for covariates. The current finding of an association between lower lycopene intake and vascular depression subgroup was consistent with a previous study that found plasma levels of lycopene to be negatively associated with white matter hyperintensities in elderly subjects (Schmidt et al 1997), particularly considering that depression subtype was determined by the presence of MRI lesions. However, lesion volumes were not found to be associated with lycopene intake. This lack of association may have been due to our focus on depression subjects (rather than never-depressed elders), inadequate detection of individual differences in lycopene intake, the lesion quantification methodology, inadequate sample size, or another not yet elucidated factor.

Whole grains, recently investigated for their cardioprotective properties, had not been investigated previously in depression, but the finding of lower intake among both depression groups is consistent with other studies showing an association between other vascular nutrients and depression (Payne et al In press). However, the positive association found between brain lesions and whole grain consumption was surprising. The known beneficial effects of whole grains on cardiovascular morbidity and mortality would seem to indicate their possible protective qualities for ischemic brain lesions (Jacobs et al 1998; Liu et al 2000; Liu et al 1999). However, the Atherosclerosis Risk in Communities (ARIC) also failed to find whole grains to be protective against ischemic stroke although they were shown to be protective for CAD (Steffen et al 2003). Whole grains were not found to be associated with an increased risk in the ARIC study (Steffen et al 2003) as was the case with this dissertation research. One possible explanation for the current finding is that whole grains may be correlated with brain lesions because of the association of whole grain consumption with inadequate mineral status (especially of zinc and iron), a known risk factor for neuropsychological impairment (Sandstead 2000). However, mineral inadequacy is purely speculative since it is unknown if whole grain consumption was related to mineral status in this study or whether any relationship exists between minerals and brain lesions.

Given the recent interest in fish consumption and omega-3 fatty acids (ώ-3FAs) as protective for depression, it is noteworthy that no relationship was found between ώ-3FA intake and either depression subgroup or lesion volume. This negative finding may be explained by the Block 1998 FFQ assessment tool which is not

optimal for estimating ώ-3FAs given the lack of specificity of fish types. However, this finding of no association is actually consistent with previous depression studies that have assessed dietary intake (rather than plasma levels) of ώ-3FAs. Ecologic and cohort studies which promoted interest in ώ-3FAs showed negative correlations between fish consumption and depression, depressive symptoms, and general mental health (Hibbeln 1998; Silvers and Scott 2002; Tanskanen et al 2001). Clinical and population studies have shown diminished ώ-3FA levels in serum phospholipids and erythrocytes, as well as elevated ratios of plasma omega-6 to omega-3 polyunsaturates, among depressed subjects (Adams et al 1996; Maes et al 1999; Tiemeier et al 2003). In addition, these alterations have been associated with depression severity (Adams et al 1996).

A different picture emerges when looking at dietary intake of ώ-3FAs. Population studies in Australia (n=755) and Finland (n=29,133) found no association between dietary ώ-3FAs and depression or depressed mood (Hakkarainen et al 2004; Jacka et al 2004). The one study which measured both dietary and plasma levels of ώ-3FAs found that dietary differences did not explain plasma levels (Adams et al 1996). Some researchers have concluded that fatty acid metabolism is altered in subjects with depression and that this abnormality may influence both the etiology and course of depression (Maes et al 1999; Tiemeier et al 2003). Although dietary deficiencies likely exacerbate ώ-3FA plasma abnormalities, ώ-3FA intake itself may not be the most critical factor for depression. Since fish consumption but not ώ-3FA intake has been associated with depression, perhaps a component of fish other than ώ-3FAs is protective for depression, or fish consumption may be an indicator of

other healthful behaviors.

Education was likely the most influential covariate for the nutrition and group analyses. Not only was lower education associated with being in one of the depression groups but it was also associated with poorer dietary behaviors. Given that educational level did not differ significantly between the two depression groups, the association between education and diet may have made it difficult to detect differences between the vascular and non-vascular depression groups. Evaluation of covariates for this project provided support for several known associations, including the positive relationships between age and brain lesions, diabetes and BMI, and hypertension and BMI. The associations of being male and diabetic with poorer dietary behaviors indicate the importance of considering these variables in future studies.

The absence of previous research into the association between nutritional factors and brain lesions in late-life depression provided little framework with which to interpret the mostly negative current results. The ARIC study found that consumption of fruits and vegetables decreased the risk of coronary artery disease (CAD) during an 11-year follow-up period but had no effect on risk of ischemic stroke (Steffen et al 2003). The present study supported this finding if one accepts the prevailing view that brain lesions occurring with late-life depression are etiologically similar to those seen with ischemic stroke. These findings may indicate that a somewhat different disease process (beyond ischemia) is responsible for brain lesions and strokes than for CAD. The finding of a possible association between high-fat dairy products and brain lesions is consistent, however, with the ischemic

nature of brain lesions seen in late-life depression, given that saturated fat, a prominent component of fatty dairy foods, is known to be a cardiovascular risk factor (Hu et al 1997). Some saturated fatty acids, including those found in dairy products, may be more atherogenic than other saturated fatty acids (Kris-Etherton and Yu 1997). This atherogenicity may help explain why high-fat dairy consumption but not total saturated fat was associated with brain lesion volume. To further complicate this issue are results of recent studies which cast doubt on the premise that lower fat diets promote cardiovascular health, particularly findings from the Women's Health Initiative (WHI) which found that a low-fat diet modification regimen did not reduce risk of coronary heart disease, stroke, or cardiovascular disease in postmenopausal women (Howard et al 2006). The WHI finding may in part be due to emphasis that was placed on reducing total fat rather than altering intake of specific types of fat.

The current study failed to replicate previous findings of negative associations between brain lesions and α-tocopherol, lycopene (Schmidt et al 1996), and alcohol consumption (Mukamal et al 2001); however, both previous studies were done with non-depressed subjects. The failure to detect these associations may have been due to the small sample, the quantitative lesion methodology, differing nutrition assessment methodologies, special characteristics of lesions in depression, or to a combination of factors. Lesion investigations among depression subjects may require consideration of specific factors which may affect the occurrence of brain lesions in depression, including genotypic polymorphisms like the apolipoprotein E (apoE) allele (Nebes et al 2001). Regarding lycopene, the Block 1998 FFQ may have been insufficient since supplemental lycopene was not assessed. A cross-

sectional study may have been unable to detect an association between nutritional factors and lesions because individuals with known vascular disease may have already changed their diets. Alternatively lesions in certain brain regions such as the basal ganglia, believed to be related to depression, may have lead to changes in dietary behavior (Siegel 1999).

The lack of significant longitudinal findings between dietary quality and depression and lesion outcomes may have been due to either the small sample size or to the general nature of the HEI measure. HEI encompasses ten dietary attributes including intake of the five Food Pyramid (Herring et al 2000) food groups (grains, fruit, vegetables, meat, dairy), total fat, saturated fat, cholesterol, and sodium, as well as dietary variety (Kennedy et al 1995). This generality of HEI may have precluded detection of associations between depression, lesion outcomes, and HEI if in actuality only specific dietary components were important. Since no prior research has been done looking at dietary quality or vascular nutritional factors and depression and lesion outcomes, there were no prior findings to confirm or refute. However, the determination of predictors of depression outcomes in late-life depression is critical to maximizing the success of treatment. In addition, given the detrimental effects of lesion volume progression on depression outcomes and cognition (Chen et al 2006; Taylor et al 2003; van den Heuvel et al 2006), it is equally important to determine dietary factors predictive of change in lesion volumes.

Potential Mechanisms

A variety of mechanisms are possible to explain the findings from this project. In reviewing the original mechanism proposed in CHAPTER III (see Figure 3.1) this

project provided support for the association of several nutrients and foods with vascular depression (see Figure 8.1 for revised diagram). In particular, high-fat dairy and whole grains were found to be positively associated with lesion volumes in vascular depression subjects. In addition, lycopene and low-fat dairy consumption were associated with the vascular depression group but not the non-vascular depression group, indicating a potential relationship with brain lesions since depression group assignment was determined by the presence of brain lesions. Regarding nutrients and foods that were not found to be associated with vascular depression or brain lesions, alternative mechanisms may help explain these findings.

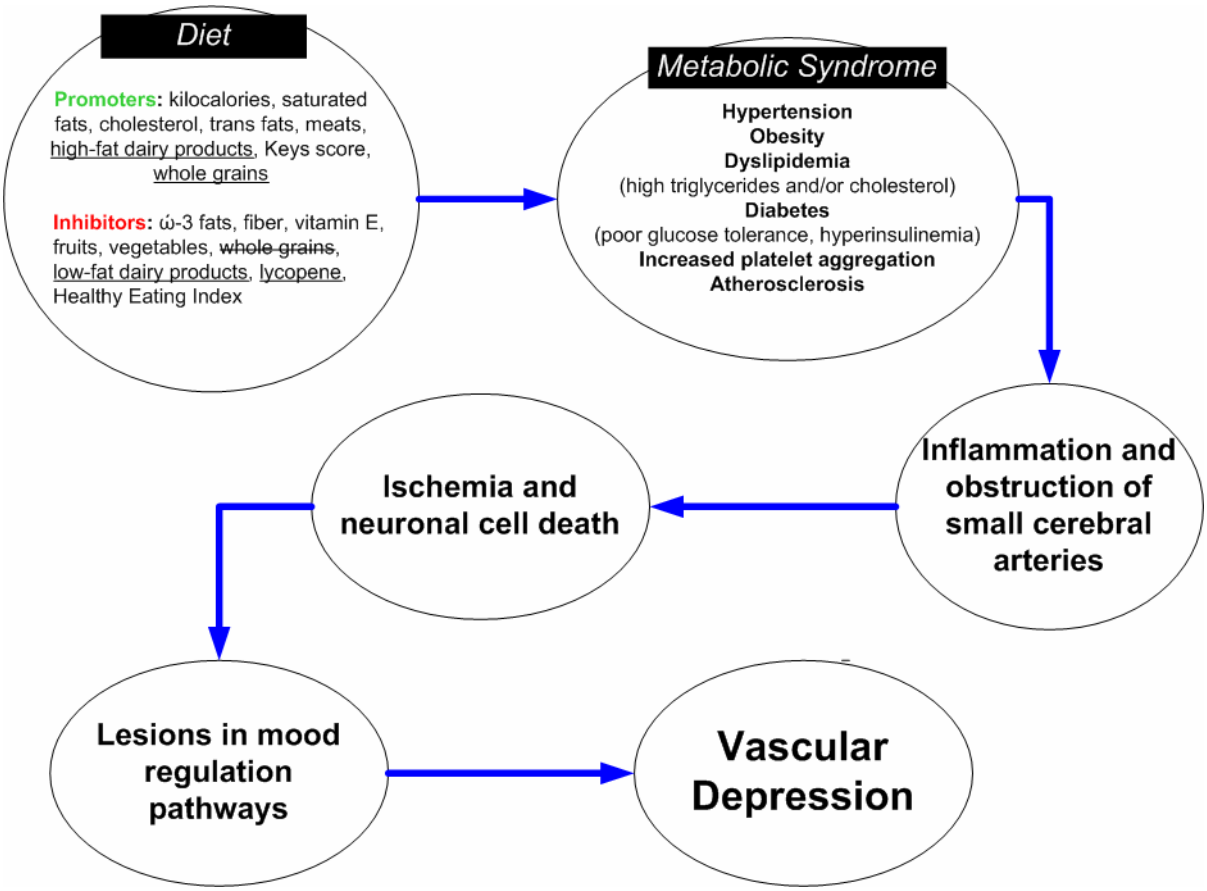

Figure 8.1. Evidence for proposed nutritional mechanism for vascular depression (evidence provided by this project for nutrients/foods that are underlined) (Payne, 2006)

Diet may exert its influence on depression via other mediators besides brain lesions which may influence vascular depression directly or by interaction with cardiovascular diseases (see Figure 8.2). Potential mediators include genetic polymorphisms for the serotonin transporter (5HTT), apolipoprotein E (apoE), folate metabolism (including MTHFR), and tryptophan hydroxylase-2 (hTPH2), which was recently identified as being related to depression (Zhang et al 2005). Other mediators may include the inflammatory response as indicated by recent evidence for an association between C-reactive protein (CRP) and depression (Danner et al 2003; Ford and Erlinger 2004), homocysteine levels (Sachdev et al 2005), glucose tolerance (Winokur et al 1988), and visceral fat deposition (Weber-Hamann et al 2002; Weber-Hamann et al 2005). These mediators do not exclude the possibility that ischemic brain lesions may also serve as important mediators between diet and depression. This project may not have had the power to detect such an association. Equally important is the likelihood that these mediators may interact with one another and with chronic disease occurrence and progression. Sociodemographic

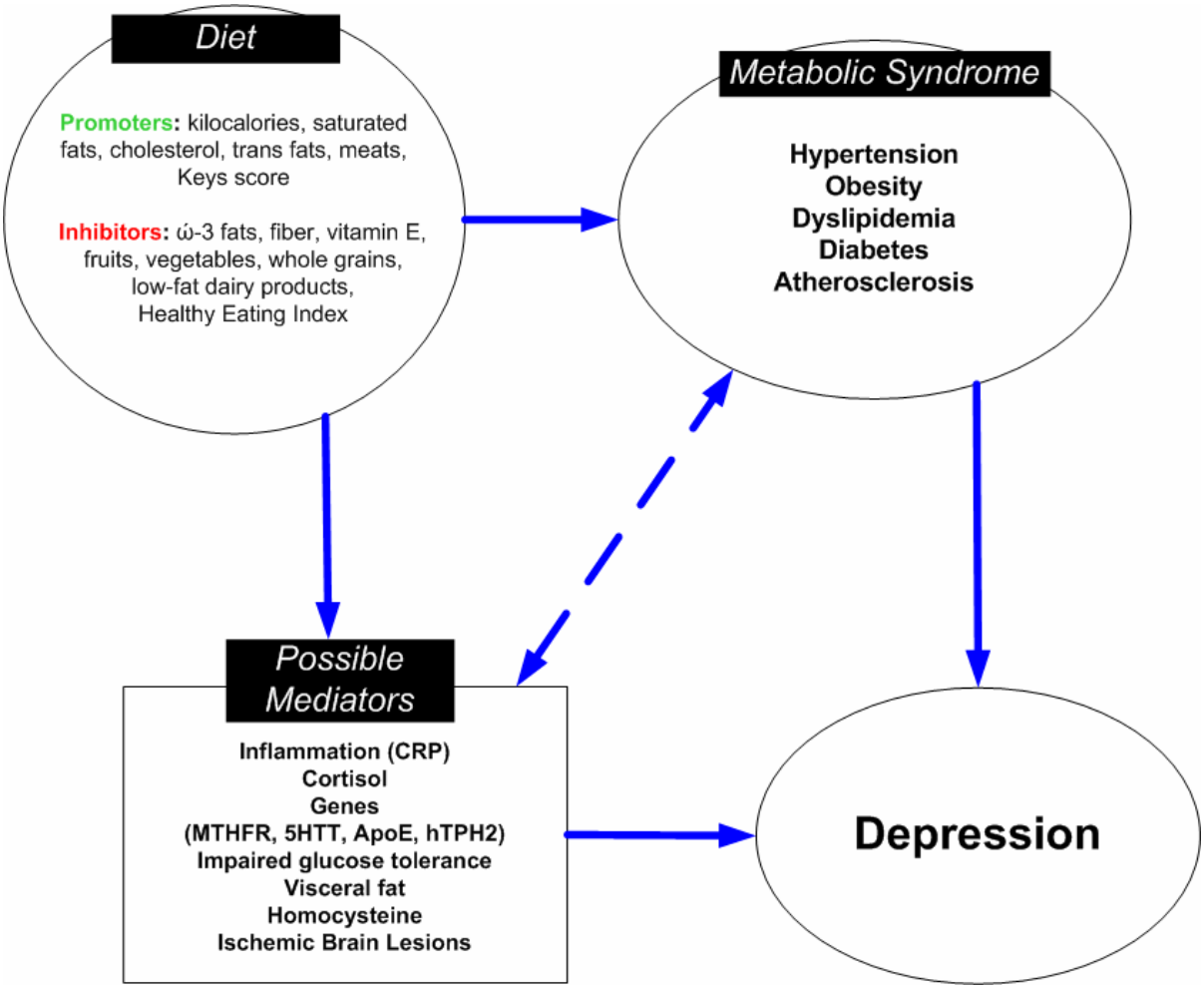

Figure 8.2. Proposed alternative nutritional mechanism for depression (Payne, 2006)

and psychosocial factors may further complicate this scenario by influencing dietary intake, mediating factors, comorbid disease, and depression itself.

Strengths and Limitations

This nutrition-depression project had several strengths including a unique combination of data that included diagnosis of depression by a psychiatrist, structural brain MRI (with precise lesion quantification), and a detailed nutrition assessment. The majority of studies investigating diet and depression have suffered from inadequate dietary assessment, poor control for depression confounders, or the

absence of a psychiatric assessment, using self-report of depressive symptoms in lieu of a depression diagnosis. In this project, an important first study of vascular nutritional factors in late-life depression, acquisition of food frequency data has provided an important glimpse into dietary patterns and allowed for comparison to both depression and MRI attributes. The Block FFQ was designed to measure average intake over a one year period and was advantageous because it suffers less from the day-to-day variation inherent to human diets than do 24-hour recall and food record assessment methods. An FFQ may be more representative of long-term intake than other measures. Given that cardiovascular disease and ischemic brain lesions develop over many years and that diets of older adults may be more stable than those of younger adults, the retrospective Block FFQ may have better allowed speculation about possible etiological factors than other assessment tools. The interdisciplinary team involved in this project allowed for a broad-based and critical approach to the issue of diet and late-life depression.

Some of the strength of this project stems from that of the parent grant. The depression project, now in its thirteenth year, is the largest single-site longitudinal clinical study of individuals with late-life depression. The multidisciplinary approach used for this project provided an unparalleled set of assessments including MRI, detailed psychiatric interviews, neuropsychological testing, genetics, personality, social support, religiosity, stress, and nutrition. These assessments have allowed for not only comprehensive evaluation of depression, brain lesions, and diet, but also inclusion of important covariates of depression and brain lesions including educational level, stress, social support, and medical comorbidity. The brain lesion

measurements used for this project offered several advances over previously-used methods including quantification rather than qualitative assessment of lesions, detailed anatomical criteria for lesion selection, and high reliability (Payne et al 2002).

This research project had a number of limitations including the modest sample sizes, especially for the depression subgroups, and the large number of statistical comparisons made. In addition, since diet was not assessed until after diagnosis of depression, it was not possible to distinguish dietary factors that may have been the result of depression or brain lesions from possible etiological factors. A further complication is the changing nature of depression over time combined with the nutrition assessment period of one year. Not only were both currently and recently depressed individuals included in the depression group, but some individuals were depressed part of the year and remitted for the remainder. The Block FFQ may be insufficient to detect dietary differences in individuals due to problems associated with self-report and the inherently high intra-individual to inter-individual variation of human diets. Self-report of diet has several limitations including selective underreporting by obese individuals. Given that 50% of our sample was overweight or obese (BMI $\geq$ 25) and that mean BMI was higher among the depression subjects, this underreporting may have impaired our ability to detect true differences in diet between the depression and comparison groups. Self-report of weight and height has limitations as well, particularly for geriatric studies because of underestimation of BMI when compared to that calculated from measured weights and heights (Kuczmarski et al 2001). In addition, the Block 1998 FFQ was not optimal for some

measures including ώ-3FAs and whole grains given the lack of specificity about food items. There were no biochemical measures related to vascular dietary risk, including serum cholesterol, triglycerides, and homocysteine, or clinical measures of vascular disease such as blood pressure readings. Antidepressants and other medications, it should be noted, may have affected appetite and weight in this study. Medication data were not available to evaluate these relationships. Finally, the results may be generalizable only to geriatric individuals with depression who have received psychiatric treatment.

Future Directions

Continuation of this research is strongly recommended given the impact of late-life depression and brain lesions on health and quality of life of older adults. This project provided evidence that vascular nutritional factors differ between depression and comparison subjects but tend to be similar across depression subgroups. This association underscores the importance of vascular nutrients to late-life depression, regardless of the presence of comorbid cerebrovascular disease. From another perspective the less healthful diets found among depression subjects as compared to never-depressed subjects raise concern about the occurrence and exacerbation of other health problems and poorer outcomes of those conditions among depressives. The findings of a positive association between brain lesion volume and consumption of both high-fat dairy and whole grains among individuals with vascular depression need to be confirmed in a larger sample, particularly the positive association for whole grains given the limitations of the Block 1998 FFQ.

As shown in Figure 8.2, an atherogenic diet is speculated to be related to late-

life depression via mechanisms other than the development of brain lesions. To this end future research needs to evaluate other factors that may mediate the effects of diet upon depression. These factors possibly include inflammation, visceral fat, cortisol, glucose tolerance, insulin sensitivity, physical activity, smoking, medication use, and genotype. Future nutrition assessments should include serum biomarkers of nutrient intake and more accurate assessment of whole grain and ώ-3FA intake. In addition, weight, height, and waist-to-hip ratio should be measured by a trained anthropometrist; clinical assessments should include blood pressure readings; and lab measures should include serum cholesterol, triglycerides, homocysteine, and C-reactive protein.

Further research is needed to confirm the findings from this project and to differentiate dietary factors which affect the etiology of depression from those which are a result of depression, as well as to identify dietary factors which may affect the course and treatment of late-life depression, comorbid medical conditions, and brain lesion progression.

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