DIET AND DEPRESSION: A SECONDARY ANALYSIS FROM NHANES 1999-2002

by

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This dissertation is dedicated with love to several members of my family; without their love, ever-present encouragement, and enthusiasm this dissertation would not have been possible.

This dissertation is for:

Steve, Dad, Mom, Ivan, Uncle David, Aunt Sandi, Aunt Joy, Uncle Sid, and Marcia

Also, for my two children, Lucas and Jocelyn, who often waited patiently while I worked on this dissertation.

(pma/car.pony.nickel)

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ABSTRACT

This Ph.D. dissertation presents results that shed light on whether there is an association between dietary intake and depressive disorder, feelings of sadness, or thoughts of death. This question is investigated in the context of a secondary data analysis using cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) 1999-2002. Subjects in this study were identified as a subpopulation of the NHANES survey that completed the Composite International Diagnostic Interview questionnaire for major depression. The presence of depression may lead to a decline in dietary intake and nutritional status. Conversely, poor dietary intake may have a role in the etiology of depression. Specifically, depression is associated with lower plasma, erythrocyte, phospholipid, and adipose tissue omega-3 fatty acids. Little is known about the comprehensive dietary intake of those with depression or depressive symptoms. Initially, comparisons of the dietary profile between those with and without depression or depressive symptoms were investigated. Secondly, analysis was done to determine the relationship between dietary omega-3 fatty acids and depression or depressive symptoms. Lastly, to clarify the relationship between diet and depression, misreporting of dietary energy intake was evaluated.

No significant differences in the dietary profile or nutritional biochemistries were found between the altered mood and normal mood groups. No significant differences were found in dietary omega-3 fatty acids between the depressed and non-depressed groups, even after adjusting for confounding variables. Misreporting of energy intake was not significantly associated with altered mood status and remained non-significant

after adjusting for confounding variables. In both groups, a significant decreasing trend in the ratio of energy intake to estimated basal metabolic rate (EI:$BMR_{est)}$ was found as body mass index increased.

Based on dietary intake alone, the relationship between depression and specific nutrients may not be apparent. Dietary intake among those with depression and depressive symptoms appears to be adequate, but adequacy may not be sufficient as a route for prevention or management of depression. Further investigation of diet and depression ought to measure diet, including nutrition supplements, and biochemical levels of nutrients from a broader age range of adults and children and those with comorbid illnesses.

INTRODUCTION

Explanation of the Problem and Its Context

Depression is a leading cause of disability in the United States (Surgeon General Report, 1999; World Health Organization, 2001; Üstün et al., 2004; NIMH, 1999[a]). Individuals are at risk for depressive disorder regardless of ethnicity, education, income or marital status. The effects of depression are readily observed by measurable reductions in quality of life, lost work productivity, and increased health care costs (Simon, 2003). Depressive disorder can also contribute to substantial personal, social, and financial burden (Surgeon General Report, 1999; NIMH, 1999[a]; NIMH, 2001[b]; Pincus and Pettit, 2001; Rush, 2001).

The burden of depression is often chronic and episodic, requiring individuals afflicted with depression to make considerable lifestyle changes. In order to reduce that burden, it is of interest to examine the relationship between lifestyle choices and depression and/or depressive symptoms. Specifically, the relationship between diet and depression is of interest, since dietary modifications may provide a cost-effective approach to reducing the burden of depression. Additionally, depression may contribute to an overall decline in nutritional status, particularly when depression is paired with comorbid illnesses (Pouwer et al., 2005). Symptoms of depression, such as dysphoric mood or thoughts of suicide, may be associated with diet (Zhang et al., 2005) and depression itself is frequently associated with poor appetite, changes in weight, and reduced motivation (NIMH, 1999[c]; NIMH, 2001[b]). An abnormal appetite and poor

quality of food intake could result in a further decline in overall nutritional status and possibly exacerbate the state of depression. Furthermore, these same symptoms may contribute to inaccurate reporting of dietary habits making it very difficult to determine true relationships between diet and depression or depressive symptoms.

The current data on diet and depression are inconclusive. Christensen and Somers (1994) found the dietary intake in 22 women with depression to be adequate in meeting or exceeding the 1989 Recommended Dietary Allowances for 15 nutrients and total energy. Other reports suggest that major depression may be associated with specific nutrient inadequacies, such as folate, vitamin B12, selenium, omega-3 fatty acids, dietary fat and cholesterol, selenium, zinc, and sugar (Hakkarainen et al., 2005; Hvas et al., 2004; Hibbeln, 1995; Hintikka et al., 2003; Westover and Marangell, 2002; Carney, 1990; Coppen and Bailey, 2000; Coppen and Bolander-Gouaille, 2005; Bodnar 2005; Maher, 2000). Whether overall dietary intake is inadequate among those with depression or depressive symptoms or single nutrient inadequacies are the predominant dietary problem remains to be determined. For example, there is compelling evidence of an association between low omega-3 fatty acid status and depression (Table 1). However, few studies have examined dietary omega-3 fatty acid intake or have addressed whether a low omega-3 fatty acid status is a consequence of an overall inadequate dietary intake. Examination of dietary omega-3 fatty acid intake in individuals with depression has been equivocal. In a multinational comparison, a significant inverse correlation was reported between annual fish consumption and annual prevalence of major depression (Hibbeln, 1998). Infrequent consumption of fish was inversely associated with mild depression;

those with self-reported attempted suicide had lower polyunsaturated fatty acid intake, and women who seldom ate fish were at increased risk of depression (Timonen et al., 2004; Zhang et al., 2005; Tanskanen et al.; 2001). However, other reports demonstrate no relationship between dietary intake of omega-3 fatty acids or fish consumption with depression (Jacka et al., 2004; Hakkarainen et al., 2004; Sarlio-Lahteenkorva et al.; 2004). A higher dietary intake of omega-3 fatty acids was associated with less severe depression, yet no significant difference in the overall omega-3 intake was reported between patients with depression and healthy controls (Edwards et al., 1997). Additionally, there were no significant relationships between the duration of depression and any of the individual dietary PUFA levels measured (Edwards et al., 1997). Also, it has been suggested that a high ratio of dietary omega-6 fatty acid to omega-3 fatty acid may contribute to an increased incidence of depression and worsening in severity of depression (Adams et al., 1996; Bruisma and Taren, 2000). Adipose tissue DHA content was significantly lower in subjects with depression, where the use of adipose tissue as a biomarker reflects a habitual intake of omega-3 fatty acids (Mamalakis et al., 2002). Therefore, whether dietary intake of omega-3 fatty acids and/or fish consumption is related to depression remains unresolved.

In the case of dietary omega-3 fatty acids, it is unclear to what extent dietary intake affects depression or depressive symptoms. Therefore, medical nutrition therapy may provide a pivotal role in the management and/or prevention of major depression. However, in order for medical nutrition therapy to be effective for individuals with depression, accurate assessment of energy and nutrient intake is essential. Misreporting

of dietary intake is problematic even among a relatively healthy population group. Thus, possible misreporting of diet by those with depression or depressive symptoms may have a substantial impact on dietary recommendations for this population. Furthermore, symptoms of depression, such as a change in appetite or weight, poor motivation or concentration, and increased fatigue, may make the task of reporting dietary intake more challenging for those with depression. There is a concern that an accurate reporting of dietary intake may be more difficult to obtain from individuals experiencing depression or depressive symptoms, thus contributing to the controversial relationship between diet and depression.

The present Ph.D. dissertation is aimed at contributing to the state of knowledge on three fundamental questions of nutritional and epidemiological concern. These questions are:

1) Does the dietary profile differ between young adults with and without depression, self-reported sadness, and self-reported thoughts of death?
2) Is there an association between dietary intake of omega-3 fatty acids and depression, self-reported sadness, or self-reported thoughts of death?
3) Does the reporting of dietary intake differ between young adults with and without altered mood? Is there an association between altered mood and misreporting of dietary energy?

The specific aims of this study are:

Specific Aim 1: To characterize the dietary profile of a nationally representative sample of young adults with and without depression, self-reported sadness, or self-reported thoughts of death using NHANES 1999-2002 data.

Specific Aim 2: To evaluate the associations between the dietary intake of omega-3 fatty acids and fish/seafood consumption and depression, self-reported sadness, and self-reported thoughts of death in a nationally representative sample of young adults who participated in the 1999-2002 NHANES.

Specific Aim 3: To assess the association between altered mood and misreporting of energy intake in a nationally representative sample of young adults using data from the 1999-2002 NHANES.

A descriptive cross-sectional design and secondary data analysis was conducted in order to address the relationship between diet and mood disturbances using data from the 1999-2002 National Health and Nutrition Examination Survey. Dietary micro- and macronutrients are needed for normal brain function (Bodnar and Wisner, 2005), therefore it was anticipated that evidence of dietary differences would be found between those with altered mood and those with normal mood. Based on previously published results from studies that examined omega-3 fatty acid status and depression (Ellis and

Sanders, 1977; Fehily et al., 1981; Maes et al., 1996; Adams et al., 1996; Edwards et al., 1998; Peet et al., 1998; Maes et al., 1999; Mamalakis et al., 2002; Hibbeln et al., 1998; Stoll et al., 1999; Peet and Horrobin, 2002; Nemets et al., 2002) it was anticipated that young adults with depression or depressive symptoms, such as sadness or thoughts of death, would have a lower dietary intake of omega-3 fatty acids and lower fish/seafood consumption. Additionally, since changes in appetite and body weight often accompany depression (APA-DSM-IV, 1994), it was anticipated that misreporting of energy intake would be more prevalent among those adults with altered mood compared to those without.

Clarification of dietary intake among young adults with depression and depressive symptoms has clinical and therapeutic implications. The main contributions of this dissertation can be summarized as follows: It was shown that in a nationally representative sample of young adults with depression, self-reported sadness, or self-reported thoughts of death, dietary intake of macro- and micro-nutrients and distribution of calories did not differ significantly from young adults without altered mood. Additionally, the current reported level of dietary omega-3 fatty acids and fish/seafood consumption among young adults participating in NHANES 1999-2002 did not differ between those with and without depression, sadness, or thoughts of death. Finally, the prevalence of misreporting of dietary energy did not differ between young adults with and without altered mood.

A more detailed explanation of the problem and the relevant scientific background corresponding to each specific aim is provided in the next section.

Background and Literature Review

Epidemiology and Description of Depression

Major Depressive Disorder (MDD) is estimated to affect approximately 6.7 million women (6.5%) and 3.2 million men (3.3%) each year in the United States. In a given year, depressive disorder affects approximately 9.9 million Americans age 18 and older (approximately 5% of the US adult population), with the average age of onset most commonly in the mid-twenties (NIMH, 1999[a]; NIMH, 2001[b]; APA-DMS-IV, 1994). The effects of depression are readily observed by measurable reductions in quality of life, lost work productivity, and increased health care costs (Simon, 2003). Major depressive disorder, which is often episodic or chronic, causes substantial personal, social, and financial costs (Surgeon General Report, 1999; NIMH, 1999[a]; NIMH, 2001[b]; Pincus and Pettit, 2001; Rush, 2001). Even after a depressive episode ends, many patients continue to have "residual symptoms" which can contribute to a reduction in daily functioning (Rush, 2001). Marital dissatisfaction is associated with depression and children of depressed parents are three times more likely to experience depression themselves than children of non-depressed parents (Pincus and Pettit, 2001; Birmaher et al., 1996; Whisman, 1999). Employers incur the burden of depression in the work place, where 80% have reported depression being largely problematic for work productivity (Pincus and Pettit, 2001; Conti and Burton, 1994). Employees with depression are more likely to require disability days than employees with chronic back pain, heart disease, other mental disorders, hypertension, or diabetes (Pincus and Pettit, 2001; Conti and Burton, 1994). Medical costs for patients with MDD are approximately 50% higher than the costs of a

chronic illness alone (Kanton, 2003). The estimated cost of depression in the U.S. ranges from $43.7 to $52.9 billion per year, including costs due to health care, work- time loss, and suicide (Pincus and Pettit, 2001; Greenberg et al., 2003). An individual with depression is likely to spend twice as much on health care costs compared to an individual without depression, such that the direct burden of depression on the health care system is estimated to cost $12.7 billion per year (Pincus and Pettit, 2001; Simon, 2003; Kanton, 2003). Individuals with major depression have been reported to perceive their social functioning and health as more impaired than patients with other medical conditions (Wells et al., 1989). Depression often co-occurs with other serious illnesses, such as heart disease, stroke, diabetes, cancer, multiple sclerosis, and Parkinson's disease (NIMH, 2000[b]). When depression occurs along with these other medical conditions, a considerable decline in self-care management and a delay in recovery from and/or worsening of these other medical conditions has been shown (Kanton, 2003; NIMH, 2000[b]).

The pathophysiology of depression is unclear. Evidence from neuroscience, genetics, and clinical investigations demonstrates that depression is a disorder of the brain (NIMH, 1999[c]; NIMH, 2001[b]). In depression, neural circuits responsible for the regulation of moods, thinking, sleep, appetite, and behavior fail to function properly due to an imbalance of neurotransmitters. Common symptoms of major depressive disorder or unipolar depression include a persistent sad mood, loss of interest or pleasure in activities that were once enjoyed, changes in appetite or weight, difficulty sleeping or oversleeping, physical slowing or agitation, energy loss, feelings of worthlessness or

inappropriate guilt, difficulty thinking or concentrating, and recurrent thoughts of death or suicide. A diagnosis of major depressive disorder is made if a person has five or more of these symptoms and experiences impairment in usual functioning nearly every day during the same 2-week period (SAMSHA, 2005; APA-DSM-IV, 1994). Unipolar depression typically presents in discrete episodes that recur during a person's lifetime. Dysthymic disorder (or dysthymia), a less severe yet typically more chronic form of depression, is diagnosed when depressed mood persists for at least 2 years in adults and is accompanied by at least two other depressive symptoms. Many people with dysthymic disorder also experience major depressive episodes. Unipolar major depression and dysthymia are the primary forms of clinical depression (NIMH, 1999[c]; NIMH, 2001[b]). Left untreated, clinical depression can lead to severe consequences, such as suicide.

Improving the health of those with mental health disorders is an objective of the Healthy People 2010 (DHHS, 2005). Improved recognition, treatment, and prevention of depression are critical public health priorities set by the National Institute of Mental Health:

> "There is considerable variation among people with depression in terms of symptoms, course of illness, and response to treatment, signifying that depression may have several complex and interacting causes. This variability poses a major challenge to researchers attempting to understand and treat the disorder. One such challenge involves treating those with refractory or hard to treat depression. Approximately 80 percent of people with depression respond positively to treatment, such as anti-depressant therapy; however a significant number of individuals remain treatment refractory. Even among treatment responders, many do not have complete or lasting improvement, and adverse side effects are common. Thus, an important goal in depression research is to determine

> more effective treatments—especially treatments for refractory depression—that also have fewer side effects than currently available treatment." (1999)

Role of nutrition in the brain

Modification of dietary intake may be one possible treatment for depression that has minimal side effects. Dietary nutrients play a vital role in the normal functioning of the brain. Both macronutrients and micronutrients are needed in sufficient quantity in the diet to serve as precursor compounds used in the synthesis of neurotransmitters (Maher, 2000). Several key nutrients, such as essential fatty acids, dietary amino acids, carbohydrates, folate, Vitamin B12, antioxidants, selenium, iron, copper, and zinc function in a variety of ways to maintain normal brain functioning (Bodnar and Wisner, 2005; Maher, 2000). These nutrients support normal brain functioning in a variety of ways including enzymatic activities, cellular and oxidative processes, receptor function, signal transduction, maintenance of neuronal tissue, and synthesis and function of neurotransmitters and catecholamines (Bodnar and Wisner, 2005). Figure 1 summarizes some of the major diet-depression pathways. Many nutrients are essential for brain function, but evidence varies as to how well some of these modify the pathophysiology of depression (Bodnar and Wisner, 2005). The relationship between diet and depression is not unidirectional. Dietary intake may affect the onset, treatment, and overall management of depression. Alternatively, those suffering from depression may alter their diet as a consequence of depressive symptoms. Several possible physiological links between nutrient status and depression have been identified, but there is less known about the dietary intake of those with depression. The nutrients presented in Figure 1, omega-3

fatty acids, folate, vitamins B12 and B6, antioxidants vitamin C and E, minerals iron, zinc, selenium, and the macronutrients carbohydrates and amino acids, are considered important in regards to public health needs. Nutrient intake and subsequent nutrient biochemical status may partially determine treatment effectiveness for those with depression. Medication alone may not be as effective in the presence of a "poorly nourished" brain (Bodnar and Wisner, 2005). The current understanding of diet and nutrient status related to depression may occur via three possible routes.

1) The first mechanism suggests modification of the diet with a single or multiple vitamins/minerals to correct an existing nutrient deficiency that contributes to depression. For example, a biochemical deficiency of vitamin B12 may cause loss of memory, mental dysfunction, and depression. A folate deficiency state can lead to fatigue, confusion, and irritability, which also are common symptoms of depression. The relationship between marginal deficiency status and depression is not as well understood.
2) Pharmacological doses of nutrients may improve mood status when metabolic nutrient needs are higher, such as with individuals who have alterations in nutrient absorption, transport, and storage. For example, a mutation in MTHFR has been reported to be associated with depression. A mutation in MTHFR would also increase the dietary folate needs of these individuals. The enzymatic and biochemical profile of those with depression is not well established in the literature. It is possible that certain dietary improvements or supplementation could be used safely and effectively to improve mood in at-risk populations.

3) Nutritional status within the brain itself may function synergistically with anti-depressant medications to improve treatment. Positive drug nutrient interaction(s) are important considerations for treatment; however optimal amounts of nutrients required for treatment are not well established. For example, there is literature that demonstrates folate and omega-3 fatty acids each have been used successfully as adjunctive therapy for treating depression.

The brain is dependent on dietary sources for essential fatty acids (Zhang et al., 2005). An inadequate intake of omega-3 fatty acids could lead to alterations in cell membrane microviscosity (Maidment, 2000; Freeman, 2000; Stoll et al., 1999; Maes et al., 1996; Edwards et al., 1998; Hibbeln, 1998). In turn, this change in neuronal cell membranes could contribute to alterations in neurotransmitter systems, which may lead to the development of many psychiatric disorders It also has been suggested that a high ratio of dietary omega-6: omega-3 fatty acids could contribute to an increased incidence of depression (Freeman, 2000; Stoll et al., 1999). The relationship between essential fatty acids and brain function is discussed more extensively below in context to Specific Aim 2.

The composition of amino acids provided by the diet contributes to normal brain function, since essential proteins are key constituents of neurotransmitters (Fernstrom, 2005; Maher, 2000). A single meal that includes various amino acids can directly affect brain uptake of amino acids, influence the synthesis of neurotransmitters, and in turn can affect the release of these newly synthesized neurotransmitters which contribute to brain function. The amino acid tryptophan is a precursor for the neurotransmitter, serotonin

(Fernstrom, 2005; Maher, 2000). Large neutral amino acids, such as the branched-chain amino acids, compete with tryptophan for transport across the blood brain barrier (Maher, 2000; Fernstrom, 2005). Therefore, a higher concentration of branched chain amino acid concentration in the plasma, as influenced by dietary protein intake, causes a decrease in tryptophan available to the brain. A decreased concentration of tryptophan in the brain results in a decline in serotonin synthesis and release, which can affect mood (Maher, 2000; Fernstrom, 2005). A balance between dietary protein and carbohydrate intake influences the synthesis of serotonin because dietary carbohydrate plays a key role in the conversion of tryptophan to serotonin (Wurtman and Wurtman, 1983; Maher, 2000). Dietary carbohydrate stimulates the release of insulin, which enhances the uptake of branched-chain amino acids into muscle. Therefore, a reduction of branched-chain amino acids in the plasma reduces the competition with tryptophan for crossing the blood brain barrier, leaving more tryptophan available for entering the brain and conversion to serotonin (Maher, 2000). The increased tryptophan and serotonin concentration in the brain have been shown to reduce depression (Maher, 2000).

Dietary micronutrients have distinct roles in supporting brain function. Folate deficiency has been shown to be associated with decreased serotonin synthesis (Young, 2002). Iron is needed for normal oxygenation and synthesis of neurotransmitters within the brain, while manganese, copper and zinc serve in enzymatic reactions to protect the brain from free radicals (Bourre, 2004). Thiamin is needed for glucose utilization within the brain, vitamin B6 and B12 also are directly needed for synthesis of neurotransmitters, vitamin C is highly concentrated in nerve endings within the brain, and alpha-tocopherol

(one form of dietary Vitamin E) is involved in maintaining nervous membrane tissue (Bourre, 2004). Vitamin C and vitamin E function as antioxidants to protect the brain from lipid peroxidation that occurs as a result of the high polyunsaturated fatty acid content within neuronal membranes (Bodnar and Wisner, 2005). Selenium in the brain is selectively maintained under conditions of a selenium deficiency and selenium is thought to play a role in mood regulation (Bodnar and Wisner, 2005; Rayman et al., 2006).

The composition and adequacy of one's diet may contribute to the etiology of abnormal brain functioning that results in depression or depressive symptoms. In turn, the presence of depression or depressive symptoms may affect behaviors such as dietary intake. Medical nutrition therapy may prove to have a positive role in the management of depressive disorder. Specific dietary modifications may be useful as adjunctive therapy or monotherapy for depression. Dietary modifications are likely to have fewer side effects than pharmacological therapy. Thus, long-term adherence to dietary modifications may be attainable. Dietary modifications specifically aimed at treating depression and depressive symptoms are likely to have the dual purpose of providing therapy for co-existing medical conditions associated with depression. Additionally, medical nutrition therapy is an appealing option in the management of depression because dietary intake is modifiable and generally there is substantial room for improving the nutritional status of most adults (Bodnar and Wisner, 2005).

Specific Aim 1: *Role of diet in depression*

Understanding the relationship between dietary intake and mood has important public health and clinical implications. There is increasing evidence of significant relationships between single- nutrient status and mood. Yet, there exists limited knowledge regarding overall dietary intake among adults with depression and depressive symptoms.

Evidence for the relationship between diet and depression can be seen from reports of single nutrient and specific food differences between subjects with and without depression. For example, a highly significant correlation was found between sugar consumption and the annual rate of depression for six countries in a multinational comparison (Westover and Marangell, 2002). Additionally, several studies have reported nutritional deficiencies in folate, vitamin B_{12}, vitamin B_6, vitamin C, selenium, and zinc in subjects with depression, yet few of these studies have assessed dietary intake (Hvas et al., 2004; Hintikka et al., 2003; Carney, 1990; Coppen and Bailey, 2000; Morris et al., 2003; Nowak et al., 2003; Rayman et al., 2006; Coppen and Bolander-Gouaille,2005). It has been suggested that a nutrient deficiency with depression might arise primarily out of a reduced food intake (Christensen and Somers, 1994). Yet, in this small study by Christensen and Somers (1994), subjects with depression consumed an overall diet meeting or exceeding the 1989 Recommended Dietary Allowances. To date, no other studies have reported the full dietary profile of adults with depression or depressive symptoms. Christensen and Somers (1994) did not evaluate serum levels of nutrients or

the possible misreporting of dietary intake among their subjects with depression. Serum levels of nutrients would have confirmed that the reported dietary intake among their subjects with depression was valid and thus sufficient to have met the dietary recommendations at that time.

However, in light of the Christensen and Somers (1994) study, it remains prudent that modifying dietary intake or supplementing with single or multiple vitamins/minerals may correct an existing inadequate nutritional state that contributes to poor mental health (Bodnar and Wisner, 2005). Individuals with recurrent or chronic depression whose symptoms include change in appetite or weight change may be more vulnerable to nutrient deficiencies, and thus their ability to meet dietary recommendations may be diminished.

Pharmacological doses of select nutrients may be used safely and effectively to improve mood or even prevent mood disorders in at-risk populations (Bodnar and Wisner, 2005). For example, compared with healthy adults, those with depression were found to have a point mutation in a gene coding for a key enzyme in folate metabolism (Coppen and Bolander-Gouaille, 2005; Bodnar and Wisner, 2005). This mutation increases the folic acid needs compared to the general population (Coppen and Bolander-Gouaille, 2005; Bodnar and Wisner, 2005). Furthermore, improving the overall nutritional state within the brain itself may enhance the effectiveness of many antidepressant medications (Bodnar and Wisner, 2005). Poor nutrition status, even marginal deficiency states, can critically alter substrate availability for the brain. Individuals with impaired nutritional status may experience more difficulty in responding

effectively to medication therapy. Therefore, using diet modification in combination with pharmacological therapy may prove to offer dramatic improvements in treating depression.

Macronutrient intake may also have an impact on mood status. For example, a subpopulation of depressed individuals, often including those with obesity, is known to experience carbohydrate cravings (Docherty et al., 2005; Maher, 2000). Is it unclear whether an overload of dietary carbohydrate exacerbates mood instability or if consuming a high carbohydrate diet elicits a type of psychopharmacological effect to improve mood (Benton and Nabb, 2003). A high carbohydrate meal may help promote tryptophan entry across the blood brain barrier, in turn increasing serotonin synthesis (Benton and Nabb, 2003). However, there does not seem to be evidence that in humans an increased level of serum tryptophan from a high carbohydrate diet necessarily equates with higher serotonin release (Benton and Nabb, 2003; Young, 2002). A minimal amount of protein consumed in the diet is sufficient to temper the carbohydrate effect on increasing the ratio of plasma tryptophan to branched chain amino acids. Thus, it is questionable if modulation of serotonin can be elicited from a high carbohydrate diet (Benton and Nabb, 2003; Young 2002). Interestingly, compared to a questionable effect of a high carbohydrate diet on mood, a low carbohydrate diet may have a stronger influence on mood due to a reduction in serotonin levels (Sarlio-Lahteenkorva et al., 2004; Van der Does, 2001). The overall balance and distribution of macronutrients may affect mood via other mechanisms beyond serotonin, such as regulation of blood glucose

levels, provision of sufficient micronutrients, and/or management of weight and body fat status.

Specific Aim 2: *Omega-3 fatty acids in depression*

Highly unsaturated fatty acids serve an important role in brain cell membranes. The lipid content within the nervous system is the highest of all tissues, excluding adipose tissue (Haag, 2003; Pouwer et al., 2004). The dry weight of an adult brain is 50-60% lipid with 35% of that lipid content accounted for by polyunsaturated fatty acids (PUFAs), particularly docosahexanenoic (DHA) and arachidonic acid (AA) (Yehuda et al., 1999; Maidment, 2000; Pouwer et al., 2004). These essential fatty acids amount to 45% of the fatty acids within the synaptic membranes (Bruinsma and Taren, 2000). Two classes of essential PUFAs that are involved in neurotransmission are omega-3 and omega-6 fatty acids. These fatty acids are not interconvertible and compete for similar metabolic enzyme systems. Dietary fatty acid intake has been shown to be associated with cell membrane fatty acid composition (Haag, 2003). Evidence suggests that a balance between omega-3 and omega-6 fatty acids in brain cell membranes is important in mental health (Haag, 2003; Bruinsma and Taren, 2000; Maidment, 2000). Dietary fatty acids may play a role in neuronal membrane signaling pathways (Haag, 2003), such that an imbalance or disruption of cell membrane omega-3 and omega-6 fatty acids can alter membrane fluidity. Interference of membrane fluidity may be of etiological significance if subsequent serotonin receptor number and/or function are affected, as occurs with depression (Maes and Smith, 1998; Maes et al., 1996; Peet et al., 1998).

In the class of omega-3 fatty acids, alpha-linolenic acid (ALA, 18:3n3) is the shortest chain and initial fatty acid structure. Through a series of enzymatic desaturations and elongations, alpha-linolenic acid is converted to eicosapentaenoic acid (EPA, 20:5n3) and docosahexaenoic acid (DHA, 22:6n3). Conversion of alpha-linolenic acid to EPA and DHA is limited to approximately 5% of the total alpha-linolenic acid available (Bruinsma and Taren, 2000; Nielsen, 2000). Therefore, dietary sources are important for providing sufficient EPA, which in turn can be converted into needed DHA. DHA is the primary omega-3 fatty acid that accumulates in membrane phospholipids (Bruinsma and Taren, 2000) and DHA is particularly important during prenatal brain development (Haag, 2003). EPA is also critical for neuronal function. EPA functions within the adrenal cortex as the precursor for eicosanoid formation (Bruinsma and Taren, 2000). The omega-3 fatty acids serve in a variety of functions such as, regulating membrane fluidity, assisting in enzymatic reactions, binding molecules with receptor sites, assisting in biochemical interactions, and allowing movement of nutrients across the membrane (Bruinsma and Taren, 2000; Yehuda et al., 1999). Additionally, omega-3 fatty acids function as anti-inflammatory and immunosuppressive agents, particularly when an overactive immune response occurs (Haag, 2003, Yehuda et al., 1999). An overactive immune or inflammatory response has been associated with major depression and mood disorders (Smith 1991; Maes and Smith, 1998; Mischoulon and Fava, 2000). Both dietary EPA and DHA are found in highest concentration in oily fish and wild game, followed by shellfish, flaxseed, walnuts, and canola oil (USDA, 1994-1996; Kris-Etherton et al., 2006; Kraus et al., 2000).

In the class of omega-6 fatty acids, linoleic acid (LA, 18:2n6) is the shortest and initial fatty acid structure. Through a series of enzymatic elongations and desaturations, linoleic acid is converted to biologically needed arachidonic acid (AA, 20:4n6). Ultimately these fatty acids are converted to prostaglandins, thromboxanes, and leukotrienes that regulate inflammation and blood pressure. Under conditions of high cell membrane omega-6 content, the formation of pro-inflammatory conditions may occur (Haag, 2003). Thus, the presence of sufficient membrane omega-3 fatty acid may limit such an increase in inflammatory response. Primary food sources of omega-6 fatty acids are vegetable oils, poultry, eggs, and margarine (USDA, 1994-1996).

In Europe and the United States, intake of linoleic acid (omega-6) has increased substantially during the past 2 decades (Sanders, 2000; Tanskanen et al., 2001; Simopoulos, 1998; Pouwer et al., 2004). Vegetable oils, such as safflower, soybean, and corn oil are widely used and these contain higher ratios of linoleic acid (omega-6) to alpha-linolenic acid (omega-3). The ratio of omega-6 to omega-3 fatty acids in the diet has increased from 2:1 to 15:1 (Simopoulos, 1998; Pouwer et al., 2004). Oils that are naturally higher in alpha-linolenic acid are often partially hydrogenated and this hydrogenation process decreases their alpha-linolenic acid content. Furthermore, the contribution of alpha-linolenic acid from ruminant animals has declined due to feeding practices that encourage a more cereal based feed in place of grass. Thus, there is concern that the dietary shift in higher omega-6 intake and lower omega-3 intake may be associated with the prevalence of major depression.

The human brain contains high concentrations of polyunsaturated fatty acids that have a vital role in neuronal function (Freeman, 2000; Maidment, 2000). Neuronal cell membranes are largely composed of phospholipids containing PUFAs and cholesterol. The phospholipid structure of neuronal membranes is critical for maintaining normal brain function (Maidment, 2000). It is suspected that the concentration and ratio of essential fatty acids in the brain and neuronal phospholipid membranes may have a role in the etiology of major depressive disorder (Maes and Smith, 1998; Haag, 2003; Maidment, 2000; Yehuda et al., 1999; Tanskanen et al., 2001). Docosohexaenoic acid (DHA, omega-3) is selectively concentrated in neural tissue and is necessary for nervous system function (Hibbeln, 1998). It is possible that low DHA intake or serum levels may play a role in the development of major depression. Among healthy volunteers, low plasma concentrations of DHA predicted a low concentration of cerebrospinal fluid 5-hydroxyindolacetic acid (CSF-5HIAA) (Hibbeln, 1998). CSF-5HIAA is a marker of brain serotonin turnover, and low serotonin levels in brain neurotransmitter synapses are associated with the occurrence of major depression. Lower omega-3 concentrations alone and/or lower omega-3 levels relative to omega-6 levels in the neuronal membranes may result in alternations in membrane function that occurs with major depression.

The pathophysiology of depression is unclear. Evidence from neuroscience, genetics, and clinical investigations demonstrate that depression is a disorder of the brain where a deficit in adrenergic and serotonergic neruotransmission occurs (Mamalakis et al., 2000; Pouwer et al., 2004). Additionally, immune-inflammatory markers are increased in depressive disorder (Mamalakis et al., 2000; Maes and Smith, 1998; Pouwer

et al., 2004). Major depression is accompanied by an increased secretion of eicosanoids, such as prostaglandins, and by excessive secretions of proinflammatory cytokines (Maes and Smith, 1998; Pouwer et al., 2004). This inflammatory response has also been correlated with a decrease in HDL levels among people with depressive disorder (Maes and Smith, 1998). Also, low HDL levels were shown to be significantly related to the prevalence of suicide attempts by women (Zhang et al., 2005). Polyunsaturated fatty acids are key factors in regulating inflammatory processes since they serve as precursors for eicosanoids and affect eicosanoid and cytokine formation (Maes and Smith, 1998). Possibly, omega-3 fatty acids could suppress some of the pathophysiological characteristics of depressive disorder by reducing inflammation and immune activity (Mamalakis et al., 2000; Maes and Smith, 1998; Freeman, 2000).

Many studies have examined the relationship between omega-3 fatty acids and mood and produced conflicting results (Table 1). For example, increased levels of plasma and red blood cell membrane total omega-3 fatty acid and EPA and DHA fractions have been reported among subjects with depression (Maidement, 2000; Ellis and Sanders, 1977; Fehily et al., 1981). In 1977, Ellis and Sanders found that the proportion of alpha-linolenic metabolites (EPA and DHA) was greater in six depressive patients verses healthy matched controls. Another small study by Fehily et al. (1981) reported that a group with depression had significantly higher plasma and erythrocyte concentrations of EPA and DHA compared to a healthy matched control group. Also, erythrocyte concentration of linoleic acid (omega-6) was significantly lower in the depressive group compared to controls. Furthermore, DHA concentration was positively

correlated with the severity of depression, as measured by the Beck Depression Inventory.

Conversely, altered fatty acid compositions in erythrocyte cell membranes, serum phospholipids, cholesteryl esters, and adipose tissue have been found among depressed subjects (Edwards et al., 1998; Adams et al., 1996; Maes et al., 1999; Maes et al., 1996; Mamalakis et al., 2002; Peet et al., 1998; Tiemeier et al., 2003; Mamalakis et al., 2004; Frasure-Smith et al., 2004; Assies et al., 2004) (Table 1, pg. 80). Lower erythrocyte EPA levels and higher erythrocyte and plasma AA: EPA ratios have been shown to occur as severity of depression worsens (Adams et al., 1996). Maes et al. (1996) found a significantly higher AA: EPA ratio in serum cholesteryl esters and phospholipids among major depressed patients compared to minor depressed patients and healthy controls. Additional findings included a significantly increased total omega -6:omega-3 ratio, decreased total omega -3, and lower alpha-linolenic acid and EPA fractions in serum cholesteryl esters among subjects with major depression compared to subjects with minor depression and healthy controls. In a follow-up study, Maes et al. (1999) reported a significant difference in serum phospholipid fatty acid profile in subjects with major depression compared to healthy subjects. This study demonstrated significantly lower AA fractions and higher AA: EPA and AA: DHA ratios among the depressed subjects compared to controls. Major depressed subjects had significantly lower total omega -3, alpha-linolenic acid, EPA, and DHA phospholipid levels than healthy controls. Major depressed subjects also had significantly lower cholesteryl ester levels of alpha-linolenic acid and EPA, and significantly higher total omega -6: omega -3 and AA: EPA ratios.

Phospholipid and cholesteryl ester levels of alpha-linolenic acid and EPA were significant predictors to identify subjects with major depression verses healthy controls. Peet et al. (1998) found a significantly lower red blood cell membrane level of DHA in a group of patients with major unipolar depression compared to healthy age and gender matched controls.

Mamalakis et al. (2002) examined the relationship between depression and adipose tissue omega-3 compounds. Adipose tissue fatty acid measurements were used to represent longer-term dietary fat intake or habitual intake over several months. Measurements of fatty acids in plasma phospholipids, cholesteryl esters, or erythrocyte membranes are generally more reflective markers of fatty acid intake over a recent few weeks. Subjects diagnosed with mild depression were found to have a significantly lower adipose DHA level compared to non-depressed subjects. A weak, but significant inverse relationship between depression and adipose tissue DHA was found in a simple correlation and supported by stepwise multiple regression analysis. The authors speculated that the higher adipose DHA among non-depressed subjects might have an inhibiting effect on the production of certain cytokines. Inhibiting these cytokines involved in the etiology of depressive disorder possibly offers a protective benefit against depression. Also, these findings are important in that only 18% of the subjects were determined to have mild depression and no subjects met the criteria for a diagnosis of moderate or more severe depression. Further assessment of the relationship between adipose or long- term dietary intake and more severe depression may help clarify studies yielding contradictory results. In a follow up study, depression was significantly

associated with a higher total omega-6: omega-3 ratio in adipose tissue, but high alpha-linolenic acid level was significantly associated with less depression (Mamalakis et al., 2004).

Several studies have demonstrated a link between low omega -3 tissue levels and depression. There have been other studies, however, which have not produced associations between omega -3 sites and depression. It is possible that the plasma phospholipid, cholesteryl esters, erythrocyte, and adipose content of omega -3 fatty acid may not truly reflect the brain or synaptic omega -3 fatty acid content (Llorente et al., 2003; Moore et al., 1991). What continues to remain unclear is: 1) whether low omega -3 fatty acid levels are a precursor to the onset of depression, 2) whether depression causes a depletion of omega -3 fatty acid levels, and 3) how dietary intake of omega -3 or omega -6 fatty acids directly impacts the development and/or treatment of depression.

Dietary intake of omega-3 fatty acids was not addressed in many of the above studies. However, the relationship between dietary omega-3 fatty acids and/or fish consumption and depression appears to be elusive. Hibbeln (1998) first identified a significant inverse association between high dietary fish consumption and lower annual prevalence of depression in a multinational study. In a large Finnish cohort study, the likelihood of having mild to severe depression was 31% higher among those who infrequently consumed fish compared to those that consumed fish once a week or more (Tanskanen et al., 2001). Additionally, among women, symptoms of depression were significantly related to fish consumption 2 or less times per month. Timonen et al. (2004) also reported, among women, an increased risk of depression associated with infrequent

or rare fish consumption. Among men, there was no association between fish consumption and risk of depression. Among young adults who self-reported attempting suicide, a significantly lower percentage of calories from polyunsaturated fatty acids (including omega-3 fatty acids) was found compared to non-attempters (Zhang et al., 2005). However, Jacka et al. (2004) found no significant differences in self-reported dietary intake of fish oil or seafood between women with and without depression. Hakkarainen et al. (2004) also reported no significant association between dietary intake of omega-3 fatty acids or fish consumption with depression or suicide among males in a large cohort study. In a matched case control study, Edwards et al. (1998) found no significant differences between the depressive and non-depressive groups for dietary intake of omega-3 fatty acids as measured by a 7-day weighted food record. Interestingly, the dietary alpha-linolenic acid intake and the red blood cell membrane omega-3 level were significantly correlated in the depressed group. Contributing to the conflicting results is the inherent problem that these dietary studies often used different measurements of depression and different assessment tools for dietary intake. Furthermore, dietary intake of omega-3 fatty acids varies considerably by region. For example, in the Finnish population, reported intake of omega-3 fatty acids by older males was 2.2g/day or 0.47 g/day from fish (Hakkarainen et al., 2004). However, US consumption data shows lower intakes of omega-3 fatty acids (USDA, 1994-1996). Previous USDA data reported males 20 years and older consumed 1.62 gm/day omega-3 fatty acids, 16.29 gm/day omega-6 fatty acids, with a ratio of 10:1 omega-6:omega-3 (USDA, 1994-1996). For US women the omega-3 fatty acid intake was 1.17-gm/day and

omega-6 fatty acid intake was 11.3/gm/day, with a ratio of 9.7:1 omega-6:omega-3 (USDA, 1994-1996). Omega-3 fatty acids accounted for only 0.6% of total kilocalories consumed by US adult men and women, while 5.9% and 5.7% of total kilocalories consumed came from omega-6 fatty acids for men and women, respectively (USDA, 1994-1996). Therefore, formulating conclusions about the relationships between dietary omega-3 fatty acids or fish consumption and depression or depressive symptoms is more difficult due to the lack of consistency among the dietary studies presented.

Randomized, placebo-controlled trials provide further conflicting evidence of the relationship between omega-3 fatty acids and depression. Stoll et al. (1999) found that after 120 days (4 months) of supplemental 5-10 gm/d omega-3 fatty acid, mood stabilizing significantly improved and there was an increased duration of time before relapse in 30 bipolar patients compared to non-treated bipolar patients. Llorente et al. (2003) investigated whether 1) DHA supplementation of ~200 mg/d for 4 months in postpartum women would either increase or prevent the usual decline in plasma phospholipid DHA, and 2) DHA supplementation is associated with fewer depressive symptoms. DHA supplementation did significantly increase the plasma phospholipid content by 8% while the placebo group's plasma phospholipid DHA level decreased by 31% ($p<0.05$). The DHA content of the supplemented group was 50% higher than the placebo group 4 months after delivery ($p<0.001$). Unfortunately, no statistically significant correlations were found between the plasma phospholipid DHA content and measures of depression at baseline or after 4 months of supplementation. However, the majority of women (n=89) in this study were classified as only having minimal

depression and only 2 women in the placebo group and 4 women in the supplement group had a depression score suggesting moderate depression. The authors state the difference between the two groups was small; therefore the final conclusions might have low statistical power. Furthermore, dietary intake was not assessed at baseline or during post-baseline visits to offer additional information about the omega-3 status of these women. In another study examining 2 gm supplemental EPA as adjunctive therapy, a significant improvement in depression was detected after 2, 3, and 4 weeks (Nemets et al., 2002). Peet and Horrobin (2002) also demonstrated effectiveness in improving depression after 12 weeks with 1gm/day EPA as adjunctive therapy. However, 2gm and 4gm/day supplemental EPA was not found to be significantly more effective than placebo. After 4 weeks, the use of a combination EPA plus DHA supplement (9.6gm/day) as an adjunct to antidepressant medications elicited significantly lower depression scores in patients compared to a placebo group (Su et al., 2003). Su et al. (2003) also found a significant increase in red blood cell DHA after the addition of omega-3 supplementation among subjects with depression, whereas no differences in red blood cell DHA were found between pre- and post-treatment in the placebo group. In spite of these results, Marangell et al. (2003) found that 2gm/day DHA monotherapy was not more effective than a placebo in improving depression in men and women with major depressive disorder. Furthermore, no evidence of an association was found between baseline mood and dietary fish or omega-3 fatty acid intake among a group of adults with depression, nor was there evidence at any time during 12 weeks that 3-g/day omega-3 fish oil supplementation improved mood in these subjects (Silvers et al., 2005). The use of high

supplemental dosages of omega-3 fatty acids as a treatment for depression remains equivocal.

Additionally, dietary intake of omega-3 fatty acids is rarely reported in these supplement studies and there is limited baseline data on dietary omega-3 or omega-6 intake among individuals diagnosed with major depressive disorder. Clarification is needed to determine if the dietary omega-3 and omega-6 fatty acid intake among individuals with major depression is adequate. If it were to be assumed that omega-3 fatty acids are helpful in the management of depression or depressive symptoms, it is unclear if supplementation of omega-3 fatty acids is helpful only when the dietary intake is insufficient or if simply improving the dietary intake itself would be therapeutic. Furthermore, should the omega-3 fatty acid intake among depressed individuals be adequate, it would be important to explore increasing dietary sources, as well as supplementation dosages, to determine the effectiveness of recommending omega-3 fatty acids as a treatment option for depression.

Also, omega-3 fatty acid intervention trials have not measured effectiveness of treatment beyond 4 months. At this time it is not clear if patients would adhere to the use of omega-3 fatty acids as a treatment option or if long-term effects would be observed. Finally, the current dietary reference intakes for alpha-linolenic acid for U.S. adults are 1.1gm/day for women and 1.6 gm/day for men. However, neither dietary recommendations for EPA and DHA nor dosages of supplemental omega-3 fatty acids have been well established at this time. There is a need to continue to explore the relationship between dietary intake of omega-3 fatty acids and depression.

Specific Aim 3: *Dietary reporting and mood*

Medical nutrition therapy may provide a pivotal role in the management and/or prevention of major depression. In order for medical nutrition therapy to be effective for individuals with depression, accurate assessment of energy and nutrient intake is essential. Misreporting of dietary intake is problematic when trying to assess the dietary habits within a population group, even among a relatively healthy population group. For instance, Ard et al. (2006) found that both healthy men and women overreported their total energy intakes, by 7.6% and 10.3% respectively. Since a change in appetite and/or weight status is commonly associated with altered mood, there is a concern that an accurate reporting of dietary intake may be more difficult to obtain from individuals experiencing depression or depressive symptoms. Poor concentration and motivation are common symptoms of depression, making the task of dietary recall possibly more challenging in subjects with depressive symptoms or altered mood. If eating patterns are inconsistent due to altered mood, the ability to accurately recall food intake may also lead to measurement error. Taren et al. (1999) found that distress, as a measure of depression, was not associated with underreporting in women. However, Price et al. (1997) found that underreporting was more common in women who experienced emotional trouble in the previous year.

Other psychological factors that influence eating behaviors may render dietary recall methods unreliable as well (Ard et al., 2006). For example, some individuals conscientiously restrict their energy intake for the purpose of weight management; this is

considered dietary restraint (Ard et al., 2006). Dietary disinhibition is when the tendency to overeat occurs after dietary restraint and when particularly appealing foods are present (Ard et al., 2006). It could be speculated that this tendency to overeat would likely be underreported, particularly in a 24-hour recall, if the individuals' felt their overeating was atypical or if they felt uncomfortable disclosing what foods or quantity of foods were actually consumed. It could be further speculated that individuals with depression or depressive symptoms may be more likely to experience dietary restraint and/or disinhibition as a consequence of their altered mood. Thus, the accurate reporting of dietary intake may be more difficult to obtain in these individuals. Recently, Ard et al. (2006) discovered that the use of a single 24-hour recall from the USDA Automated Multiple Pass method sufficiently estimated energy intake, and that neither dietary restraint nor disinhibiton were significantly related to the accuracy of reported intake among healthy volunteers. Contrary to Ard et al. (2006) findings, other studies have shown that men with dietary restraint are more likely to underreport energy intake (Tooze et al., 2004; Asbeck et al., 2002). In one study, in which doubly labeled water was used to measure energy expenditure as a comparison to reported energy intake, men with high dietary restraint were 3.5 times more likely to underreport energy intake compared to men with low dietary restraint (Tooze et al., 2004; Ard et al., 2006). Women who were identified as restrained eaters were more likely to underreport their energy intake (Asbeck et al., 2002), particularly when a 24-hour recall method was used (Bathalon et al., 2000; Ard et al., 2006).

The impact which dietary misreporting may have on the relationship between mood and diet is another concern. Self-reported poor mental health was shown to be associated with poor dietary habits (Sarlio-Lahteenkorva et al., 2004). For example, depressed adults were found to be more likely to skip breakfast and eat fish less often and depressed women were shown to consume less fruits and vegetables than non-depressed women (Sarlio-Lahteenkorva et al., 2004; Tanskanen et al., 2001; Allgöwer et al., 2001). Poor mental health was associated with being less likely to eat lower fat dairy foods, fresh vegetables, fruits on a daily basis, or high fiber cereal (Sarlio-Lahteenkorva et al., 2004; Cohen et al., 2002). Underreporters were found to report diets higher in protein, lower in fat, and more micronutrient rich than those who presented plausible dietary reports (Price et al., 1997). It could be speculated that misreporting could occur to compensate for what would appear to be undesirable eating habits among those with depression, and particularly in those with accompanying obesity.

If diet has an etiological role in the development of depression or depressive symptoms, it is imperative that this relationship be examined based on accurate dietary intake measurements. For example, obesity is associated with depression (Needham et al., 2005) and obese individuals are more prone to underreporting dietary intake (Macdiarmid and Blundell, 1993; Black and Cole, 2001; Price et al., 1997; Goldberg et al., 1991). Individuals who became overweight more recently and those with longer duration of being overweight were more likely to underreport energy intake (Price et al., 1997). Part of the link between obesity and depression has to do with distress from dieting (Needham et al., 2005). Purposeful dieting for weight reduction due to obesity

could generate dietary data that is misrepresentative of habitual intake. Thus, bias in underreporting of dietary intake among obese individuals would not be random and could lead to considerable difficulty in evaluating the true relationship between diet and altered mood. Additional bias could occur as a result of unintentional misreporting among subjects with depression or depressive symptoms simply due to forgetfulness or lack of concentration secondary to their altered mood. Those with altered mood may be able to produce plausible dietary intake records, even if intentional misreporting of dietary intake occurred. As a result, individuals with altered mood may be more likely to be either unwilling to disclose foods they ate that have negative health image or overreport foods which have a positive health image (Macdiarmid and Blundell, 1998). Therefore, the presence of certain behaviors or symptoms associated with depression could result in reduced energy intake and contribute to difficulty in deciphering purposeful misreporting from legitimate reduced intake.

Figure 1. Diagram of Diet and Depression

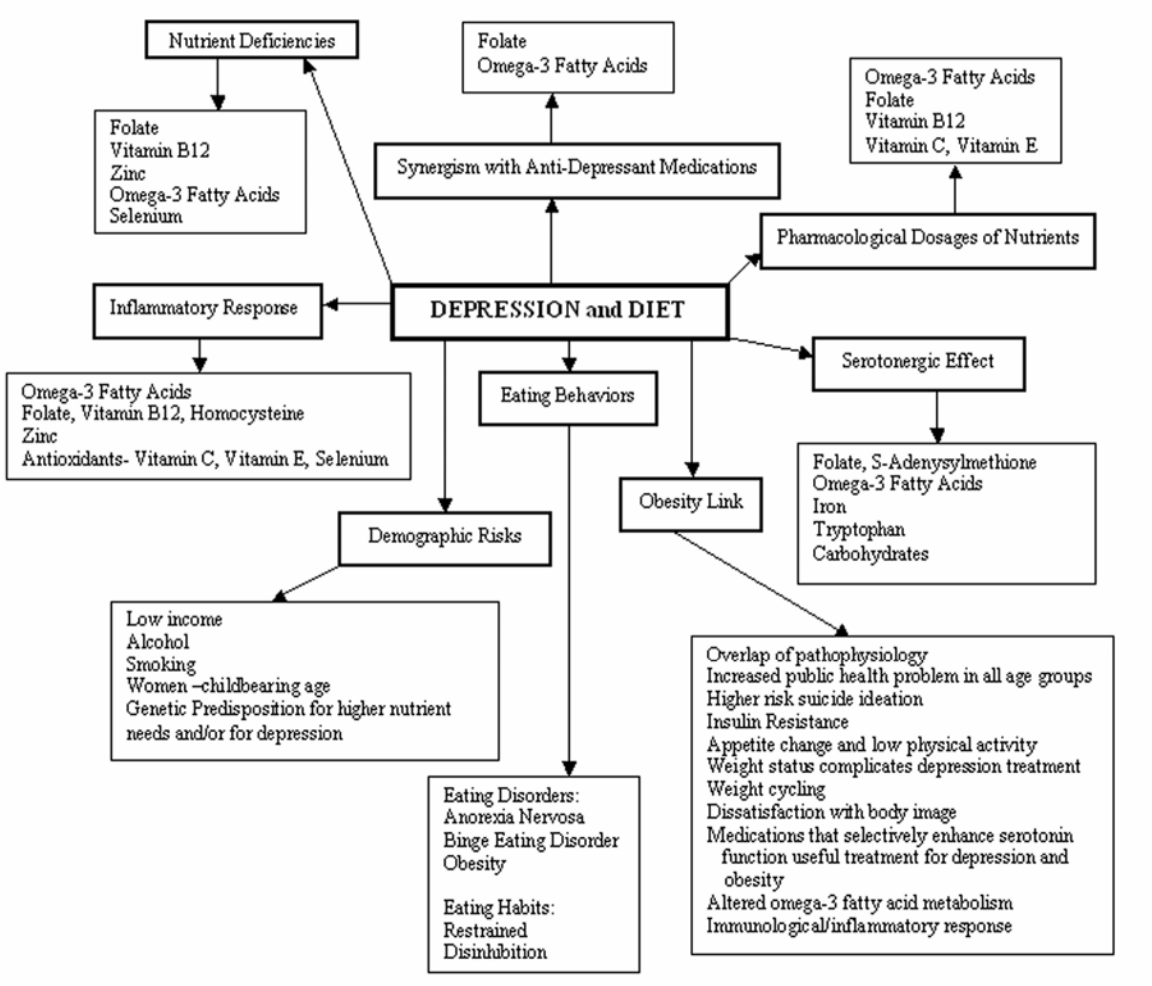
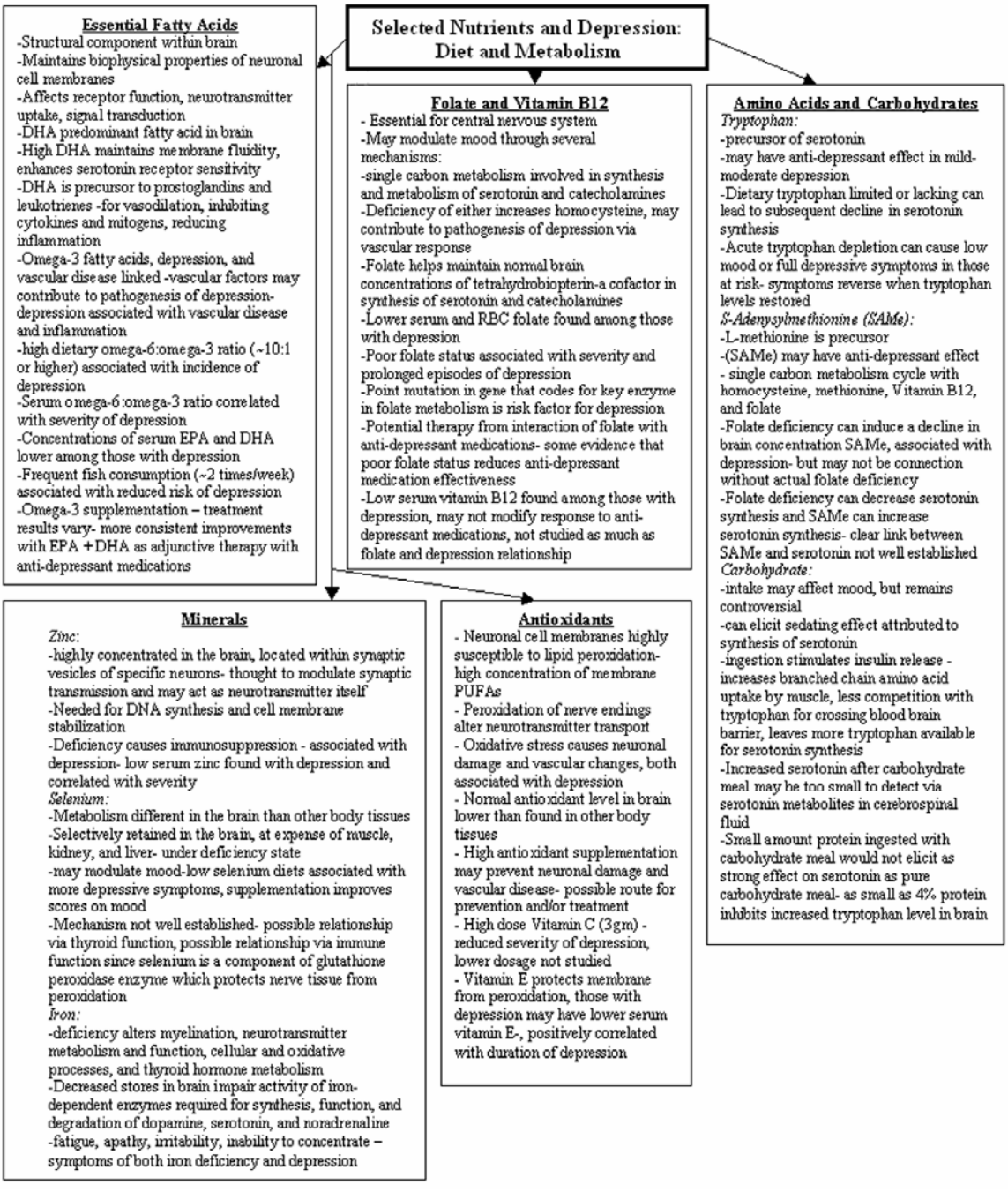


Figure 1a. Selected Nutrients and Depression: Diet and Metabolism



Explanation of the Dissertation Format

This dissertation is based on three papers, which are included as appendices A, B, C. This subsection explains the relationship of the appended papers and my original contribution to the research and production of these papers.

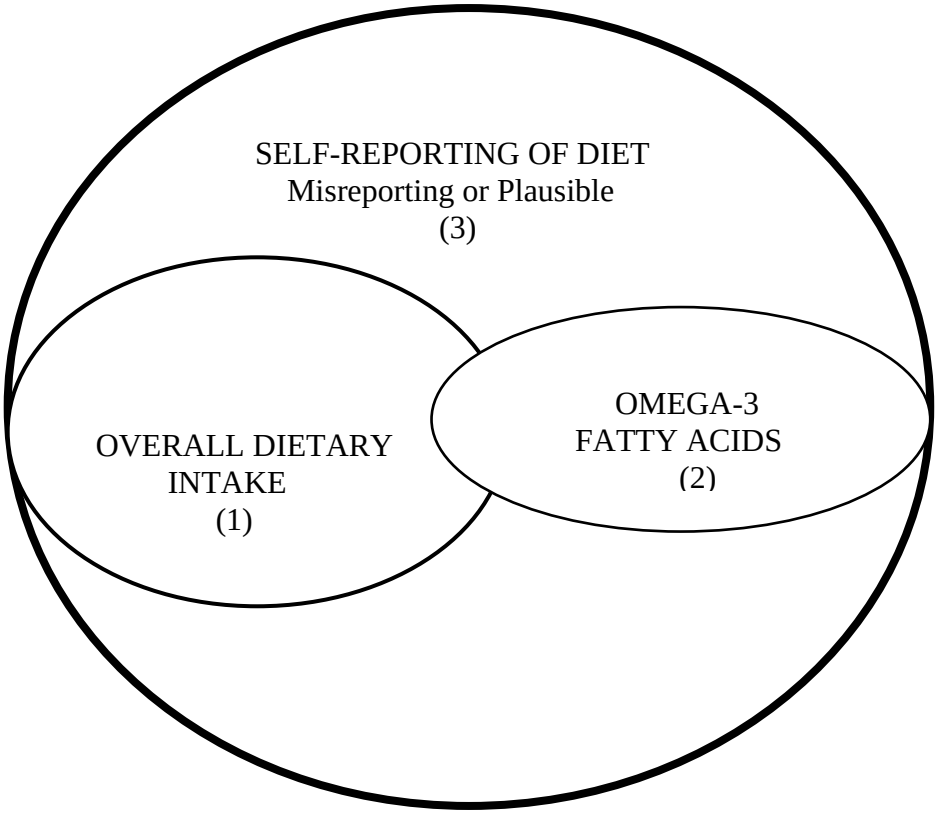
The research herein is based on secondary data analysis from the 1999-2002 National Health and Nutrition Examination Survey (NHANES). The study was cross sectional in design and included a random sample of nationally representative adults age 20-39 years old. The sample included Mexican-American, Non-Hispanic White, Non-Hispanic Black, Other Hispanic, and Other/Multi-racial adults. To account for NHANES' complex survey sample, weighted measures were used for analysis of the 1554 observations analyzed in this study. Subjects participated in the Composite International Diagnostic Interview for major depression and completed a 24-hour dietary recall. Three papers were generated examining the relationship between dietary intake and depression, self-reported sadness, and self-reported thoughts of death. The first paper described the dietary profile of adults with depression and depressive symptoms. The second paper explored the relationship between dietary omega-3 fatty acids and fish/seafood consumption and depression and depressive symptoms. The third paper examined the association of dietary energy misreporting and depression and depressive symptoms.

In the last 3 years I have been working extensively on this NHANES sample by carrying out statistical analyses and meeting regularly with my research advisor to discuss research progress, new developments and creative ideas, as well as to ensure that the different project objectives were related and successfully accomplished. The paper included in appendix A has been submitted for review to the Journal of Affect Disorders. The papers included in appendices B and C have not yet been submitted for publication, but are in publication format. I carried out the literature research along with the statistical analyses, and wrote and prepared the original as well as final versions of the manuscripts for publication. All the co-authors read and edited the manuscripts, and contributed toward the successful completion of these papers.

PRESENT STUDY

The methods, results, and conclusions of this study are presented in the papers appended to this dissertation. Figure 2 depicts how the three papers were organized and adjoined in content for this overall dissertation. The following is a summary of the most important findings in these papers.

Figure 2. Graphic depiction of the overlap among the three studies. (1) Initially began with a broad assessment of the overall diet comparing those with and without depression and depressive symptoms. (2) Narrowed focus to assessment of specific nutrients, omega-3 fatty acids and depression, based on literature support for role of omega-3 fatty acids in depression. (3) Concluded by assessment of validity of self-reported diet to help lend support for findings regarding overall diet and omega-3 fatty acids related to depression and depressive symptoms.



The study population for the papers presented in appendices A, B, and C was derived from the 1999-2000 and 2001-2002 National Health and Nutrition Examination Surveys. The study included subjects who were a randomly selected national representation of adults aged 20-39 years old. The study included 1554 young adults who completed both the Composite International Diagnostic Interview for major depression (CIDI) and the 24-hour dietary recall.

Specific Aim 1: Dietary Profile of Young Adults with Depression, Self-Reported Sadness, and Self-Reported Thoughts of Death from the 1999-2002 NHANES

Methods

To account for the survey design of these NHANES data sets, the two-year NHANES data sets, 1999-2000 and 2001-2002, were combined to allow use of the full four-year weighting as recommended by the NHANES analytic guidelines. Only variables that were collected using identical research methods for both data sets were included in the final analysis. All analyses for this study were based on the population estimates for the sample that completed the CIDI- Major Depression questionnaire and all numbers reported in the text and tables are weighted, except for the total sample size of 1554 subjects.

The three outcome variables- *depression,* self-reported *sadness,* and self-reported *thoughts of death*-were all dichotomous variables measured by a yes or no response. *Depression* was the composite final score as determined by responses to the full CIDI questionnaire. The variable *sadness* was based on the first question on the CIDI

questionnaire regarding sadness, emptiness, or depression reported over a two-week period. The variable *thoughts of death* was based on the first question in a series of questions in the CIDI questionnaire related to thoughts of death and suicide. Dietary data were collected at the mobile examination centers (MEC) using a "multiple pass" 24-hour dietary recall interview format administered by trained personnel. The 24-hour recall data were analyzed using the USDA 1994-1998 Survey Nutrient Database. The dietary data from the 24-hour recall used in this study included: total energy, macronutrients, micronutrients, individual fatty acids, caffeine, and alcohol. All dietary variables were analyzed as raw values and as nutrient density values (nutrient/1000 kcal). Additional dietary variables that were derived from the data included total omega-6, total omega-3, and omega 6: omega 3 ratio. Nutritional biochemistry data were collected at the MEC during the NHANES data collection. The laboratory data included in this analysis were consistently measured in the full four-year NHANES collection (1999-2002). The following biological measurements were evaluated for the purpose of this research: serum folate, red blood cell folate, serum vitamin B12, homocysteine, serum iron, total iron binding capacity (TIBC), and serum ferritin. Anthropometric data were collected at the MEC during the NHANES data collection process and included body mass index (BMI), height, and weight. Based on standard BMI categories, a variable BMI group was created representing BMI cutpoints for *underweight* (BMI <18.5), *appropriate weight* (BMI =18.5 –24.9), *overweight* (BMI= 25.0-29.9), and *obese* (BMI ≥30.0) (DHHS, 2005). Data from the NHANES 1999-2002 demographic questionnaires used in the current analysis included gender, age, race/ethnicity, income, education, marital status,

and pregnancy status. To determine smoking status, a cutpoint of ≥15ng/mL serum cotinine was used to determine smokers and < 15ng/mL determined non-smokers (SRNT, 2002; Bernert, 2005 pers.comm; Caraballo, 2005 pers. comm.).

The main effects analyzed were estimates of mean differences for individual nutrients, total energy intake, nutrient density, nutritional biochemistries, and anthropometrics between each mood disorder group. Estimates of mean differences were assessed by t-test for independent samples. Estimates of mean differences for demographic and categorical variables between each mood disorder group were tested by chi-square statistics. Due to the potential for multiple comparisons when analyzing the nutrient profiles of subjects, statistical significance was interpreted as p-value ≤0.01.

Results

Specific Aim 1 was to compare the dietary profile of young adults with and without depression, self-reported sadness, or self-reported thoughts of death. The total prevalence of major depression for this nationally representative sample of young adults was 7.8%. The prevalence of depression among women was 7.9% and 7.6% among men. The total prevalence of adults with self-reported feelings of sadness was 16.8%. The prevalence of sadness among women was 15.1% females and 18.5% among males. The total prevalence of adults with thoughts of death was 31.3%. The prevalence of thoughts of death among women was 33.6% and 29.2% among men.

Dietary adequacy was explored by comparing mean nutrient intakes to the current dietary reference intakes (DRI). Both men and women from all subject groups with and without depression, sadness, and thoughts of death consumed between 55-69% of the

DRI/RDA for Vitamin E (15 mg/d). The mean calcium intake of males with *thoughts of death* was 83% of the current DRI/RDA of 1000 mg/d. Males with and without *sadness* and *thoughts of death* consumed between 68-84% of the DRI/RDA for magnesium (400-420 mg/d). Regardless of gender, fiber intake was between 41-79% of the DRI (38gm/d-males, 25 gm/d-females). Nutritional adequacy was met for all other nutrients.

There was only one significant finding in the dietary profile of adults with and without *depression, sadness,* or *thoughts of death.* Adults with *thoughts of death* consumed significantly lower carbohydrate per 1000 kcal than those without *thoughts of death* ($p < .001$). No other significant differences in the dietary profile or nutritional biochemistries were found between the *depression* groups, *sadness* groups, or *thoughts of death* group.

Specific Aim 2: Association Between Dietary Omega-3 Fatty Acids and Depression and Mood

Methods

To account for the survey design of these NHANES data sets, the two-year NHANES data sets, 1999-2000 and 2001-2002, were combined to allow use of the full four-year weighting as recommended by the NHANES analytic guidelines. Only variables that were collected using identical research methods for both data sets were included in the final analysis. All analyses for this study were based on the population estimates for the sample that completed the CIDI- Major Depression questionnaire and all

numbers reported in the text and tables are weighted, except the total sample size of 1554 subjects.

The indicator variables- *depression, sadness, thoughts of death,* and *altered mood*-were all dichotomous variables measured by a yes or no response. *Depression* was the composite final score as determined by responses to the full CIDI questionnaire. *Sadness* was based on the first question on the CIDI questionnaire regarding sadness, emptiness, or depression reported over a two-week period. *Thoughts of death* was based on the first question, which read "did you think a lot about death?" in a series of questions in the CIDI questionnaire related to thoughts of death and suicide. The outcome variable *altered mood* was derived to include subjects with a positive (*yes)* response to any one of the three indicator variables: *depression, sadness,* or *thoughts of death* as determined by The World Health Organization (WHO) Composite International Diagnostic Interview, Version 2.1 (CIDI) (NHANES ref. manual[b,c]). The dietary data were derived from a single 24-hour recall data and analyzed for total energy, macronutrients, micronutrients, individual fatty acids, alcohol, and fish/seafood consumption. All dietary variables were initially analyzed as raw values and subsequently as nutrient density values (nutrient/1000 kcal). Nutrient density values were used in the final analysis and reported results. Additional dietary variables that were derived from the data included: total omega-3, omega 6: omega 3 ratio, and weekly fish/seafood consumption. Weekly fish/seafood consumption was further categorized into four groups (zero servings/week, greater than zero up to one serving/week, greater than one and less than or equal to two servings/week, greater than two servings per week). Nutritional biochemistry data were

collected at the MEC during the NHANES data collection. The laboratory data included in this analysis were consistently measured in the full four-year NHANES collection (1999-2002). The following biological measurements were evaluated for the purpose of this research: total serum cholesterol, HDL, and glycohemoglobin. Data from the NHANES 1999-2002 demographic questionnaires used in the current analysis included gender, age, race/ethnicity, income, education. The variable age was categorized into two groups: 20-29 years old, and 30-39 years old. To determine smoking status, a cutpoint of ≥15ng/mL serum cotinine was used to determine smokers and < 15ng/mL determined non-smokers (Bernert pers. comm., 2005; Caraballo pers. comm., 2005; SRNT, 2002).

Multiple logistic regression models were used to estimate the relationships between dietary intake of omega-3 fatty acids or fish/seafood consumption and *depression, sadness*, *thoughts of death*, and *altered mood*. Dietary intake values were measured and fitted into separate logistic regression models for omega-3 fatty acids based on the raw intake or density (omega-3 fatty acid/1000 kcal). Potential risk factors for both mood disorders and omega-3 fatty acid intake were determined a priori and entered into the models as covariates. The covariate variables used included: age groups (20-29 and 30-39), BMI groups (underweight, appropriate weight, overweight, obese), race/ethnicity, education, family poverty income ratio, smoking status, alcohol consumption, dietary cholesterol, serum total cholesterol, serum HDL, and glycohemoglobin. All analyses were performed using weighted sample analysis following NHANES analytical guidelines. No significant gender differences related to

dietary intake or depression status were found; therefore all models were reported as the total sample. Results were interpreted using a significance level of p-value < 0.05.

Results

Specific Aim 2 was to examine the association of dietary omega-3 fatty acid intake and fish/seafood consumption to depression and altered mood. The average dietary intake of omega-3 fatty acids among all mood disorder subjects in this study was 1.77 gm/ day with an average fish/seafood consumption of 0.98 servings/week compared with 1.52 gm/day of omega-3 fatty acids and 0.92 servings/week for individuals without mood disorders. The mean reported energy intake was not significantly different between adults with and without *depression, self-reported sadness, self-reported thoughts of death,* or *altered mood.* No significant associations were found between dietary intake of omega-3 fatty acids (alpha-linolenic acid, EPA, DHA, or total omega-3 fatty acid) or fish/seafood consumption and *depression, self-reported sadness, self- reported thoughts of death, or altered mood.* These results remained non-significant even after adjusting for confounding variables. These findings were consistent whether dietary omega-3 fatty acids were measured as raw values or as density values (per 1000 kcal).

Specific Aim 3: Misreporting of Caloric Intake in Adults with Depression, Sadness, or Thoughts of Death

Methods

The subjects were a nationally representative sample of males and females age 20-39 years old who participated in the 1999-2000 and 2001-2002 National Health and

Nutrition Examination Survey (NHANES 99-02). The total eligible sample of subjects who completed both the Composite International Diagnostic Interview for Major Depression and the 24-Hour Dietary Recall consisted of 1554 individuals.

Dietary energy measured as total kilocalories (kcal) was collected using a 24-hour recall questionnaire administered by trained personnel. Extreme values were found in the kcal variable, therefore the 24 observations with values <500 kcal/day and >6000 kcal/day were recoded to missing. Energy in kcal was converted into megajoules (mjoule) measurement for use in the energy: basal metabolic ratio formulas (EI:$BMR_{est)}$. Based on standard BMI categories, a variable BMI group was created representing BMI cutpoints for *underweight* (BMI <18.5), *appropriate weight* (BMI =18.5 –24.9), *overweight* (BMI= 25.0-29.9), and *obese* (BMI ≥30.0) (DHHS-CDC 2005). The outcome variable *total mood* was derived to include subjects with a positive (*yes)* response to any one of the three indicator variables: *depression, sadness,* or *thoughts of death* as determined by The World Health Organization (WHO) Composite International Diagnostic Interview, Version 2.1 (CIDI) (NHANES ref. manual[b,c]). Data from the NHANES 1999-2002 demographic questionnaires used in the current analysis included gender, age, race/ethnicity, income, education, marital status, and family poverty income ratio. The variable age was categorized into two groups: 20-29 years old and 30-39 years old. The variable marital status was further categorized into three groups: married and living with partner, previously married (widowed, divorced, separated), and never married. To determine smoking status, a cutpoint of ≥15ng/mL serum cotinine was used to determine smokers and < 15ng/mL determined non-smokers (Bernert, pers.

comm.2005; Caraballo pers. comm.2005; SRNT, 2002). The variable appetite change was derived to include any subjects who reported an increase or decrease in their appetite from the CIDI questionnaire for major depression. The variable weight change was derived to include any subject who reported an increase or decrease in weight from the CIDI questionnaire for major depression.

Three categories were created to classify reporting of energy intake: plausible reporters (PR), underreporters (UR), and overreporters (OR). To determine misreporting, a ratio of reported energy intake (EI) to estimated basal metabolic rate (BMR_{est}) was calculated. Reported energy intake was derived from a single 24-hour dietary recall. Estimates of basal metabolic rate were calculated using age and gender specific formulas derived by Schofield (1985). The following formulas were used:

Males 20-29	0.063 * (weight) - 0.042 * (heightm) + 2.953
Males 30-39	0.048 * (weight) - 0.011 * (heightm) + 3.670
Females 20-29	0.057 * (weight) + 1.184 * (heightm) + 0.411
Females 30-39	0.034 * (weight) - 0.006 * (heightm) + 3.530

Misreporting was then defined by using Black's gender and age specific Goldberg and PAL cutoffs (Black, 2000; Goldberg et al., 1991):

a) *underreporters*	Male 20-29 EI:BMR_{est} < 1.52
	Male 30-39 EI: BMR_{es} < 1.46
	Female 20-29 EI: BMR_{es} < 1.42
	Female 30-39 EI: BMR_{es} < 1.43
b) *plausible reporters*	Male 20-29 EI:BMR_{est} ≥ 1.52-2.18
	Male 30-39 EI:BMR_{est} ≥ 1.46-2.08
	Female 20-29 EI:BMR_{est} ≥ 1.42-1.98
	Female 30-39 EI:BMR_{est} ≥ 1.43-1.93
c) *overreporters*	Male 20-29 EI:BMR_{est} >2.18
	Male 30-39 EI:BMR_{est} >2.08

Female 20-29 EI:BMR_{est} >1.98
Female 30-39 EI:BMR_{est} >1.93

Statistical differences between mean levels of energy and BMR were tested using two-sided *t*- tests. Mean ratios of energy intake to estimated basal metabolic rate (EI:BMR_{est}) were calculated separately for population subgroups based on age, gender, mood status and body mass index (BMI) level. Stepwise multiple logistic regression models, stratified by gender, were used to examine the relationship of misreporting energy intake to altered mood. The following potential confounding variables were tested in the logistic regression models: age group, BMI group, reported weight change, reported appetite change, race/ethnicity, education, marital status, poverty level, smoking status, alcohol intake, serum cholesterol and plasma glycohemoglobin. Linear regression was used to assess the relationship between EI:BMR_{est} and mood status. Linear regression was used to detect a trend across BMI groups (underweight, normal weight, overweight, obese). All continuous variables were examined for normality. Natural log transformations were performed for skewed data, which included serum cholesterol and glycohemoglobin. All analyses were performed using weighted sample analysis following NHANES analytical guidelines. Results were interpreted using a significance level of p-value < 0.05.

Results

Specific Aim 3 determined whether mood status was associated with reporting of energy intake. Among young adults with altered mood, 25% of the population plausibly reported energy intake, while 45% underreported and 30% overreported. There were no

significant differences in the mean ratios of energy intake to estimated basal metabolic rate (EI:BMR_{est}) between adults with altered mood and those without.

Men had significantly lower mean EI:BMR_{est} compared to women and the mean EI:BMR_{est} decreased with age in the males, but not in the females. No differences were found in the mean EI:BMR_{est} stratified by mood status and age group. In both mood groups, the mean EI:BMR_{est} ratio decreased as BMI increased ($p < .001$). In the altered mood group, those classified with obesity had higher mean EI:BMR_{est} than the overweight group, but this difference was only significant in males age 30-39 years old ($p< .05$).

Among those with altered mood, 36% and 55% of females and males, respectively, were classified as underreporters. Roughly, 38% and 23% of females and males, respectively, were classified as overreporters in the altered mood group. There were no significant differences between mood status groups for misreporting or plausible reporting based on marital status, poverty level, education status, or race/ethnicity.

Compared to plausible reporters, a significantly higher proportion of males with altered and normal mood were underreporters (53%, $p < .001$ and 57%, $p < .001$, respectively). Among altered mood, a significantly lower proportion of those who underreported were smokers (33.5%, $p < .05$) compared to plausible reporters. No other significant differences were found between misreporting and plausible reporting among those with altered mood. There were no significant differences in the proportion of those who misreported or gave plausible reports between the mood status groups for each BMI category.

From stepwise logistic regression, no significant associations were found between misreporting (either under- or over-reporting) and altered mood for males and females after adjusting for confounding variables, poverty income ratio, appetite change, BMI status, education, and alcohol intake. Among women, a significant interaction was found between mood status (altered mood) and self -reported appetite change associated with underreporting compared to plausible and overreporting (interaction OR = .12, 95% CI = .02-.62, $p < .01$). No significant interaction terms between mood status and self-reported appetite change were found among men. No significant interaction of mood status and self-reported appetite change was found associated with overreporting in either gender. No other significant interactions were found with mood status.

From linear regression analysis, the ratio of EI:BMR_{est} was not significantly associated with altered mood in either males or females and after adjusting for confounding variables. A significant negative association was found between the ratio of EI:BMR_{est} and BMI for both males ($\beta = -.03$, 95% CI= -.04-.02, $p< .001$) and females ($\beta = -.04$, 95% CI= -.04-.03, $p< .001$) with altered mood. There was a non-significant relationship between EI:BMR_{est} and the interaction of mood status by BMI group. There was a significant interaction between mood status and self-reported appetite change associated with EI:BMR_{est} among women ($\beta = .44$, 95% CI= .09-.80, $p < .001$) .

Study Limitations

There are several limitations to the studies presented in this dissertation. The limitations involve study design, reliance on self-reported data, lack of biochemical or other direct measurements, and statistical analysis.

Study Design

The study designs were cross sectional and limit the ability to determine a temporal relationship between dietary factors and mood. The cross sectional design is descriptive and does not allow for determining an etiological role of diet in the development of depression or depressive symptoms. The inability to distinguish whether certain aspects of dietary intake preceded depression or depressive symptoms or whether the presence of depression or depressive symptoms alters dietary intake allowed only an evaluation of the presence of an association between diet and mood. Thus, these studies provided information about the prevalence or frequency of the association between diet and mood during the 1999-2002 time period. However, this snapshot view of the relationship between diet and depression provides a platform for considering future questions regarding diet and mood.

While these studies were based on a nationally representative sample of young adults age 20-39 years old, the results from these studies are not generalizable across all age groups with depression or depressive symptoms. The sample is limited to those age 20-39 years old, as this was the subsample selected by NHANES 1999-2002 for questions on depressive symptoms. These results are comparable to NHANES III, which included a similar evaluation of depression among young adults ages 17-39 years old

(Kinder et al., 2004). Furthermore, suicide is the third leading cause of death among adolescents and young adults (DHHS-Surgeon General's Report, 1999), and depression is a primary risk factor for attempted suicide. Alcohol and drug misuse have also been identified as risk factors for depression, which may be common among young adults. Young adults may be more vulnerable socially and psychologically to depression in response to stressful life events, such as divorce or loss of a child or other family member (DHHS- Surgeon General's report, 1999). However, the selection of subjects between the ages of 20-39 years old presents a population that may be overlooked regarding the relationship between diet and depression and depressive symptoms.

The prevalence of depression among older adults is higher than that represented in these studies (NIMH, 2003[d]; Steffens et al., 2000). Additionally, co-morbid conditions are more likely to occur among the older population with depression (NIMH, 2003[d]) and dietary intake would be expected to be quite different among the older adults as compared to this population of 20-39 year olds. Thus, examining the relationship between diet and depression would be appropriate in an older population, including those with co-morbid conditions, who may be at high risk for both depression and poor dietary intake. Additionally, comorbid conditions were not examined extensively in these studies. Specific serum biomarkers were used as surrogate markers of disease status in place of self-reported disease or confirmed diagnosis of disease status. For example, lipid profiles were considered in lieu of self-reported cardiac disease and glycohemogobin, was used in lieu of self-reported diabetes. Dietary intake was not adjusted to account for other medical illnesses that routinely use diet therapy as part of their disease management

or treatment. Medication and nutritional supplement usage were not included in these studies, therefore is it not clear what role drug-nutrient interactions may have played in moderating the relationship between mood and diet.

Furthermore, selection bias may have occurred in this study. It appears that the population characteristics may not be describing the true population of those with depression. For example, there was no significant difference in the mean alcohol consumption between those with and without depression or depressive symptoms, as would typically be expected. Also unexpectedly, there was no significant difference in the proportion of smokers based on mood status. Differences in alcohol consumption and smoking status often are confounding factors when examining the relationship between diet and disease, particularly among those with depression. In this NHANES study, neither alcohol consumption nor smoking status appeared to be related to dietary intake, dietary misreporting, or depression. Per NHANES protocol, subjects were randomly selected in order to reduce selection bias. However, individuals suffering from depression or depressive symptoms may have found it difficult to volunteer for a study such as NHANES. For example, the time involved in the interview and examination at the MEC may be considered burdensome for someone who is already experiencing dysfunction in his/her usual daily life. It is possible that the participants in this study were experiencing fewer symptoms or more mild depression, and therefore, were not representative of those with more severe depression. This may also partially explain the lack of differences in the diet found between the depressed and non-depressed groups.

Reliance on self-reported data

Another limitation was that dietary and depression data were based on self-reporting. As a result of relying on self-reported data, misclassification of subjects could have occurred with respect to their exposure (dietary intake) and/or disease state (depression and/or depressive symptoms). The misreporting of diet that was found and the possible misreporting of depressive symptoms cannot be ruled out as potentially contributing to misclassification of subjects. However, the diet and depression questionnaires used by NHANES are standardized instruments, administered by trained interviewers, and assessed for quality control. Therefore, attempts within the NHANES data collection process were made to reduce possible measurement errors. The NHANES CIDI questionnaire is a validated and standardized instrument that provides a diagnosis of depression in the past twelve months. The CIDI was not designed to assess whether subjects with depression, sadness, or thoughts of death experienced a chronic condition. One might speculate that individuals suffering from chronic depression and/or frequent recurrences or remittent mood disturbances may experience more altered dietary intake over time, and thus poorer nutritional status. Consequently, if subjects experienced an acute episode of depression, sadness, or thoughts of death at the time of completing the CIDI questionnaire, the single 24-hour recall may yield a very different dietary assessment than would otherwise result during a time of recovery or remission from depression, sadness, or thoughts of death.

The use of a single 24-hour dietary recall presents considerable limitations regarding interpretation of these data. The accuracy of the dietary intake data is

dependent on the subject's short-term memory and correct quantification of amounts of foods consumed (Buzzard, 1998; Willet, 1998). Poor concentration and motivation are common symptoms of depression, making the task of dietary recall possibly more challenging in subjects with depressive symptoms. If eating patterns are inconsistent due to depressive symptoms, the ability to accurately recall food intake may also lead to measurement error. Repeated measures of dietary intake would have provided more support for determining if habitual dietary intake was measured or if a valid reporting of dietary intake was obtained. Dietary biomarkers were available for several nutrients, which provided some assurances that the 24-hour recall was accurate. However, the use of the 24-hour dietary recall allows for more comparable analysis with previous and future NHANES studies on the associations between diet and mood. The use of a 24-hour recall can be sufficient when comparing group differences to determine if medical, health, or disease state are associated with misreporting (Livingstone and Black, 2003), as was the objective of Specific Aim 3.

Lack of biochemical markers and other direct measurements

Specific Aim 2 was additionally limited by the fact that no biomarkers or supplement data for the omega-3 fatty acids were obtained to better clarify the relationship between dietary intake and *depression*, *sadness*, or *thoughts of death*. Biomarker data may have provided more refined information about the omega-3 fatty acid derivatives, EPA and DHA, as well as provide more confirmatory results shown with alpha-linolenic acid. As such, analyzing dietary EPA and DHA intake was difficult because of such low detection levels within the diet itself. Biomarker data may have

demonstrated confirmatory low serum or tissue level EPA and DHA. Additionally, having specific supplement usage data on EPA and DHA may have provided alternative results in these subjects with mood disorders. One could speculate that much higher dosages of total or individual omega-3 fatty acids than were achieved in this sample via diet alone may be beneficial in the management or prevention of depression. It is not known whether the remaining subjects had chosen to use supplemental omega-3 fatty acid as a form of self-medication for their mood disorder. Nor is it clear how these subjects would have responded differently on the depression questionnaire if supplemental omega-3 fatty acids were used for self-medicating purposes.

In regard to Specific Aim 3 study, basal metabolic rate was estimated based on standard age and gender calculations but it was not measured or validated by biomarkers, such as doubly labeled water or calorimetry measurements. Activity level was not measured or included in the estimation of energy expenditure. Depending on the amount of physical activity regularly performed, the true energy expenditure could have been greatly distorted as compared to what was estimated, thus contributing to bias in the degree of misreporting detected. The ratio of energy intake to estimated basal metabolic rate ($EI:BMR_{est}$) cutoffs used in this study were based on gender and age specific cutoffs assuming a sedentary lifestyle. Thus, the ratios of $EI:BMR_{est}$ used were less accurate than measuring energy expenditure, and as a result, a proportion of misreporters were likely not detected (Macdiarmid and Blundell, 1998). Conversely, it is possible that the equations used to estimate basal metabolic rate tend to overestimate BMR in the general public, which could then result in overestimating the prevalence of misreporting

(underreporting) (Macdiarmid and Blundell, 1998). Furthermore, the cutoffs used in the present study were higher than used in previous NHANES studies (Briefel et al., 1997), thus if alternative cutoffs were used the proportion of those classified as misreporting would have been lower than reported here. However, the intent of this paper was to examine differences in energy reporting status between those with and without altered mood and it did not appear that using a more conservative cutoff would have yielded significant differences in reporting status between the mood groups.

An additional consideration in evaluating misreporting of diet in the relationship between diet and mood is to recognize that a consequence of altered mood may be behaviors that result in reduced energy intake. The ability to identify and characterize subjects with dietary restraint or disinhibition would be an important component to consider when assessing validity of reported dietary intake. However, in a national survey study design, such as NHANES, it would likely be unfeasible, time-consuming, and costly to identify these eating behaviors in all subjects (Ard et al., 2006). Therefore, it is recognized that a trade-off occurred between possibly obtaining more accurate reporting of energy intake for the convenience of using a 24-hour recall for dietary measurement with a large sample. In order to improve on the precision of recall data, additional questionnaires may need to be used that identify subjects with dietary restraint or disinhibition (Ard et al., 2006). Identifying such eating habits among a group of subjects with altered mood would help elicit further detail as to why this group of individuals misreport dietary intake.

In addition, these studies are limited by not having included detailed information about actual foods consumed by the subjects. Having included data about the foods consumed would have been particularly useful in each of the three studies. Having included the actual foods consumed with Specific Aim 1 would have allowed for more detailed comparisons of the dietary profile between adults with and without depression and depressive symptoms. Inclusion of actual foods consumed in the analysis of Specific Aim 2 would have allowed for more detailed information about all omega-3 food sources. Analysis of fish/seafood consumption accounted for the major contributing foods for omega-3 fatty acids. However, knowledge of other omega-3 food sources could have clarified if subjects with depression or depressive symptoms were self-selecting or self-medicating with higher omega-3 foods from other food sources as well. In regard to Specific Aim 3, knowledge of the actual foods consumed would have greatly enhanced the analysis of determining misreporting among adults with altered mood. An actual food count could have helped identify plausible reporting and reduce possible misclassification of subjects as misreporters. Furthermore, inclusion of the actual foods consumed would have helped identify which food groups were more likely to be misreported among adults with depression and depressive symptoms.

Statistical analysis

Finally, one component of the NHANES protocol for obtaining the subject sample was the use of established strata and primary sampling units (PSU) within each stratum to provide data that is well represented by the population. Based on NHANES analytic guidelines and use of statistical methods for complex survey designs, collapsing of strata

is permissible when only one PSU is available for a particular set of variables and analysis is expected to remain robust under this condition. However, throughout the statistical analysis of this study, collapsing or merging of strata was done multiple times when one PSU was detected for particular variables of interest. Therefore, the final analysis may not have best represented a comprehensive distribution of subjects throughout the U.S. as well as it could have if all strata had been complete with at least 2 PSUs.

Conclusions

The present study attempted to discern a connection between diet and depression or depressive symptoms. Depression is a leading cause of disability in the United States and contributes to considerable detriment in individuals, family, and the work place (DHHS- Surgeon General Report, 1999; World Health Organization, 2001; Üstün et al., 2004; Simon, 2003; NIMH, 1999a; NIMH, 2001b; Pincus and Pettit, 2001; Rush, 2001; Conti and Burton, 1994). When depression is coupled with other chronic diseases, severe reductions in health can occur, more so than from experiencing depression or chronic disease alone. Many standard treatments for depression are ineffective for individuals with refractory depression (NIMH, 1999), which might occur when individuals have other medical conditions as well. Dietary intake may affect the development of mood disorders or the presence of depression or depressive symptoms may affect behaviors such as dietary intake (Cohen et al., 2002). Allgöwer et al. (2001) showed that young men and women with depressive symptoms were more likely to practice less healthful

dietary behaviors. Poor dietary intake could result in substantial reductions in the availability of nutrients critical for normal brain function, such as synthesis and function of neurotransmitters (Maher, 2000). Sufficient quantities of dietary essential fatty acids, amino acids, carbohydrates, folate, Vitamin B12, Vitamin C, Vitamin E, selenium, iron, copper, and zinc are needed for supporting enzymatic activities, cellular and oxidative processes, receptor function, signal transduction, and maintenance of neuronal tissue within the brain (Bodnar and Wisner, 2005; Bourre 2004).

This NHANES study was one of the largest studies to date exploring and analyzing dietary consumption and nutritional biomarkers in relation to depression. In this nationally representative study, broad dietary differences were not found between those with and without depression or depressive symptoms. Although micronutrient differences have been reported between subjects with depression and without (Bodnar and Wisner, 2005; Bourre, 2004; Morris et al., 2003; Young, 2002; Coppen and Bailey, 2000; Coppen and Bolander-Gouaille, 2005), it appears that the comprehensive dietary intake does not differ significantly between these groups of subjects. However, this observation does not negate interest in identifying possible nutritional therapeutic options in the management or treatment of individuals with depression and mood disturbances. It is possible that single nutrient deficiencies or changes in nutrient metabolism are related to depression or depressive symptoms. For example, folate deficiency has been shown to be associated with decreased serotonin synthesis (Young, 2002, Coppen and Bailey, 2000; Coppen and Bolander-Gouaille, 2005) and a genetic mutation involved in folate metabolism has been found in adults with depression, therefore those with depression

may have higher dietary folate requirements than the general population (Bodnar and Wisner, 2005). Future studies could obtain a more inclusive description of the relationship between diet and depression with the inclusion of usage and dosage of nutritional supplements among subjects. Also, exploration of possible drug-nutrient interactions among the depressive or depressive symptom group would be warranted, as absorption or metabolism of nutrients may demonstrate clearer inadequacies between those with and without depression.

While broad dietary differences were not detected in this study, there was compelling evidence in the literature that a need existed to examine the relationship between depression and dietary intake of essential fatty acids. The omega-3 fatty acids, alpha-linolenic acid, eicosapentanoic acid, and docosohexanoic acid, are specific polyunsaturated fatty acids that are highly concentrated in the phospholipid membranes of brain and neuronal tissue (DHHS- Surgeon General Report 1999; Maidment, 2000; Freeman, 2000; Yehuda et al., 1999). Lower omega-3 fatty acid concentrations and higher ratio of Arachadonic Acid (omega-6) to Eicosapentaenoic Acid (omega-3) incorporation into the neuronal membranes may interfere with membrane function that occurs with major depression (Freeman, 2000; Maes et al., 1996; Adams et al, 1996; Edwards et al., 1998). Low omega-3 fatty acid status may lead to alterations in cell membrane microviscosity, which in turn, could contribute to disruption of neurotransmitter systems and the development of mood disorders (Maidment, 2000; Maes et al., 1999; Edwards et al., 1998; Hibbeln, 1998). In developed countries, the ratio of dietary omega-6 fatty acid to omega-3 fatty acid has increased from 2:1 to 15:1

over the past 20 years (Simopoulos et al., 1998; Pouwer et al., 2004) and multinationally a significant inverse correlation between dietary fish intake and depression has been shown (Hibbeln, 1998). A decreased ratio of plasma omega- 3 to omega-6 has been associated with major depression (Peet et al., 1998; Maes et al, 1996; Adams et al., 1996; Edwards et al., 1998; Maes et al., 1999). Erythrocyte cell membrane omega-3 fatty acid concentration has been shown to be positively associated with improved depression inventory scores and inversely associated with severity of depression (Adams et al., 1996; Peet et al., 1998; Maes et al., 1996; Edwards et al., 1998). Adipose tissue DHA was significantly lower in those with depression compared to non-depressed (Mamalakis et al., 2002).

The current reported level of dietary omega-3 fatty acids and fish/seafood consumption among young adults participating in NHANES 1999-2002 did not differ between those with and without *depression*, *sadness*, or *thoughts of death.* On average, the total omega-3 fatty acid intake in those with altered mood was 1.77gm/day, with only 0.10 gm from EPA + DHA directly. The current Adequate Intake (AI) recommended by the USDA for dietary omega-3 fatty acid is 1.1gm/day for women and 1.6gm/day for men, with approximately 10% of that from EPA and/or DHA (USDA-DRI, 2005). Also, among those with altered mood, the average fish/seafood consumption was < 1 serving per week, which is less than the current recommendation by the American Heart Association (Kris-Etherton et al., 2006). The AHA recommends that the general population consume fish and other high omega-3 fatty acid foods 2 times/week and those with known coronary heart disease or high triglycerides should consume 1 gm EPA +

DHA per day or 2-4 gm EPA +DHA per day, respectively (Kris-Etherton et al., 2006). However, the reported omega-3 fatty acid intake for this study is consistent with results reported by several other studies of various designs and population groups (Hakkarainen et al., 2004; Edwards et al., 1998; Su et al., 2003). Hakkarainen et al. (2004) found no association between fish consumption nor dietary omega-3 fatty acids and depression in a large cohort of men from Finland, where the fish consumption was on average > 2 servings/week. Conversely, where no associations between dietary omega-3 fatty acid intake and depression have been shown, supplementation studies suggest omega-3 fatty acids may play a role in treating depression when coupled with mood disorder medication (Stoll et al., 1998; Su et al., 2003; Nemets et al., 2002; Peet and Horrobin, 2002). Therefore, a drug-nutrient interaction may occur whereby the medications used for treating depression have a positive effect on the absorption or metabolism of omega-3 fatty acids. The improved absorption or metabolism of the omega-3 fatty acids would result in increased serum levels and subsequent incorporation into cell membranes. The increased tissue level omega-3 fatty acids may contribute to the improvements seen in subjects with depression. On the other hand, high supplemental dosages of omega-3 fatty acids could interact with the medications in such a way as to increase absorption or cellular uptake of the medications, thus improving their effectiveness. Clarifying the relationship between high dietary or supplemental omega-3 fatty acids and anti-depressant medications would be beneficial in determining an optimal dosage of omega-3 fatty acid for those with depression or depressive symptoms.

In view of the fact that significant dietary differences were not observed between those with and without depression or depressive symptoms, misreporting of dietary intake could not be ruled out. Misreporting of dietary data can be problematic when relying on a single 24-hour recall from a large random sample, as was done in the present study. Additionally, the challenge of inferring that a single 24-hour recall is representative of habitual intake among a population of depressed subjects is difficult. In this study, the proportion of males and females who under- and over-reported were not significantly different based on mood status.

Since those with altered mood were not significantly more prone to misreporting than those with normal mood, it was of interest to examine if a possible interaction between reporting and weight status occurred. Given the reciprocal relationship between obesity and depression this subgroup may have demonstrated evidence of greater dietary disparity between the altered and normal mood groups. Evidence supports that those who are overweight and/or obese often misreport dietary intake (Macdiarmid and Blundell, 1998; Price et al., 1997). Further evidence has shown a U-shaped relationship between weight status and mood (Carpenter et al., 2000), which could interfere with validity of dietary reporting as well. Therefore, it may be that body weight moderates the relationship between diet and dietary reporting and depression. In this study, BMI status was significantly related to underreporting compared to plausible reporting, but there was no significant interaction between BMI and mood. However, there was an increase in odds ratios across BMI groups for both altered and normal mood groups, whereby the odds of underreporting increased as BMI increased. This trend was only significant

among the normal mood group. Interestingly, among the obese group with altered mood less underreporting occurred than among the overweight group with altered mood. This suggests that those with obesity and altered mood present a unique subsample where the relationship between dietary intake and mood may be the most challenging to decipher. Since overall dietary misreporting was prevalent in this study among both altered and normal mood groups, the validity of reported dietary intake could have played a role in the lack of associations found between diet and depression.

Finally, it cannot be overlooked that comorbid conditions are likely an important component of a possible relationship between diet and mood. Greater differences in diet may be found among those with depression and co-existing illnesses compared to those with depression alone. For example, those with diabetes rely on dietary modification in managing their diabetes. However the additional burden of having depression or depressive symptoms along with diabetes may result in poorer dietary intake compared to those with depression alone. Additionally, it is possible that the lack of association between diet and depression or depressive symptoms was in part related to the young, population studied. More disparities in diet among those with depression may occur within an older population who would be expected to have more comorbid conditions. It is possible that the combination of depression plus a comorbid condition increases nutrient needs to greater extent than depression alone and that specific dietary modifications may be required that elicit effects in both conditions. In a review of the literature on diabetes, depression, and omega-3 fatty acids, Pouwer et al. (2005) concluded that supplementation with omega-3 fatty acids, in particular EPA, may be a

helpful tool in the management of type 2 diabetes and depression. Therefore, future studies on the relationship between diet and mood should target the combined relationship between diet, depression or depressive symptoms, and the accompanying comorbid condition. Additionally, assessment of dietary misreporting in those with depression and comorbid conditions, rather than depression alone, may help distinguish more dietary inconsistencies compared to those with normal mood.

In this study, it was hypothesized that having depression or depressive symptoms would be negatively associated with dietary intake, particularly omega-3 fatty acids, and that those with altered mood would be more prone to misreporting of energy intake. Few differences were found in the reporting of dietary intake or the relationship between diet and depression or depressive symptoms in this population of young adults. It appears adults with altered mood as defined within the NHANES population are similar to those with normal mood in ability to report energy intake, in overall dietary intake, and particularly in their intake of omega-3 fatty acids. From a public health and clinical standpoint, the finding that young adults with altered mood are not more prone to dietary misreporting than healthy adults is important. This demonstrates that, while dietary misreporting is problematic, studying dietary intake, dietary habits, and nutritional status can be done with individuals who have altered mood with the same precision (or lack thereof) as can be done in a healthy population.

Table 1. Review of Omega-3 Fatty Acids and Depression Literature

Authors	*N*	Sex	Study Description	Methods	Results/Conclusions
Ellis & Sanders 1977	16	M, F	Matched case control - Six inpatients treated for depression, 4 inpatients treated for other psychiatric disorder, 6 healthy controls -No age reported	-Plasma and erythrocyte fatty acids -No method for depression diagnosis reported -No diet	EPA and DHA greater in 6 subjects with depression vs. healthy controls
Fehily et al. 1981	120	M, F	Matched case control -Major depression, Bipolar Disorder, other psychiatric disorders, and healthy controls -Ages 19 - 74 years old	-Plasma & erythrocyte fatty acids -Beck Depression Inventory -No diet	Erythrocyte and plasma EPA and DHA significantly higher in depressed subjects vs. healthy; erythrocyte linoleic acid (omega-6) significantly lower in depressed subjects vs. controls; DHA significantly correlated with severity of depression (r=.80, p<.01)
Maes et al. 1996	74	M, F	Case control -Ages 29 – 65 years old -Flemish Population	-Serum cholesteryl esters & phospholipids essential fatty acids -DSM-III-R & Hamilton Depression Rating Scale -No diet	Significantly higher serum cholesteryl ester and phospholipid AA: EPA ratio among major depression vs. minor depression and vs. healthy controls; significantly higher omega-6:omega-3 ratio, decreased total omega-3, and lower alpha-linolenic acid and EPA in serum cholesteryl esters with major depression compared to minor depression and control

Adams et al. 1996	20	M, F	Cross Sectional -Ages 19 - 79 years old	-Plasma erythrocyte omega-3 and omeg-6 fatty acids -DSM-IV -3 month FFQ & 1 week dietary record	Dietary intake of omega-3 foods ranged from 0-2 fish meals/week to 3-4 fish meals/week; significant negative correlation between erythrocyte EPA and depression scale (r=-0.546, p<. 05); significant positive correlation between erythrocyte and plasma ratio of AA: EPA with depression scale (r= 0.729, p<.001, r=0.527, p<.05 respectively); no significant relationship between DHA levels and depression diagnosis or severity
Edwards et al. 1998	24	M, F	Matched case control -Ages 28 – 49 years old	-Erythrocyte membrane EPA, DHA, total omega-3 -DSM-IV & Beck Depression Inventory -7 –day weighted food record	Erythrocyte EPA, DHA, and total omega-3 fatty levels significantly decreased in depressed patients vs. healthy controls; no significant differences in dietary omega-3 intake between groups, no association between duration of depression and PUFA level; significant negative correlation between erythrocyte membrane omega-3 levels and dietary omega-3 levels with depression scores; dietary and erythrocyte membrane omega-3 levels strongest predictors of depression score
Peet et al. 1998	30	M, F	Matched case control -Ages 18- 65 years old	-DSM-IV -RBC membrane fatty acids -No diet	Significantly lower erythrocyte membrane omega-3 and DHA levels in major depression vs. healthy controls
Maes et al. 1999	48	M, F	Matched case control -Ages 38 – 65 years old -Flemish Population	- DSM-III-R & Hamilton Depression Rating Scale -Serum phospholipids & cholesteryl ester omega-3 fatty acids -No diet	Significantly lower AA and higher AA:EPA and AA:DHA ratios among depressed subjects compared to healthy controls; among major depressed significantly lower levels of total omega-3, alpha-linolenic acid, EPA and DHA in phospholipid; phospholipid and cholesteryl ester level of alpha-linolenic and EPA significant predictors to identify major depression; depressed group with lower serum zinc had significantly more pronounced alterations in fatty acid composition vs. depressed with normal zinc

Mamalaskis et al. 2002	139	M, F	Cross Sectional -Mean age 39 years old -Greek Population	-Adipose tissue omega-3 fatty acids -24 hour dietary recall for total fat and caloric intake	Mild depression significantly lower adipose DHA level compared to non-depressed; weak but significant inverse relationship between depression and adipose tissue DHA; no subjects identified with moderate or severe depression; no significant differences in overall dietary fat or total calories
Mamalaskis et al. 2004	63	M	-Cross Sectional - Elderly population ages 80-96 years old -Greek Population	-Adipose tissue omega-3 fatty acids -Geriatric Depression Scale -No diet	Significantly higher omega6:omega3 ratio in adipose tissue among depressed compared to non-depressed subjects. High alpha-linolenic acid significantly associated with less depression
Frasure-Smith et al. 2004	54	M, F	Case Control-nested in prospective cohort study -Ages 48 – 68 years old	-Structural Clinical Interview for DSM-IV & Beck Depression Inventory -Plasma phospholipid omega-3 and omega-6 fatty acids -No diet	Significantly lower concentrations of total omega-3 fatty acids and DHA, higher ratio omega-6:omega-3 in depressed compared to healthy controls
Assies et al. 2004	44	M, F	Cross Sectional-randomly selected from cohort study of recurrent MDD -Ages 18-65 years old	-DSM-IV & Hamilton Rating Scale of Depression -Plasma and erythrocyte omega-3 fatty acids -No diet	No significant association between plasma or erythrocyte membrane omega-3 fatty acid levels and depression

Dietary Studies					
Hibbeln 1998	35,000	M, F	Cross sectional -Multinational	-Annual prevalence of depression (rate/100 people) -Annual apparent fish consumption (pounds/person)	Low plasma concentration of DHA from fish intake predicted low concentration of cerebrospinal fluid-5 hydroxyindolacetic acid (CSF-5IAA); low fish consumption significantly associated with higher prevalence of depression ($r=-0.84$, $p<0.005$)
Tanskanen et al. 2001	3204	M, F	Cross sectional -Random sample Finnish Population age 25-64 years old	-Self-report depression & Beck Depression Inventory -Frequency of fish consumption range from ≤ 1x/month to ≥1x/day	Fish consumption 2 times per month or less (infrequent consumption) significantly associated with depression; likelihood of mild to severe depression 31% higher among infrequent fish consumers compared to consumption 1 time per week or more (frequent consumption) (OR=1.31, 95% CI= 1.10-1.56, $p<.01$); among women depression symptoms significantly associated with infrequent fish consumption (OR=1.40,95% CI=111-1.78, $p<.01$)
Hakkarainen et al. 2004	29,133	M	Cross sectional - Subjects part of larger trial in Finland -Ages 50 - 69 years old	-Self-report depression, hospital treatment for depression, suicide -1 year FFQ	No association between dietary omega-3 fatty acids or fish consumption and depressed mood, major depression, or suicide
Sarlio-Lahteenkorva 2004	6242	M, F	Cross sectional-part of Helsinki Health Study -Ages 40- 60 years old -Finnish Population	-12 item version of GHQ-12 by Goldberg measurement of mental health -4 week FFQ	No association between fish consumption and mental health

Jacka et al. 2004	755	F	Cross sectional- part of Geelong Osteoporosis Study (age stratified, community sample of women) -Ages 23 – 97 years old -Australian Population	-Self report depression and DSM-IV -FFQ at baseline, 2, 4, and 6 year follow- up -Weekly consumption of seafood at each 2 year measurement -Supplement use and intake recorded at each 2 year measurement	No significant differences in self-reported dietary intake of fish oil or seafood between depressed and non-depressed
Timonen et al. 2004	5689	M, F	Cross sectional- part of Northern Finland 1966 Birth Cohort study -Age 31 years old at time of data collection for depression	-Self report depression, doctor diagnosed lifetime depression & Hopkins Symptom Checklist- 25 depression subscale -6 month FFQ	In women, infrequent fish consumption (once a month or less) associated with increased risk of depression, compared to regular fish consumption (weekly or more often). No association of dietary fish consumption and depression among men.
Zhang et al. 2005	8249	M, F	Cross-sectional -Random sample of US adults 17-39 year old - NHANES III	-Self report suicide attempts -24 hour recall	Identified suicide attempters consumed significantly lower percentage of kcal from PUFA vs. non-attempter; overall kcal not significantly different between attempter and non-attempter; lowest percentage kcal PUFA from smokers who were suicide attempters (interaction of smoking and diet); dietary fiber intake significantly lower in suicide attempters vs. non-attempters

Supplement Studies					
Stoll et al. 1999	30	M, F	Randomized, double blind, placebo controlled trial -Bipolar Disorder -Ages 18 – 65 years old	-DSM-IV -4- month trial - 9.6 gm EPA + DHA/day (with mood disorder medications) -No diet	Supplementation 9.6 gm/day omega-3 fatty acids for 120 days significantly improved mood stabilizing and increased duration before relapse among subjects with bipolar disorder vs. placebo
Peet and Horrobin 2002	70	M, F	Randomized double blind placebo controlled trial -Ages 18 – 70 years old -Intention to treat and per-protocol	-Hamilton Depression Rating Scale, Beck Depression Inventory, & Montgomery-Asberg Depression Rating Scale -1, 2, or 4 gm EPA/day (with anti-depressant medications) -Baseline, 2, 4, 8, 12 week measurements -No diet	Significant improvements in depressive symptoms within 4, 8, and 12 weeks of 1gm/day EPA adjunctive therapy combined with standard depressive therapy
Nemets et al. 2002	20	M, F	Randomized double-blind, placebo controlled trial -Ages 18 - 75 years old	-DSM-IV -2 gm EPA/ day (with anti-depressant medications) - 4 – week trial -No diet	2 gm/day EPA administered as adjunctive therapy showed significant improvement in depressed group vs. placebo group
Su et al. 2003	22	M, F	Randomized double blind placebo controlled trial	-DSM-IV & Hamilton Depression Rating Scale -8 -week trial	No significant difference in dietary frequency of fishconsumption or total PUFAs between subjects with and without depression; significant improvement in supplementation group vs. placebo group after 4 weeks; significant increase in

			-Ages 18- 60 years old -Japanese Population	- 9.6 gm/day EPA + DHA (with anti-depressant medications) -3 – day food record & 24-hour recall	erythrocyte EPA and DHA after supplementation vs. placebo
Marangell et al. 2003	36	M, F	Randomized double-blind, placebo controlled trial -Ages 18 - 65 years old	-DSM-IV & Montgomery-Asberg Depression Rating Scale 2 gm DHA – monotherapy -6 week trial -No diet	2 gm DHA supplementation as monotherapy showed no significant effect on depression compared with placebo group
Silvers et al. 2005	77	M, F	Randomized, double blind placebo controlled trial - Currently treated for depression; age 18-65 years old -Intention to treat and per-protocol	-Diagnosis confirmed via medical records -Hamilton Depression Rating Scale-short form & Beck Depression Inventory at 2, 4, 8, 12 weeks -3- gm EPA+ DHA/day (with anti-depressant medications) - RBC membrane phospholipids EPA and DHA -FFQ baseline and modified FFQ at 12 weeks to assess dietary changes	No significant association between mood and dietary omega-3 fatty acids among adults with depression; no significant improvement in mood among depressed adults after 12 weeks of 3 g/day omega-3 fish oil supplementation

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APPENDIX A. DIETARY PROFILE OF ADULTS WITH AND WITHOUT DEPRESSION, SADNESS, AND THOUGHTS OF DEATH

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Keywords: Diet; Nutrition; NHANES; Depression; Sadness

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Appendix A 1. Body of Paper

Dietary profile of adults with and without depression, sadness, and thoughts of death

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ABSTRACT:

Background: Depression is frequently associated with poor appetite and symptoms of depression may be associated with a decline in nutrition status. The present study explored the dietary profile of adults with and without *depression*, *sadness*, and *thoughts of death*.

Methods: Subjects were 1554 nationally representative males and females, ages 20-39 years, who participated in the 1999-2000 and 2001-2002 National Health and Nutrition Examination Survey. Estimates of mean differences for individual nutrients, total energy intake, nutrient density, nutritional biochemistries, and anthropometrics were analyzed between each mood disorder group. Dietary adequacy was explored by comparing mean nutrient intakes to the current dietary reference intakes (DRIs).

Results: No significant differences in the dietary profile or nutritional biochemistries were found between the *depression* groups, *sadness* groups, or *thoughts of death* groups compared to those with normal mood. Nutritional adequacy was met for all nutrients, except vitamin E, calcium, magnesium, and fiber were lower than current DRIs.

Limitations: This study was cross sectional in design and detecting a cause and effect relationship between diet and *depression, sadness,* or *thoughts of death* was not possible.

Dietary measurement error may have occurred due to possible inconsistent eating patterns as a result of depressive symptoms, which could diminish accuracy in recalling food consumption.

Conclusions: No broad dietary differences between subjects with and without depression or mood disturbances was observed. However, the relationship of diet and depression remains elusive. These findings do not negate the public health need for exploring nutritional therapies in the management and/or treatment of individuals with depression and mood disturbances.

INTRODUCTION:

Major Depressive Disorder (MDD) is a leading cause of disability in the United States (DHHS- Surgeon General Report, 1999; World Health Organization, 2001; Üstün et al., 2004). Individuals are at risk for MDD regardless of ethnicity, education, income or marital status. It is estimated that approximately 6.7 million women (6.5%) and 3.2 million men (3.3%) suffer from MDD each year in the United States. In a given year, MDD affects approximately 9.9 million Americans age 18 and older (approximately 5% of the US adult population), with the average age of onset most commonly in the mid-twenties (NIMH, 1999a; NIMH, 2001b; APA- DMS-IV, 1994).

The effects of depression are readily observed by measurable reductions in quality of life, lost work productivity, and increased health care costs (Simon, 2003). MDD, often episodic or chronic, causes substantial personal, social, and financial costs (DHHS-Surgeon General Report 1999; NIMH, 1999a; NIMH, 2001b; Pincus and Pettit, 2001; Rush, 2001). Even after a depressive episode ends, many patients continue to have

"residual symptoms" which can contribute to reduced daily functioning (Rush, 2001). Marital dissatisfaction is associated with depression and children of depressed parents are three times more likely to experience depression themselves than children of non-depressed parents (Pincus and Pettit, 2001; Birmaher et al., 1996; Whisman, 1999). Employers incur the burden of depression in the work place, where 80% have reported depression being largely problematic for work productivity (Pincus and Pettit, 2001; Conti and Burton, 1994). Employees with depression are more likely to require disability days than employees with chronic back pain, heart disease, other mental disorders, hypertension, or diabetes (Pincus and Pettit, 2001; Conti and Burton, 1994). Medical costs for patients with MDD are approximately 50% higher than the costs of a chronic illness alone (Kanton, 2003). The estimated cost of depression in the US ranges from $43.7 to $52.9 billion per year, including costs due to health care, work time loss, and suicide (Pincus and Pettit, 2001; Greenberg et al., 2003). An individual with depression is likely to spend twice as much on health care costs as compared to an individual without depression, such that the direct burden of depression on the health care system is estimated to cost $12.7 billion per year (Pincus and Pettit, 2001; Simon, 2003; Kanton, 2003). Individuals with major depression have been reported to perceive their social functioning and health as more impaired than patients with other medical conditions (Wells et al., 1989). When depression occurs along with comorbid conditions, such as coronary artery disease, diabetes, Parkinson's, cancer, HIV, and multiple sclerosis a considerable decline in self-care management has been shown (Kanton, 2003).

Since the burden of depression can be chronic and episodic, requiring lifestyle changes and self- management skills, it is compelling to examine possible relationships

between lifestyle choices and depression. Specifically the relationship of diet and depression is of interest, given that diet may provide a cost effective approach to reducing the financial burden of depression. Additionally, depression may possibly contribute to an overall decline in nutritional status. Symptoms of depression, such as dysphoric mood or thoughts of suicide, may be associated with dietary factors and depression itself is frequently associated with poor appetite, changes in weight, and reduced motivation. An abnormal appetite and poor quality of food intake could result in a further decline in overall nutritional status. However, current data on diet and depression are equivocal. Christensen and Somers found the dietary intake in 22 women with depression to be adequate in meeting or exceeding the 1989 RDAs for 15 nutrients and total energy (Christensen and Somers, 1994). Other reports suggest that major depression may be associated with specific nutrient inadequacies, such as folate, vitamin B12, selenium, omega-3 and omega-6 fatty acids, dietary fat and cholesterol, selenium, zinc, and sugar (Hakkarainen et al., 2005; Hvas et al., 2004; Hibbeln, 1995; Hintikka et al., 2003; Westover and Marangell, 2002; Carney, 1990; Coppen and Bailey, 2000; Coppen and Bolander-Gouaille, 2005). Therefore, the purpose of this study was to explore and characterize the dietary profile of a nationally representative sample of young adults with and without depression, sadness, and thoughts of death. We hypothesized that adults with depression, sadness, or thoughts of death would have a different dietary profile than those adults without mood disorders.

METHODS AND MATERIALS:

Study Sample

The subjects were a nationally representative sample of males and females age 20-39 years who participated in the 1999-2000 and 2001-2002 National Health and Nutrition Examination Survey (NHANES 99-02). These NHANES data were derived from a national probability sample of the civilian non-institutionalized US population from 1999-2002 identified using a 2-stage cluster design (NHANES, 2004a; NHANES, 2005b; NHANES, 2005c). The total sample of subjects who completed both the Composite International Diagnostic Interview for Major Depression and the 24-Hour Dietary Recall consisted of 1554 individuals. The sample included subjects who identified themselves within the following race/ethnicities: Mexican-American, Other Hispanic, Non Hispanic White, Non Hispanic Black, African-American, and Other/Multiracial.

Measurements

Depression: The World Health Organization (WHO) Composite International Diagnostic Interview, Version 2.1 (CIDI) was used to determine if a subject had depression during the previous 12 months (NHANES, 2005b; NHANES, 2005c). The CIDI is a comprehensive and standardized interview used to assess and provide a diagnosis of major depression and is in accordance to the criteria and definitions of major depression by the ICD-10 (10th revision of the International Classification of Disease, World Health Organization 1992, 1993) and DSM IV (Fourth edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (1994). If all criteria for a diagnosis were positive, the diagnosis of major depression was considered to be present.

Diet and Anthropometric Data: Dietary data were collected at the mobile examination centers (MEC) using a 24-hour recall questionnaire administered by trained personnel. The 24-hour recalls were conducted in person. The 24-hour recall data were analyzed for total energy, macronutrients, micronutrients, individual fatty acids, caffeine, and alcohol. All dietary variables were analyzed as raw values and as nutrient density values (nutrient/1000 kcal). Additional dietary variables that were derived from the data included: total omega-6, total omega-3, and omega 6: omega 3 ratio. Anthropometric data were collected at the MEC during the NHANES data collection process and included body mass index (BMI), height, and weight. Based on standard BMI categories, a variable BMI group was created representing BMI cutpoints for *underweight* (BMI <18.5), *appropriate weight* (BMI =18.5 –24.9), *overweight* (BMI= 25.0-29.9), and *obese* (BMI >=30.0) (DHHS, 2005).

Laboratory: Nutritional biochemistry data were collected at the MEC during the NHANES data collection. Detailed methodology of laboratory data collection can be found in the NHANES 1999-2002 documentation manuals for laboratory procedures (NHANES, 2001d; NHANES, 2001e; NHANES,2001f). The laboratory data included in this analysis were consistently measured in the full four-year NHANES collection (1999-2002). The following biological analysis were evaluated for the purpose of this research: serum folate, red blood cell folate, serum vitamin B12, homocysteine, serum iron, total iron binding capacity (TIBC), and serum ferritin. To determine smoking status, a cutpoint of >=15ng/mL serum cotinine was used to determine smokers and < 15ng/mL determined non-smokers (SRNT, 2002; Bernert, 2005 pers.comm; Caraballo, 2005 pers. comm.).

Other Relevant Variables: Data from the NHANES 1999-2002 demographic questionnaires used in the current analysis included gender, age, race/ethnicity, income, education, marital status, and pregnancy status.

Study Design

To account for the survey design of these NHANES data sets, the statistical analysis was completed using the 1999-2002 NHANES analytic guidelines (NHANES, 2004a). The two-year NHANES data sets, 1999-2000 and 2001-2002, were combined to allow use of the full four-year weighting as recommended by the NHANES analytic guidelines. Only variables that were collected using identical research methods for both data sets were included in the final analysis. The sample weights, primary sampling units (PSUs), and stratum used were obtained from within the CIDI-major depression data set and the demographic and weighting data sets (CIDI subsample 4 year MEC weight, masked variance pseudo-PSU, masked variance pseudo-stratum). The PSUs were established based on the state, county, and metropolitan partitioning set by the US Bureau of the Census (NHANES, 2004a; NCHS, 1995). Within each state the PSUs are partitioned further into strata based on similar PSU characteristics. Within each stratum, two PSUs are selected based on a probability proportional to size sampling method. Smaller states may only have 1 PSU drawn. The sampling weights were established to attempt to optimize sampling conditions and reduce bias estimates for each level of sampling available. Thus, the actual sampling weights used were adjusted for non-response and were ratio adjusted. The CIDI measured only a sub-sample of the total NHANES population sample, thus the masked variance pseudo-PSU and masked variance pseudo-stratum were created by NHANES to protect confidentiality and allow

for analysis of these data sets. When strata only contained one PSU, strata were collapsed to create two pseudo-PSUs were created. The collapsing of strata allows for conservative standard errors and this method is robust for analyzing subsetted data (NHANES, 2004a; NCHS, 1995). All analyses were based on the population estimates for the CIDI major depression sample and all numbers reported in the text and tables are weighted, except the total sample size reported above.

The three outcome variables, *depression score, sadness*, and *thoughts of death*, were all dichotomous variables measured by a yes or no response. *Depression score* was the composite final score as determined by responses to the full CIDI questionnaire. The variable *sadness* was based on the first question on the CIDI questionnaire regarding sadness, emptiness, or depression reported over a two-week period. The variable *thoughts of death* was based on the first question in a series of questions in the CIDI questionnaire related to thoughts of death and suicide.

Due to the smaller sample size of subjects responding, "yes" to *thoughts of death*, select variables had strata with only one PSU. In order to correct for this, strata found with only one psu were collapsed to create new strata containing at least two PSUs. Within the 2001-2002 data set all variables analyzed for *thoughts of death* were found to have a strata with only one PSU. Each strata with only one PSU was collapsed with the next closest strata, in order to create new strata that contained 2 or more PSUs, thereby allowing all variables to be analyzed for the full four-year data. The possible distortion of other variables after collapsing strata could generate less representative results for this group of subjects. However, collapsing the strata allowed for estimating means for a more thorough dietary profile of individuals who experienced *thoughts of death*.

Statistical Analysis

All independent variables were examined for normality. Natural log transformations were completed for skewed data. In the final analysis the only variables that were not transformed were: kcalories, fiber, TIBC, α-linolenic acid, total omega-3. All comparisons were assessed using transformed variables, unless indicated otherwise. Alpha-linolenic acid and total omega-3 variables were not transformed, despite right tailed skewness, because no extreme outliers were found. The main effects analyzed were estimates of mean differences for individual nutrients, total energy intake, nutrient density, nutritional biochemistries, and anthropometrics between each mood disorder group. Estimates of mean differences were assessed by t-test for independent samples. Estimates of mean differences for demographic and categorical variables between each mood disorder group were tested by chi-square statistics.

To account for possible gender differences in the prevalence of depression and nutritional intake, gender stratified results were tested for each variable mean comparison and each mood disorder group. A significant gender interaction was found for the mean serum folate (ng/ml) and RBC folate, thus results for these variables were reported separately for males and females. A gender interaction was also found for homocysteine in subjects with *thoughts of death.* No other significant gender by depression score, sadness, or thoughts of death interaction terms were found, therefore all other results are reported for the total sample and not stratified by gender.

Due to the potential for multiple comparisons when analyzing the nutrient profiles of subjects, we only interpreted significance for those p-values ≤ 0.01. Intercooled Stata 8.0 (Stata Corporation, College Station, TX) was used for all statistical analysis.

RESULTS:

The total prevalence of major depression for this nationally representative sample of young adults was 7.8%. The prevalence of depression among women was 7.9% and 7.6% among men. The total prevalence of adults with self-reported feelings of sadness was 16.8%. The prevalence of sadness among women was 15.1% females and 18.5% among males. The prevalence of sadness for pregnant women was 8.4%, which was lower than the prevalence of non-pregnant women with sadness (18.1%), although this difference was not significant. The total prevalence of adults with thoughts of death was 31.3%. The prevalence of thoughts of death among women was 33.6% and 29.2% among men (Table 1).

There were no significant differences between those with and without *depression* by race/ethnicity, education, marital status, poverty, smoking status, body mass index, or alcohol consumption. There was a significant difference in *sadness* among the marital groups (p=. 01). Mean BMI was significantly higher in adults who experienced *thoughts of death* compared to those that did not (p=. 004). Adults who experienced *thoughts of death* were older than adults who did not experience *thoughts of death,* but this did not reach statistical significance (Table 1). Mean energy intake did not differ significantly between any mood disorder group when compared by categorical BMI classifications.

Dietary adequacy was explored by comparing mean nutrient intakes to the current dietary reference intakes (DRI). The current recommended dietary allowance (RDA) for Vitamin E is 15 mg/d for men and women ages 20-39, as represented by this subject pool (37). Both men and women from all subject groups with and without depression, sadness, and thoughts of death consumed between 55-69% of the DRI/RDA for Vitamin

E. The mean calcium intake of males with *thoughts of death* was 83% of the current DRI/RDA of 1000 mg/d. Males with and without *sadness* and *thoughts of death* consumed between 68-84% of the DRI/RDA for magnesium (400-420 mg/d). Regardless of gender, fiber intake was between 41-79% of the DRI (38gm/d- males, 25 gm/d- females). Nutritional adequacy was met for all other nutrients.

There was only one significant finding in the dietary profile of adults with and without *depression, sadness*, or *thoughts of death.* Adults with *thoughts of death* consumed significantly lower carbohydrate per 1000 kcal than those without *thoughts of death* (p=. 001) (Table 2).

However, notable differences were found with respect to dietary omega- 3 fatty acids, serum folate, homocysteine, RBC folate, serum iron, and TIBC. Adults with *sadness* had higher mean α-linolenic acid (1.62 ± 0.1 mg/d) and total omega-3 intake (1.74 ± 0.1 mg/d) compared to those without *sadness* (1.40 ± 0.0 mg/d α-linolenic acid, 1.47 ± 0.0 mg/d total omega-3). When these nutrients were assessed by nutrient density (mean intake per 1000 kcal), there was no longer a difference between the *sadness* groups (Table 2). Subjects who experienced *thoughts of death* had higher α- linolenic acid and DHA per 1000 kcal than subjects who did not experience *thoughts of death*. Serum folate was lower and homocysteine was higher for those subjects with *thoughts of death* compared to those without. RBC folate was higher in those subjects with depression compared to those without. Serum iron was higher in subjects with *depression* compared to those without and TIBC was lower in subjects with *thoughts of death* compared to those without. No other significant differences in the dietary profile or nutritional

biochemistries were found between the *depression* groups, *sadness* groups, or *thoughts of death* group (Tables 2-3).

DISCUSSION:

In this nationally representative sample, we found that the dietary profile of individuals with major depression, self-reported feelings of sadness, or thoughts of death did not differ greatly from adults without these mood disturbances. All nutrients met nutritional adequacy based on current DRIs except of intakes for Vitamin E, calcium, magnesium and fiber that were below the DRI. This study found a higher prevalence of major depression when compared to the recent National Comorbidity Survey Replication (NCS-R) (7.8% vs. 6.7%, respectively) (Kessler et al., 2005). Consistent with this study, the NCS-R used the CIDI questionnaire and DSM-IV diagnostic criteria for assessing a 12-month diagnosis of major depression. However, the population used in the NCS-R included adults 18 years of age and older, where this study only included subjects age 20-39. Depression is commonly diagnosed in these early adult years, therefore the higher prevalence of depression reported in this study is not unexpected. Additionally, these findings are similar to earlier 12-month mental health prevalence studies, such as Epidemiologic Catchment Area Study and the first NCS, despite the difference in sampling and measurements of these other studies (Jonas et al., 2003; Kessler et al., 2005).

In this study, no significant prevalence differences between genders and *depression, sadness, or thoughts of death* was observed, although gender differences are often reported in the literature. It is possible that the subjects in this study were hesitant to participate in a mental health survey or underreported behaviors that may have elicited

a different prevalence of *depression*, *sadness*, or *thoughts of death* between genders (Kessler et al., 2005). Conversely, it could be speculated that with increased public health awareness of and more treatment options for mood disorders, there might be less reluctance of males in this age group to report feelings or symptoms of depression, thus contributing to a prevalence of mood disorders similar to that of women.

Single nutrient and specific food differences have been reported between subjects with and without depression. For example, a highly significant correlation was found between sugar consumption and the annual rate of depression for six countries in a multinational comparison (Westover and Marangell, 2002). Additionally, several studies have reported nutritional deficiencies in folate, vitamin B_{12}, vitamin B_6, vitamin C, selenium, and zinc in subjects with depression, yet few of these studies have assessed dietary intake (Hvas et al., 2004; Hintikka et al., 2003; Carney, 1990; Coppen and Bailey, 2000; Morris et al., 2003; Nowak et al., 2003). We found that dietary consumption of micronutrients did not differ between subjects with and without *depression, sadness*, or *thoughts of death*. Reported high intakes of omega-6 fatty acids relative to omega-3 fatty acids and low dietary omega-3 fatty acids alone have been associated with increased levels of depression (Hibbeln and Salem, 1995). Higher national seafood consumption was a significant predictor of lower prevalence rates of bipolar disorder (Simona and Hibbeln, 2003). However, no significant association of fish or omega-3 fatty acid consumption with depression, low mood, or suicide was found in a large longitudinal study of Finnish males age 50-69 years (Hakkarainen et al., 2004). We found higher absolute intakes of α-linolenic acid and total omega-3 in subjects with *sadness*, but no differences when caloric density was assessed. Interestingly, subjects with *thoughts of*

death were found to have higher α-linolenic acid, but lower DHA consumption per 1000 kcal. Neither plasma nor tissue essential fatty acid measurement data were available in this study to help discern the dietary results. Thus, essential fatty acid consumption in subjects with mood disorders remains an issue worthy of further investigation.

Nutrient density can be critical when assessing nutrition adequacy. No global nutritional inadequacies were observed among subjects with major depression, feelings of sadness, or thoughts of death. The only other dietary profile comparing nutrient intake of adults with depression assessed nutritional adequacy of 29 adults with depression using the 1989 RDAs (Christensen and Somers, 1994). The Christensen and Somers study found subjects with depression consumed an overall diet meeting or exceeding the 1989 RDAs. In the present NHANES study, no significant differences were found in nutrition adequacy between subjects with depression or depressive symptoms and those without. These findings are similar to finding by Christensen and Somers.

The question arises as to why no significant dietary differences are seen between the depressed and non-depressed groups? The prevalence of depression, the total energy intake, and the BMI did not significantly differ between males and females, which could have a bearing on the dietary results. The mean energy intake and the overweight classification of BMI were similar across all mood groups. It is possible that underreporting of dietary intake occurred. Underreporting of total energy intake has been shown to occur to a greater extent among obese individuals than lean adults and is associated with social desirability (Broyles et al., unpublished). In this NHANES study, the mean BMI only differed significantly between the group with *thoughts of death* compared to those without. The adults who experienced *thoughts of death* had the highest

mean BMI found among all subject groups. The mean BMI categorized all subjects in the "overweight" range and the mean kcal intake did not differ between the mood disorder groups. Therefore, whether overt obesity or an overweight status accounts for an appreciable underreporting of dietary intake by these subjects is unclear.

Additionally, the NHANES CIDI questionnaire provides a diagnosis of depression in the past twelve months. However, the CIDI was not designed to assess whether subjects with depression, sadness, or thoughts of death experienced a chronic condition. One might speculate that individuals suffering from chronic depression and/or frequent recurrences or remittent mood disturbances may experience more altered dietary intake overtime, and thus poorer nutritional status. Consequently, if subjects experienced an acute episode of depression, sadness, or thoughts of death at the time of completing the CIDI questionnaire, the single 24-hour recall may yield a very different dietary assessment than would otherwise result during a time of recovery from depression, sadness, or thoughts of death.

There are limitations in using one self- reported 24-hour recall to assess the dietary intake of the subjects in this study. The accuracy of the dietary intake data is dependent on the subject's short-term memory and correct quantification of amounts of foods consumed (Buzzard, p.50-73, 1998; Willet, 1998). Poor concentration and motivation are common symptoms of depression, making the task of dietary recall possibly more challenging in subjects with depressive symptoms. If eating patterns are inconsistent due to depressive symptoms, the ability to accurately recall food intake may also lead to measurement error. It has been suggested that a nutrient deficiency with depression might arise primarily out of a reduced food intake (Christensen and Somers,

1994). In this NHANES study, 59% of subjects with depression reported significantly less appetite than non-depressed subjects (40.9%, p=. 006). Eighty-three percent of subjects with sadness reported less appetite compared to subjects without sadness (64.1%, p=. 006). Since a change in appetite is a common symptom of depression, the influence of those subjects reporting a decline in appetite suggests that the dietary measurements could have been negatively affected.

Using nutrient biomarkers enhances the validity of the 24-hour recall data (Buzzard, p.50-73, 1998; Willet, 1998). In the present study, we found no significant differences in the nutrition biomarkers between individuals with *depression, sadness,* or *thoughts of suicide* compared to those without. Interesting differences were noted for serum folate, homocysteine, RBC folate, iron, and TIBC, yet these could be explained by gender differences. For example, consistent with the literature, we found a lower serum folate and higher serum homocysteine among subjects with *thoughts of death,* yet a gender interaction was detected that eliminated the initial relationship observed between serum homocysteine and folate and *thoughts of death* (Carney, 1990*).* Contrary to current literature, we found RBC folate to be higher among adults with depression compared to those without (Morris et al., 2003). As above, this did not reach statistical significance and a gender interaction also occurred where males with depression had a significantly higher mean RBC folate than males without depression. The mean RBC folate levels did not differ significantly for the female subjects with and without depression. Again, not statistically significant, serum iron was higher in subjects with depression than those without and TIBC was lower in subjects with *thoughts of death* compared to those without. A significant gender interaction was not found in serum iron levels. However,

males with depression had a higher mean serum iron level than females with depression and males without depression. Thus, likely contributing to the overall higher serum iron level noted. The female subjects with *thoughts of death* had significantly lower TIBC levels compared to females without *thoughts of death* and therefore the probable reason for the differences noted in TIBC.

The presence of depression, sadness, and thoughts of death may affect behaviors such as dietary intake. As well, dietary intake may affect the development of mood disorders. Being that this study was cross sectional in design it was not possible to detect a cause and effect relationship between diet and depression, sadness, or thoughts of death. However, this NHANES study was one of the largest studies to date exploring and analyzing dietary consumption and nutritional biomarkers. In this nationally representative study we did not observe broad dietary differences between subjects experiencing depression or mood disturbances and those without depression or mood disturbances. This observation may have public health implications, but does not negate interest in identifying possible nutritional therapeutic factors in the management or treatment of individuals with depression and mood disturbances. Although micronutrient differences have been reported between subjects with depression and without, it appears that the comprehensive dietary intake does not differ significantly between these groups of subjects.

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Table 1: Characteristics of US adults' age 20-39 years old with and without depression, sadness, and thoughts of death

Characteristics	1999-2002 Depression			Sadness			Thoughts of Death		
	YES	NO	p	YES	NO	p	YES	NO	p
Age, y*	29.3 (1.6)	29.6 (0.5)	.89	31.0 (1.4)	29.2 (0.5)	.27	33.3 (2.7)	26.5 (1.5)	.05
Female, %	7.9	92.1	.88	15.1	84.9	.12	33.7	66.4	.61
Male, %	7.6	92.4		18.4	81.5		29.2	70.8	
Race/Ethnicity (%)			.48			.38			.45
Mexican-American	5.7	94.3		13.2	86.8		22.1	77.9	
Other Hispanic	8.2	91.8		21.8	78.2		14.4	85.6	
Caucasian	8.9	91.1		17.1	82.9		37.1	62.9	
African American	6.3	93.7		16.5	83.5		27.4	72.6	
Other/Multiracial	8.3	91.7		21.4	78.6		37.1	62.9	
Education (%)			.89			.91			.25
< High School	7.9	92.1		15.9	84.1		32.7	67.3	
High School or GED	8.7	91.3		17.2	82.8		19.8	80.3	
> High School	7.3	92.7		16.8	83.2		38.9	61.2	
Marital Status			.45			**.01**			.47
Never Married	8.8	91.2		17.0	83.0		33.2	66.8	
Married	4.8	95.2		13.3	86.7		38.2	61.8	
Living with Partner	7.4	92.6		12.0	88.0		34.4	65.6	
Separated	12.0	88.0		25.8	74.2		19.4	80.6	
Divorced	10.6	89.4		34.1	65.9		13.4	86.6	
Widow	11.6	88.4		22.8	77.2		59.5	40.5	
Smoking Status, %[a]			53			.29			.36
Smoker	8.5	91.6		18.4	81.6		27.5	72.5	
Non-Smoker	7.4	92.6		15.9	84.1		33.9	66.1	
Income%**			.83			.84			.32
Family Poverty	8.4	91.6		16.9	83.1		38.6	61.4	
No Family Poverty	7.9	92.1		16.4	83.6		26.5	73.5	
BMI*	26.6 (0.7)	26.1 (0.2)	.38	26.7 (0.7)	26.0 (0.2)	.29	28.5 (0.8)	25.7 (0.7)	**.004**
Alcohol, g/d*	7.5 (3.5)	10.0 (2.3)	.60	8.5 (2.6)	10.1 (2.5)	.70	13.9 (5.0)	7.7 (3.8)	.36

Results based on 1554 observations using weighted data to be nationally representative for adults age 20-39 years old.

* Age, BMI, Alcohol reported as mean and standard error.

** Income- cutpoint family poverty income ratio, <1= poverty, >1=no poverty

[a] Smoking classified by cutpoints, smoker = cotinine >=15 ng/mL, non-smoker = cotinine <15ng/mL

Table 2: Mean Nutrient Density (Nutrient/1000 kcal) of adults' age 20-39 years old with and without depression, sadness, and thoughts of death

	Depression			Sadness			Thoughts of Death		
	YES	NO	p	YES	NO	p	YES	NO	p
Kcal	2410.4 (103.2)	2242.3 (42.2)	.26	2603.0	2381.6 (68.5)	.24	2200.8 (163.3)	2100.7 (57.4)	.52
Fat (gm/d)	37.2 (1.5)	35.9 (0.4)	.39	(132.7)	36.0 (0.4)	.90	39.8 (1.8)	35.8 (1.0)	.07
Protein (gm/d)	35.6 (1.8)	36.7 (0.5)	.59	35.8 (1.1)	36.6 (0.5)	.94	38.4 (2.1)	34.2 (1.0)	.10
Carbohydrate (gm/d)	129.8 (4.1)	130.5 (1.0)	.86	36.7 (0.8)	130.2 (1.1)	.82	116.9 (4.7)	135.3 (2.9)	**.001**
Fiber (gm/d)	7.1 (0.6)	6.7 (0.1)	.52	131.2 (3.5) 6.5 (0.3)	6.8 (0.2)	.27	6.9 (0.8)	6.6 (0.4)	.77
Dietary Cholesterol (mg/d)	113.5 (7.9)	125.4 (3.0)	.15		125.9 (3.1)	.22	125.3 (11.0)	117.1 (7.1)	.51
Saturated Fat (gm)	12.2 (0.3)	12.1 (0.2)	.87	118.6 (5.7)	12.2 (0.2)	.63	12.5 (0.6)	12.2 (0.4)	.61
Sat Fat 4:0	.24 (0.0)	.24 (0.0)	.94	11.9 (0.4)	.24 (0.0)	.92	.21 (0.0)	.25 (0.0)	.22
Sat Fat 6:0	.13 (0.0)	.13 (0.0)	.82	.24 (0.0)	.13 (0.0)	.95	.11 (0.0)	.14 (0.0)	.19
Sat Fat 8:0	.11 (0.0)	.11 (0.0)	.65	.13 (0.0)	.12 (0.0)	.30	.09 (0.0)	.12 (0.0)	.10
Sat Fat 10:0	.20 (0.0)	.20 (0.0)	.84	.11 (0.0)	.20 (0.0)	.71	.17 (0.0)	.21 (0.0)	.14
Sat Fat 12:0	.36 (0.1)	.38 (0.0)	.83	.19 (0.0)	.38 (0.0)	.32	.30 (0.0)	.45 (0.1)	.10
Sat Fat 14:0	1.0 (0.0)	1.0 (0.0)	.95	.34 (0.0)	1.0 (0.0)	.59	.95 (0.1)	1.1 (0.1)	.32
Sat Fat 16:0	6.7 (0.2)	6.6 (0.1)	.70	1.0 (0.0)	6.7 (0.1)	.77	7.1 (0.3)	6.6 (0.2)	.22
Sat Fat 18:0	3.0 (0.1)	3.0 (0.0)	.98	6.6 (0.2) 3.0 (0.1)	3.1 (0.0)	.71	3.3 (0.2)	3.0 (0.1)	.10
Polyunsaturated Fat (gm)	8.2 (0.5)	7.2 (0.1)	.07		7.2 (0.1)	.33	8.4 (0.7)	7.4 (0.4)	.21
Linoleic Acid	7.3 (0.5)	6.4 (0.1)	.07	7.5 (0.3)	6.4 (0.1)	.39	7.5 (0.6)	6.6 (0.3)	.19
Arachidonic Acid	.06 (0.0)	.06 (0.0)	.45	6.7 (0.3)	.06 (0.0)	.55	.06 (0.0)	.06 (0.0)	.46
Total Omega-6	7.3 (0.5)	6.4 (0.1)	.07	.06 (0.0)	6.5 (0.1)	.39	7.6 (0.6)	6.6 (0.3)	.19
Alpha-Linolenic Acid	.70 (0.1)	.63 (0.0)	.15	6.7 (0.3)	.63 (0.0)	.17	.71 (0.1)	.64 (0.0)	.04
Eicosapentaeoinc Acid	.02 (0.0)	.01 (0.0)	.48	.67 (0.0)	.01 (0.0)	.07	.01 (0.0)	.02 (0.0)	.10
Docosahexaenoic Acid	.03 (0.0)	.03 (0.0)	.48	.02 (0.0)	.03 (0.0)	.15	.026 (0.0)	.034 (0.0)	.04
Total Omega-3	.75 (0.1)	.67 (0.0)	.12	.04 (0.0) .73 (0.0)	.67 (0.0)	.09	.75 (0.1)	.69 (0.0)	.34
Monounsaturated Fat (gm)	13.7 (0.7)	13.5 (0.2)	.76		13.6 (0.2)	.57	15.0 (0.7)	13.3 (0.5)	.43
Mufa 16:1	.60 (0.0)	.63 (0.0)	.35	13.2 (0.5)	.63 (0.0)	.46	.68 (0.0)	.60 (0.0)	.53
Mufa 18:1	12.9 (0.6)	12.6 (0.2)	.67	.61 (0.0)	12.7 (0.2)	.57	14.0 (0.6)	12.4 (0.5)	.56
Mufa 20:1	.07 (0.0)	.08 (0.0)	.65	12.3 (0.5)	.08 (0.0)	.47	.09 (0.0)	.07 (0.0)	.69
Mufa 22:1	.02 (0.0)	.02 (0.0)	.69	.07 (0.0) .02 (0.0)	.02 (0.0)	.71	.02 (0.0)	.02 (0.0)	.26

Vitamin A (mcg)	522.3 (197.9)	349.5 (14.9)	.39	407.4 (84.9)	354.0 (16.7)	.53	631.5 (311.6)	308.0 (23.7)	.30
Vitamin E (mg)	3.6 (0.3)	3.6 (0.1)	.90	3.5 (0.1)	3.6 (0.1)	.25	3.4 (0.2)	3.6 (0.2)	.44
Vitamin C (mg)	42.8 (5.8)	47.0 (1.9)	.50	41.0 (3.1)	47.9 (2.2)	.08	37.6 (4.8)	42.4 (4.3)	.39
Thiamin (mg)	0.72 (0.0)	0.76 (0.0)	.52	0.75 (0.0)	0.75 (0.0)	.66	0.75 (0.1)	0.74 (0.0)	.96
Riboflavin (mg)	0.96 (0.1)	0.95 (0.0)	.81	0.95 (0.0)	0.95 (0.0)	.94	0.99 (0.1)	0.94 (0.0)	.51
Niacin (mg)	10.3 (0.7)	10.6 (0.2)	.67	10.2 (0.3)	10.7 (0.2)	.18	10.6 (0.6)	9.9 (0.5)	.43
Folate (mg)	174.6 (12.6)	180.5 (3.2)	.64	178.8 (9.4)	180.4 (3.2)	.87	171.7 (13.7)	184.1 (14.6)	.51
Vitamin B6 (mg)	0.88 (0.1)	0.84 (0.0)	.56	0.84 (0.0)	0.84 (0.0)	.96	0.89 (0.1)	0.82 (0.1)	.48
Vitamin B12 (mg)	2.0 (0.2)	2.3 (0.1)	.18	2.2 (0.1)	2.3 (0.1)	.57	2.1 (0.3)	2.2 (0.1)	.95
Calcium (mg)	411.3 (23.4)	410.9 (9.6)	.99	400.5 (15.5)	413.3 (10.5)	.52	339.5 (34.2)	410.9 (17.7)	.09
Magnesium (mg)	132.2 (8.5)	123.1 (1.7)	.32	123.0 (3.6)	123.8 (1.7)	.85	128.6 (11.2)	121.1 (5.3)	.58
Iron (mg)	7.2 (0.4)	7.5 (0.2)	.42	7.1 (0.2)	7.6 (0.2)	.06	7.0 (0.4)	7.0 (0.3)	.91
Zinc (mg)	4.9 (0.3)	5.4 (0.1)	.13	5.3 (0.1)	5.4 (0.1)	.77	5.3 (0.3)	5.1 (0.2)	.68
Copper (mg)	0.57 (0.0)	0.57 (0.0)	.97	0.56 (0.0)	0.58 (0.0)	.35	0.57 (0.0)	0.55 (0.0)	.67
Selenium (mcg)	43.5 (1.8)	48.0 (0.8)	.06	46.7 (1.2)	47.9 (0.8)	.41	47.4 (2.4)	43.4 (1.3)	.19
Potassium (mg)	1324.0 (86.6)	1208.7 (19.2)	.23	1233.5 (33.4)	1214.3 (21.1)	.67	1373.5 (132.2)	1171.4 (39.3)	.19
Sodium (mg)	1494.6 (61.6)	1542.4 (18.5)	.47	1535.1 (33.6)	1540.4 (19.0)	.88	1547.1 (57.9)	1499.6 (38.4)	.48
Phosphorus (mg)	597.1 (24.2)	600.5 (7.3)	.90	600.9 (11.7)	600.3 (7.6)	.96	567.8 (29.4)	590.5 (17.0)	.51

All values reported as mean (SE).
All p values reported for natural log transformed variables except where indicated.
* p values reported for variables without transforming

Table 3: Nutritional Biochemical Markers for US adults age 20-39 years old with and without depression, sadness, or thoughts of death

Nutritional Biomarker	Depression YES	NO	p	Sadness YES	NO	p	Thoughts of Death YES	NO	p
Folate (ng/ml)	5.5 (1.3)	14.1 (0.3)	.25	14.2 (.07)	14.2 (0.3)	.87	13.0 (0.9)	15.4 (1.0)	.05
Males	17.7 (1.7)	13.9 (0.4)	.03	14.4 (0.9)	14.1 (0.5)	.79	13.8 (1.5)	16.6 (1.3)	.16
Females	13.3 (1.4)	14.4 (0.5)	.51	14.0 (0.9)	14.3 (0.4)	.74	12.3 (1.3)	14.1 (1.2)	.28
RBC Folate (ng/ml RBC)	295.3 (9.1)	280.8 (4.9)	.02	278.9 (5.2)	282.6 (5.1)	.31	269.6 (12.8)	283.9 (10.7)	.42
Males	307.5 (15.4)	281.8 (7.8)	.14	284.8 (9.6)	283.4 (8.3)	.91	275.7 (20.5)	290.6 (14.4)	.56
Females	283.2 (14.7)	279.8 (5.9)	.83	271.9 (8.3)	281.7 (6.6)	.38	263.3 (16.3)	276.0 (13.3)	.57
Vitamin B12 (pg/ml)	575.2 (57.9)	673.6 (108.2)	.60	724.9 (178.1)	645.1 (115.4)	.63	575.4 (105.8)	840.7 (307.0)	.26
Homocysteine (umol/l)	6.8 (0.3)	7.1 (0.1)	.73	6.8 (0.2)	7.1 (0.1)	.28	7.4 (0.3)	6.4 (0.2)	.05
Males	7.2 (0.5)	7.2 (0.2)	1.0	6.8 (0.2)	7.3 (0.2)	.09	7.7 (0.5)	6.4 (0.3)	.04
Females	6.5 (0.4)	6.9 (0.1)	.23	6.7 (0.3)	6.9 (0.1)	.50	7.1 (0.5)	6.4 (0.3)	.20
Iron (ug/dl)	102.5 (4.6)	91.3 (1.5)	.05	94.3 (2.9)	91.8 (1.5)	.64	97.7 (5.1)	95.4 (4.3)	.52
Ferritin (ng/ml)	90.1 (8.6)	96.3 (5.5)	.84	83.5 (4.3)	98.3 (6.1)	.26	86.5 (11.9)	89.4 (13.0)	.53
TIBC (ug/dl)*	392.8 (8.1)	384.5 (2.7)	.38	389.6 (5.2)	384.3 (2.8)	.37	369.9 (13.1)	401.5 (7.1)	.05

All p values reported for natural log transformed variables except where indicated.
* p value reported for variable without transforming.

APPENDIX B. ASSOCIATION OF DIETARY OMEGA-3 FATTY ACIDS WITH DEPRESSION AND MOOD

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Keywords: Diet; Omega-3 Fatty Acids; NHANES; Depression; Mood

Appendix B 1. Body of Paper

Association of Dietary Omega-3 Fatty Acids with Depression and Mood

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ABSTRACT:

Background: Evidence suggests omega-3 fatty acids have a role in normal brain function and if inadequate, poor omega-3 fatty acid status could have a role in the development of depression. Omega-3 fatty acids may be useful in the treatment of depression. The present study explored the dietary intake of omega-3 fatty acids and fish consumption in adults with and without *depression*, self- reported *sadness*, and self-reported *thoughts of death*.

Methods: Subjects were 1554 nationally representative males and females, ages 20-39 years, who participated in the 1999-2000 and 2001-2002 National Health and Nutrition Examination Survey. Estimates of mean differences for fish consumption and omega-3 fatty acids, including alpha-linolenic acid, eicosopentaenoic acid, docosohexaenoic acid, and the ratio of omega-6:omega-3 fatty acids were analyzed between each mood disorder group. Logistic regression was used to evaluate an association between dietary the omega-3 fatty acids and depression or depressive symptoms.

Results: Subjects with depression or depressive symptoms consumed an average of 1.77 gm/day dietary omega-3 fatty acids, with only 0.10 gm from EPA and DHA combined.

No significant associations were found between dietary intake of any omega-3 fatty acids or fish/seafood consumption and *depression*, *sadness*, and *thoughts of death.* These results remained non-significant even after adjusting for confounding variables.
Limitations: This study was cross sectional in design and detecting a cause and effect relationship between diet and *depression*, *sadness*, or *thoughts of death* was not possible. Mean intake levels of omega-3 fatty acids were consistent with previous studies yet; it is difficult to measure associations between dietary intake and mood disorders when both diet and mood were based on subjects' self-reporting. No biomarkers or supplement data for the omega-3 fatty acids were obtained to better clarify the relationship between dietary intake and *depression*, *sadness*, or *thoughts of death*.
Conclusions: The current reported level of dietary omega-3 fatty acids and fish/seafood consumption among young adults participating in NHANES 1999-2002 did not differ between those with and without *depression*, *sadness*, or *thoughts of death.* However, studies suggest omega-3 fatty acids may play a role in the management of depression when coupled with mood disorder medication.

INTRODUCTION:

The human brain contains high concentrations of polyunsaturated fatty acids (PUFAs) that have a vital role in neuronal function (DHHS-Surgeon General Report 1999; Maidment, 2000; Freeman, 2000; Yehuda et al., 1999). The omega-3 fatty acids, eicosapentanoic acid and docosohexanoic acid, are specific polyunsaturated fatty acids that are highly concentrated in the phospholipid membranes of brain and neuronal tissue. It has been suggested that the concentration and ratio of essential fatty acids in these

phospholipid membranes may have a role in the etiology of depression. Lower omega-3 concentrations and lower omega-3 concentrations relative to omega-6 incorporation into the neuronal membranes may interfere with membrane function that occurs with major depression (Freeman, 2000; Maes et al., 1996; Adams et al., 1996; Edwards et al., 1998). Low omega-3 fatty acid status may lead to alterations in cell membrane microviscosity, which in turn, could contribute to alterations in neurotransmitter systems and the development of mood disorders (Maidment, 2000; Maes et al., 1999; Edwards et al., 1998; Hibbeln, 1998). A decreased ratio of plasma omega- 3 to omega-6 has been associated with major depression (Peet et al., 1998; Maes et al., 1996; Adams et al., 1996; Edwards et al., 1998; Maes et al., 1999). Studies examining PUFA composition in erthyrocyte cell membranes found significant inverse associations between erythrocyte omega-3 fatty acid concentration and improved scores on depression inventories and severity of depression (Adams et al., 1996; Peet et al., 1998; Maes et al., 1996; Edwards et al., 1998). Additionally, omega-3 fatty acids function as anti-inflammatory and immunosuppressive agents, particularly when an overactive immune response occurs (Haag, 2003; Yehuda et al., 1999). An overactive immune or inflammatory response has been associated with major depression and mood disorders (Smith, 1991; Maes and Smith, 1998; Mischoulon and Fava, 2000). Hence, it is of interest to consider the possible therapeutic role dietary omega-3 fatty acids may have in the management of depression or mood disorders.

Examination of dietary intake of omega-3 fatty acids in individuals with depression shows the research to be equivocal. In a multinational comparison, a

significant inverse correlation was reported between annual fish consumption and annual prevalence of major depression (Hibbeln, 1998). It has also been suggested that a high ratio of dietary omega-6 fatty acid to omega-3 fatty acid may contribute to an increased incidence of depression and worsening in severity of depression (Adams et al., 1996; Bruisma and Taren, 2000). In a case control study, a higher dietary intake of omega-3 fatty acids was associated with less severe depression, yet no significant differences in the overall omega-3 intake was reported between patients with depression and healthy controls (Edwards et al., 1997). Additionally, there were no significant relationships between the duration of depression and any of the individual dietary PUFA levels measured (Edwards et al., 1997). Measurement of adipose tissue fatty acid as a biomarker of habitual dietary fat indicated that DHA content was significantly lower in subjects with depression (Mamalakis et al., 2000). In one of the largest studies to date, no significant association of fish consumption or intake of omega-3 fatty acids was found in older males who reported depressed mood or experienced hospital treatment for depressive disorder (Hakkarainen et al., 2004).

The purpose of this paper is to study the relationship between dietary omega-3 fatty acid intake and *depression*, *sadness*, and *thoughts of death* among adults age 20-39 years old using NHANES 1999-2002 data. It was hypothesized that adults with *depression, sadness,* or *thoughts of death* would have lower reported dietary intake of total omega-3 fatty acid, alpha- linolenic acid, DHA, and EPA. Additionally, it was hypothesized that adults with *depression, sadness,* or *thoughts of death* would have higher reported dietary ratio of omega-6 to omega-3 fatty acid.

METHODS AND MATERIALS:

Study Sample

The subjects were a nationally representative sample of males and females age 20-39 years old who participated in the 1999-2000 and 2001-2002 National Health and Nutrition Examination Survey (NHANES 99-02). These NHANES data were derived from a national probability sample of the civilian non-institutionalized US population from 1999-2002 using a 2-stage cluster design (NHANES ref manual 2001-2, NHANES lab manual 1999-2000). The total eligible sample of subjects who completed both the Composite International Diagnostic Interview for Major Depression and the 24-Hour Dietary Recall consisted of 1554 individuals. The sample included subjects who identified themselves within the following race/ethnicities: Mexican-American, Other Hispanic, Non Hispanic White, Non Hispanic Black, African-American, and Other/Multiracial.

Measurements

Diet and Anthropometric Data: Dietary data were collected using a single 24-hour recall questionnaire administered by trained personnel. The 24-hour recalls were conducted in person. The 24-hour recall data were analyzed for total energy, macronutrients, micronutrients, individual fatty acids, alcohol, and fish/seafood consumption. All dietary variables were initially analyzed as raw values and subsequently as nutrient density values (nutrient/1000 kcal). Nutrient density values were used in the final analysis and reported results. Additional dietary variables that were derived from the data included: total omega-3, omega 6: omega 3 ratio, and weekly

fish/seafood consumption. Weekly fish/seafood consumption was further categorized into four groups (zero servings/week, > zero – one serving/week, > one- <= two servings/week, > two servings per week). Dietary fish/seafood consumption was assessed by 2 year weighted analysis measured for males and females in the 1999-2000 data set. Anthropometric data was collected at the mobile examination centers (MEC) during the NHANES data collection process and included body mass index (BMI), height, and weight. Based on standard BMI categories, a variable BMI group was created representing BMI cutpoints for *underweight* (BMI <18.5), *appropriate weight* (BMI =18.5 –24.9), *overweight* (BMI= 25.0-29.9), and *obese* (BMI >=30.0) (CDC 2005).

Depression: The World Health Organization (WHO) Composite International Diagnostic Interview, Version 2.1 (CIDI) was used to determine if a subject met the criteria for a diagnosis of depression during the previous 12 months (NHANES lab manual 1999-2000). The CIDI is a comprehensive and standardized interview used to assess and provide a diagnosis of major depression and is in accordance to the criteria and definitions of major depression by the ICD-10 (10th revision of the International Classification of Disease, World Health Organization 1992, 1993) and DSM IV (Fourth edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (1994). If all criteria for a diagnosis were positive, the diagnosis of major depression was considered to be present.

Laboratory: Nutritional biochemistry data were collected at the MEC during the NHANES data collection. Detailed methodology of laboratory data collection can be found in the NHANES 1999-2002 documentation manuals for laboratory procedures

(NCHS 1995, NHANES lab manuals 1999-2002). The laboratory data included in this analysis were consistently measured in the full four-year NHANES collection (1999-2002). The following biological measurements were evaluated for the purpose of this research: total serum cholesterol, HDL, and glycohemoglobin.

Other Relevant Variables: Data from the NHANES 1999-2002 demographic questionnaires used in the current analysis included gender, age, race/ethnicity, income, education. The variable age was categorized into two groups: 20-29 years old, and 30-39 years old. To determine smoking status, a cutpoint of >=15ng/mL serum cotinine was used to determine smokers and < 15ng/mL determined non-smokers (Bernert pers. comm., 2005; Caraballo pers. comm., 2005; SRNT, 2002).

Statistical Analysis

The three indicator variables, *depression, sadness*, and *thoughts of death*, were all dichotomous variables measured by a yes or no response. *Depression score* was the composite final score as determined by responses to the full CIDI questionnaire. *Sadness* was based on the first question on the CIDI questionnaire regarding sadness, emptiness, or depression reported over a two-week period. *Thoughts of death* was based on the first question, which read "did you think a lot about death?" in a series of questions in the CIDI questionnaire related to thoughts of death and suicide.

Multiple logistic regression models were used to estimate the relationships between dietary intake of omega-3 fatty acids or fish/seafood consumption and *depression, sadness*, and *thoughts of death*. Dietary intake values were measured and fitted into separate logistic regression models for omega-3 fatty acids based on the raw

intake or density (omega-3 fatty acid/1000 kcal). Potential risk factors for both mood disorders and omega-3 fatty acid intake were determined a priori and entered into the models as covariates. The covariate variables used included: age groups (20-29 and 30-39), BMI groups (underweight, appropriate weight, overweight, obese), race/ethnicity, education, family poverty income ratio, smoking status, alcohol consumption, dietary cholesterol, serum total cholesterol, serum HDL, and glycohemoglobin. All variables were examined for normality. Natural log transformations were performed for skewed data, including all dietary omega-3 fatty acid, fish/seafood consumption and all potential covariate variables. All analyses were performed using weighted sample analysis following NHANES analytical guidelines.

The effect of gender was evaluated for each regression analysis to account for possible gender differences in dietary consumption or depression. No significant gender differences related to dietary intake or depression status were found; therefore all models were reported as the total sample.

Results were interpreted using a significance level of $p\text{-value} < 0.05$. All statistical analysis was performed using Intercooled Stata 8.0 (Stata Corporation, College Station, TX).

RESULTS:

The total prevalence of major depression for this nationally representative sample of young adults was 7.8%. The total prevalence of adults with self-reported feelings of sadness was 16.8%. The total prevalence of adults with thoughts of death was 31.3%. There were no significant differences between those with and without *depression* by

race/ethnicity, education, marital status, poverty, smoking status, body mass index, or alcohol consumption. Mean BMI was significantly higher in adults who experienced *thoughts of death* compared to those that did not ($p < .05$).

The average dietary intake of omega-3 fatty acids among all mood disorder subjects in this study was 1.77 gm/ day with an average of 0.10 gm/day of EPA + DHA and the average fish/seafood consumption was 1.4 servings/week, compared with 1.52 gm/day of omega-3 fatty acids and 1.5 servings/week for individuals without mood disorders. Furthermore, the mean energy intake was not significantly different between adults with and without *depression, sadness,* or *thoughts of death.*

No significant associations were found between dietary intake of omega-3 fatty acids (alpha-linolenic acid, EPA, DHA, or total omega-3 fatty acid) or fish/seafood consumption and *depression, sadness*, and *thoughts of death* (Tables 1-4). These results remained non-significant even after adjusting for confounding variables. These findings were consistent whether dietary omega-3 fatty acids were measured as raw values or as density values (per 1000 kcal).

DISCUSSION:

In this nationally representative study of young adults, dietary intake of fish/seafood or omega-3 fatty acids did not differ between those with and without *depression,* self- reported *sadness,* or self-reported *thoughts of death.* Reasons for these results need to be understood to guide future studies. In particular, the results from this study compared with others must be reflected upon in terms of the study population and the study design.

The mean level of alpha-linolenic acid among adults with *depression, sadness*, or *thoughts of death* was 1.59 (0.09) gm/day. However, it is the EPA and DHA fractions that are most relevant regarding depression and depressive symptoms. The conversion of alpha-linolenic acid to EPA and DHA is very limited in healthy individuals; therefore it is recommended that adults consume at least 2 servings of fish and seafood/week because these foods are the most concentrated sources of pre-formed EPA and DHA (Pawlosky et al., 2001;USDA, 2005). Among US adults, the average estimated dietary intake of EPA plus DHA is 0.13 g/day (USDA, 2005). In the present study, the mean EPA plus DHA intake among adults with *depression, sadness,* or *thoughts of death* was 0.11 (.01) g/day, which is less than the average estimated intake among the general US adult population. The dietary intake of EPA and DHA in this study is considerably lower than the supplemental dosages studied for treating depression. It is suggested that the inclusion of at least two or more servings of fish or seafood per week would increase the EPA plus DHA level to about 250 mg/day or more (USDA, 2005). The USDA estimates the average fish consumption in the US is one serving/week, which is considered insufficient for achieving adequate dietary EPA and DHA. Our findings that young adults with *depression, sadness*, or *thoughts of death* consumed on average less than one serving/week (0.91 servings/week) of fish/seafood, which is below the estimated average weekly fish consumption in the general adult US population and below the recommendations set forth by the American Heart Association (Kris-Etherton et al., 2006). Interestingly, for adults with *depression, sadness, or thoughts of death* we found the actual reported weekly servings of fish/seafood ranged from 0-8.4 servings/week,

with only approximately 6% of this population having reported consumption of >2 servings fish/seafood per week. Overall, it appears that this group of young adults with mood disorders was not able to achieve an adequate intake of dietary EPA or DHA nor did they meet weekly recommendations for fish/seafood consumption. Consequently, the question remains, what level of dietary EPA and/or DHA intake or fish/seafood consumption is sufficient enough to produce a therapeutic benefit in the management of depressed individuals over that which could be achieved by otherwise healthy adults?

Studies from differing cultures have reported varying amounts of omega-3 fatty acid and fish consumption among adults with depressive disorder. We found approximately 42% of subjects with *depression, sadness, or thoughts of death* reported consuming between 0-2 servings fish/seafood per week and the mean intake of total omega-3 fatty acids was 1.70 (.10) gm/day. A study assessing a small group of Australian subjects with diagnosed depression (n=20) reported dietary fish consumption was between 0-2 servings/ week (Adams et al., 1996). Similarly, in a fish oil supplement study from New Zealand, 46 out of 77 subjects with depression consumed ≤ 2 servings fish per week and the mean intake of omega-3 fatty acid was 1.5 (1.3) and 1.8 (1.3) gm/day for placebo and treatment groups, respectively (Silvers et al., 2005). However, compared to our findings, a Finnish cohort study reported a higher mean total omega-3 fatty acid intake of 2.2 gm/day for older males (Hakkarainen et al., 2004). An average intake of omega-3 fatty acids among British adults reported consumption of 2.0gm/day for males, similar to the Finnish male study, and consumption of 1.41gm/day for females, lower than our findings (Sanders, 2000). Therefore, the dietary intake of omega-3 fatty

acids and fish/seafood consumption in this study is relatively comparable and within the range of other population groups with depression.

The lack of associations between depression and omega-3 intake found in this cross sectional study, using a single 24-hour dietary recall, is consistent with other studies of differing design and population groups. A recent cohort study of Finnish males ages 50-69 year old with depression and low mood reported no significant dietary differences in any dietary omega-3 fatty acid intake or fish consumption compared to healthy males, as measured by a one-year food frequency questionnaire (Hakkarainen et al., 2004). Also, an earlier case control study, using 7-day weighted food records reported no significant differences in dietary omega-3 fatty acids between subjects with depression compared to healthy controls (Edwards et al., 1998). Based on a 24-hour recall and 3-day food records, a recent Japanese case control study reported no differences in dietary frequency of fish or total polyunsaturated fatty acids in subjects with and without depression (Su et al., 2003). Therefore, the current study and other literature- to -date demonstrate no significant associations between dietary intake of omega-3 fatty acids and mood, even when using different dietary measurement instruments and different population groups. Additionally, even with the range of reported dietary omega-3 fatty acid and fish intakes from these various studies, higher reported dietary intakes than were achieved in the current study were still insufficient to detect differences between those with and without mood disorders.

While this study has the advantage of being based on a nationally representative sample, there are several limitations. It is a cross-sectional design and thus cannot

provide a direct cause and effect relationship between mood disorders and intake of dietary omega-3 fatty acids or fish/seafood consumption. However, the temporal limitation of this study design did limit the ability to determine a cause-effect relationship between the reported dietary intake and the diagnosis of depression or self-reported depressive symptoms. Dietary data for this study was collected from a single 24-hour recall, such that biased reporting of intake cannot be ruled out. Even though mean intake levels of total omega-3 fatty acids are consistent with previous studies, it is more difficult to measure associations between dietary intake and mood disorders when both diet and mood were based on subjects' self-reporting. Additionally, the population used in this study does not include people who were institutionalized for major depressive disorders, a group whose pre-institutionalized diet may have been significantly different. Furthermore, selection bias may have occurred, such that those participating in this study may not be representative of the spectrum of depression from mild to severe. For example, there were no differences in dietary alcohol consumption or smoking status between those with depression and those without. Both alcohol consumption and smoking status would be expected to have some degree of influence in the relationship between dietary omega-3 fatty acids and depression. Those with depression are often more prone to misuse alcohol and smoke, which in turn could contribute to poorer dietary habits. Additionally, alcohol and smoking are associated with disruption of normal nutrient metabolism and alterations in body weight. However, excess alcohol consumption and smoking status did not vary significantly between the depressed and non-depressed subjects in this study. The selection of subjects that volunteered to

participate in the depression survey may have had mild depression. Where in the larger population as a whole, those with more severe depression would typically find it too difficult to participate in such a study without compelling incentives. Therefore, the lack of association between dietary omega-3 fatty acids and depression, in part, may be due to less variation between the group with depression and those without.

Furthermore, no biomarkers or supplement data for the omega-3 fatty acids were obtained to better clarify the relationship between dietary intake and *depression*, *sadness*, or *thoughts of death*. Several studies have reported low serum, red blood cell, and tissue levels of omega-3 fatty acids among adults with depression (Maes et al., 1996; Maes et al., 1999; Peet et al., 1998; Edwards et al., 1998; Adams et al., 1996). Biomarker data may have provided more refined information about the omega-3 fatty acid derivatives, EPA and DHA, as well as provide more confirmatory results shown with alpha-linolenic acid. As such, analyzing dietary EPA and DHA intake was difficult because of such low detection levels within the diet itself. Biomarker data may have demonstrated confirmatory low serum or tissue level EPA and DHA.

Additionally, having specific supplement usage data on EPA and DHA may have provided alternative results in these subjects with mood disorders. One could speculate that much higher dosages of total or individual omega-3 fatty acids than were achieved in this sample via diet alone may be beneficial in the management or prevention of depression. As was found in this study, a marginal proportion of subjects with mood disorders (6%) reported consuming >2 servings of fish/seafood per week which could be viewed as a form of self-medication. However, it is not known if the remaining subjects

had chosen to use supplemental omega-3 fatty acid as a form of self-medication for their mood disorder. Nor is it clear if supplemental omega-3 fatty acids were used for self-medicating purposes if or how these subjects would have responded differently on the depression questionnaire.

Several studies on depression and use of omega-3 fatty acid supplements offer more insight. When 2gm/day of DHA was administered as monotherapy in the treatment of major depression, no significant effect was shown compared to the placebo group (Marangell et al., 2003). However, when 2gm/day EPA was used as adjunctive therapy with usual depressive medication, a significant improvement was found among depressive disorder patients compared to the placebo group (Nemets et al., 2002). Peet and Horrobin (2002) also demonstrated an improvement in depressive symptoms within 4, 8, and 12 weeks of 1gm/day EPA adjunctive therapy combined with standard depressive therapy. Su et al. (2003) reported a significant improvement in depression scores among subjects receiving an adjunctive omega-3 fatty acid supplement (9.6 gm EPA + DHA/day) compared to placebo group. Su et al. also found a significant increase in red blood cell DHA after the addition of omega-3 supplementation among subjects with depression, where no differences in red blood cell DHA were found between pre- and post-treatment in the placebo group. Conversely, no evidence of an association was found between baseline mood and dietary fish or omega-3 fatty acid intake among a group of adults with depression, nor was there evidence at any time during 12 weeks that 3-g/day omega-3 fish oil supplementation improved mood in these subjects (Silvers et al.,

2005). The use of high supplemental dosages of omega-3 fatty acids or increased dietary omega-3 sources alone as a treatment for depression therefore remains equivocal.

Whether the dietary intake of omega-3 fatty acids or fish consumption alone can alter one's mood remains uncertain. It is interesting that in this study, subjects with self-reported *sadness* consumed a higher mean amount of alpha-linolenic acid compared with subjects who did not report sadness, which again may suggest these subjects were choosing omega-3 food sources for self-medicating purposes. Although, once confounding variables were accounted for, there was no longer a significant difference in alpha-linolenic acid consumption between adults with self-reported *sadness* and those without. There have been no other studies of dietary omega-3 fatty acids reporting significantly higher intakes between adults with and without mood disorders. However, the Finnish study found a small marginally elevated risk of self-reported depression in the highest tertile of fish consumption compared to the lowest (RR=1.06, 95%CI= 1.00-1.12) (Hakkarainen et al, 2004). It is difficult to compare these findings to our study since the measured fish consumption reported by Hakkarainen et al. (2004) did not present actual tertile quantities and was based on a one-year food frequency questionnaire, where our fish/seafood measurement was based on a 30-day intake. We found no significant differences between high and low fish/seafood consumption among adults with mood disorders compared to those without mood disorders. It is possible that measurement error occurred since both dietary intake and diagnosis of *depression* or self-reported *sadness* were based on self-reporting.

It is not known if the subjects in this study purposefully chose to consume higher amounts of alpha-linolenic acid as a consequence of their mood disturbance or for other health related reasons. Between 1999-2002, when this NHANES data collection took place, at least 18 separate articles on the general health benefits of fish oils and/or omega-3 fatty acids were printed in the New York Times. One specific article suggested dietary omega-3 fatty acids and fish consumption as a health benefit for those with mood disorders (Robbins, 2001). In 2000 the American Heart Association emphasized the importance of omega-3 fatty acids and fish consumption for improving cardiovascular health (Kraus et al., 2000). The most current dietary recommendations for healthy adults include eating a variety of fish twice weekly and include oils and foods rich in alpha-linolenic acid, such as flaxseed, canola oil, soybean oil, and walnuts (Kris-Etherton et al., 2006). There is a known increased risk of coronary artery disease and myocardial infarction relapse associated with depression (Kris-Etherton et al., 2006; Frasure-Smith et al., 2004; Frasure-Smith et al., 2003). Thus, it is possible this population of young adults selected to consume specific foods higher in omega-3 fatty acids due to exposure from the media and public awareness of the health benefits of dietary omega-3 fatty acids. We cannot say with certainty if higher omega-3 fatty acids are protective for depression episodes. Current dietary recommendations would indicate that an overall health benefit in at-risk populations can be achieved by increasing dietary omega-3 fatty acids and this may in turn improve mood as well.

A more comprehensive exploration into all dietary omega-3 food sources consumed by subjects with these mood disturbances would be helpful in clarifying

whether intentional self-selection of omega-3 foods occurred. And from a broader nutritional epidemiology perspective, a more detailed examination about *why* people consume certain foods would strengthen the dietary component of future NHANES studies.

In conclusion, the current reported level of dietary omega-3 fatty acids and fish/seafood consumption among young adults participating in NHANES 1999-2002 did not differ between those with and without *depression, sadness,* or *thoughts of death.* These results are consistent with results reported by several other studies of various designs and population groups (Hakkarainen et al., 2004; Edwards et al., 1998; Su et al., 2003). However, studies suggest EPA and DHA may play a role when coupled with mood disorder medication.

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Table 1: Odds Ratios and 95% Confidence Intervals for associations between Depression and Omega-3 fatty acids among adults 20-39 years old[a]

Nutrient*	Depression YES Mean (SE)	Depression NO Mean (SE)	p	Crude OR (95% CI)	p	Adjusted OR** (95% CI)	p
Pufa 18:3 (ALA)	1.67 (.15)	1.40 (.04)	.08	1.31 (0.74-2.32)	.35	1.60 (.86-2.99)	.13
Pufa 20:5 (EPA)	0.03 (.00)	.03 (0.0)	.23	1.04 (.97-1.12)	.24	1.04 (.96-1.14)	.34
Pufa 22:6 (DHA)	0.07 (.01)	.06 (0.0)	.88	1.01 (.88-1.16)	.88	1.00 (.81-1.22)	.97
omega-6: omgea-3 ratio	11.2 (.53)	10.57 (0.1)	.42	1.02 (.98-1.05)	.23	1.01 (.97-1.07)	.48
Total omega-3	1.77 (.15)	1.50 (0.0)	.07	1.31 (.83-2.07)	.24	1.26 (.97-1.65)	.09

a Results based on weighted analysis of 1554 subjects

***** Omega-3 Fatty Acids reported as log transformed

** All models adjusted for the following potential confounding variables: kcalories, gender, age group (20-29, 30-39), BMI group (underweight, appropriate weight, overweight, obese), race/ethnicity, education status, family poverty income ratio, smoking status, alcohol intake, dietary cholesterol, serum cholesterol, serum HDL, and glycohemoglobin.

Table 2: Odds Ratios and 95% Confidence Intervals for associations between Sadness and Omega-3 fatty acids among adults 20-39 years old[a]

Nutrient*	Sadness YES Mean (SE)	Sadness NO Mean (SE)	p	Crude OR (95%CI)	p	Adjusted OR** (95%CI)	p
Pufa 18:3 (ALA)	**1.62 (.10)**	**1.4 (0.0)**	**.03**	1.30 (0.94-1.80)	.11	1.33 (.86-2.05)	.19
Pufa 20:5 (EPA)	0.04 (.00)	.03 (0.0)	.47	1.02 (.97-1.08)	.47	1.01 (.94-1.08)	.83
Pufa 22:6 (DHA)	0.08 (.01)	.06 (0.0)	.73	1.02 (.92-1.12)	.73	1.02 (.87-1.19)	.83
omega-6: omega-3 ratio	10.5 (.26)	10.64 (0.1)	.68	.99 (.97-1.02)	.61	.99 (.97-1.03)	.93
Total omega-3	1.74 (.11)	1.47 (0.0)	**.03**	1.31 (.94-1.83)	.11	1.20 (.99-1.45)	.06

a All results based on weighted analysis of 1554 subjects

***** Omega-3 Fatty Acids reported as log transformed

** All models adjusted for the following potential confounding variables: kcalories, gender, age group (20-29, 30-39), BMI group (underweight, appropriate weight, overweight, obese), race/ethnicity, education status, family poverty income ratio, smoking status, alcohol intake, dietary cholesterol, serum cholesterol, serum HDL, and glycohemoglobin.

Table 3: Odds Ratios and 95% Confidence Intervals for associations between Thoughts of Death and Omega-3 fatty acids among adults 20-39 years old[a]

Nutrient*	Thoughts of Death YES Mean (SE)	Thoughts of Death NO Mean (SE)	p	Crude OR (95%CI)	p	Adjusted OR** (95%CI)	p
Pufa 18:3 (ALA)	1.70 (.22)	1.5 (0.1)	.41	1.46 (0.75-2.83)	.26	.41 (.09-1.89)	.24
Pufa 20:5 (EPA)	0.03 (.01)	.04 (0.0)	.94	1.00 (.90-1.10)	.94	.92 (.79-1.08)	.30
Pufa 22:6 (DHA)	0.07 (.02)	.07 (0.0)	.49	1.06 (.89-1.27)	.50	.82 (.56-1.20)	.30
omega-6: omega-3 ratio	11.3 (.69)	10.8 (0.4)	.55	1.02 (.95-1.11)	.54	1.05 (.96-1.16)	.29
Total omega-3	1.79 (.23)	1.6 (0.1)	.47	1.38 (.71-2.67)	.33	.51 (.22-1.24)	.13

a Results based on weighted analysis of 1554 subjects

***** Omega-3 Fatty Acids reported as log transformed

** All models adjusted for the following potential confounding variables: kcalories, gender, age group (20-29, 30-39), BMI group (underweight, appropriate weight, overweight, obese), race/ethnicity, education status, family poverty income ratio, smoking status, alcohol intake, dietary cholesterol, and glycohemoglobin.

Table 4: Odds Ratios and 95% Confidence Intervals for associations between Altered Mood Disorder[a] and Omega-3 fatty acids among adults 20-39 years old

Nutrient*	Altered Mood YES Mean (SE)	Altered Mood NO Mean (SE)	p	Crude OR (95%CI)	p	Adjusted OR** (95%CI)	p
Pufa 18:3 (ALA)	**1.59 (.09)**	**1.40 (.04)**	**.05**	1.24 (.89-1.72)	.19	1.35 (.88-1.99)	.17
Pufa 20:5 (EPA)	.04 (.01)	.03 (.00)	.18	1.01 (.96-1.07)	.61	1.00 (.93-1.07)	.95
Pufa 22:6 (DHA)	.07 (.01)	.06 (.01)	.28	1.01 (.92-1.11)	.85	1.01 (.87-1.18)	.83
omega-6 : omega- 3 ratio	10.7 (.30)	10.6 (.13)	.61	1.01 (.98-1.03)	.60	1.00 (.97-1.04)	.80
Total omega-3	1.70 (.10)	1.48 (.04)	**.05**	1.24 (.89-1.75)	.19	1.19 (.99-1.43)	.06

a total mood disorder represents YES to self-reported sadness, thoughts of death, or diagnosed depression

***** Omega-3 Fatty Acids reported as log transformed

** All models adjusted for the following potential confounding variables: kcalories, gender, age group (20-29, 30-39), BMI group (underweight, appropriate weight, overweight, obese), race/ethnicity, education status, family poverty income ratio, smoking status, alcohol intake, dietary cholesterol, serum cholesterol, serum HDL, and glycohemoglobin.

APPENDIX C. MISREPORTING OF ENERGY INTAKE IN ADULTS WITH DEPRESSION, SADNESS, AND THOUGHTS OF DEATH

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Key Words: Diet, Underreporting, NHANES, Depression, Mood

Appendix C 1. Body of Paper

Misreporting of energy intake in adults with depression, sadness, and thoughts of death

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ABSTRACT:

Background: Misreporting of dietary intake is problematic when studying relationships between nutrition and disease. Depression is frequently associated with poor appetite and symptoms of depression may be associated with poor dietary intake. The present study explored whether having depression or depressive symptoms was associated with misreporting energy intake.

Methods: Subjects were 1554 nationally representative males and females, ages 20-39 years, who participated in the 1999-2000 and 2001-2002 National Health and Nutrition Examination Survey. Both underreporting and overreporting of energy intake based on 24-hour recall were used to classify subjects as misreporters. Mean ratios of energy intake to estimated basal metabolic rate (EI:BMR_{est}) were calculated separately for population subgroups based on age, gender, mood status and body mass index (BMI) level. Stepwise multiple logistic regression models, stratified by gender, were used to

examine the relationship of misreporting energy intake to altered mood. Linear regression was used to assess a relationship between the ratio EI:BMR_{est} and mood and BMI status..

Results: Among those with altered mood, 25% reported plausible energy intakes, 45% underreported, and 30% overreported. Misreporting of energy intake was not significantly associated with altered mood status in young adult males or females. Among women, a significant interaction between mood status and appetite change was associated with underreporting ($p < .05$). Regardless of mood status or gender, the ratio of EI:BMR_{est} significantly decreased as BMI increased ($p < .001$). A non-significant increase in the mean EI:BMR_{est} occurred with the obese group who had altered mood.

Limitations: Use of a single 24-hour recall to assess energy intake may not be representative of habitual intake in a group of individuals with depression or depressive symptoms. Estimating basal metabolic rate may not be sufficient to capture the true energy expenditure in a young population when physical activity level is not know and weight stability is self-reported.

Conclusions: From a public health and clinical standpoint, the finding that young adults with altered mood are not more prone to dietary misreporting than healthy adults is important. While dietary misreporting is problematic, studying dietary intake, dietary habits, and nutritional status can be done with individuals who have altered mood with the same precision (or lack thereof) as can be done in a healthy population.

INTRODUCTION:

The burden of major depressive disorder can be chronic and episodic, requiring lifestyle changes and self- management skills. It is important to examine possible relationships between lifestyle choices and depression. The relationship of diet and depression is of interest, given that diet may provide a cost effective approach to reducing the financial burden of depressive disorder. It is possible that depression may contribute to an overall decline in nutritional status. Symptoms of depression, such as dysphoric mood or thoughts of suicide, may be associated with dietary factors and depression itself is frequently associated with poor appetite and reduced motivation (Carpenter et al., 2000; McElroy et al., 2001; Cohen et al., 2002). An abnormal appetite and poor quality of food intake could result in a further decline in overall nutritional status. However, current data on diet and depression are equivocal.

Several reports suggest that major depression may be associated with specific macro- and micro- nutrient inadequacies, such as lower omega-3fatty acids, folate, vitamin B12, selenium, and zinc, higher total fat and cholesterol, and higher or lower carbohydrate (Hakkarainen et al., 2005; Hvas et al., 2004; Hibbeln, 1995; Hintikka et al., 2003; Westover and Marangell, 2002; Carney, 1990; Coppen and Bailey, 2000; Coppen and Bolander-Gouaille, 2005; Sarlio-Lahteenkorva et al., 2004;Van der Does, 2001). Therefore, medical nutrition therapy may provide a pivotal role in the management and/or prevention of major depression. In order for medical nutrition therapy to be effective for individuals with depression, accurate assessment of energy and nutrient intake are essential. Misreporting of dietary intake, such as under- or over- reporting, is considerably problematic when trying to assess the dietary habits within a population

group, even among those that are relatively healthy. Since changes in appetite, changes in weight status, and obesity are commonly associated with altered mood; there is a concern that an accurate report of dietary intake may be more difficult to obtain from individuals experiencing depression or depressive symptoms.

The primary objective of this study was to determine if differences in reporting energy intake occur between young adults with and without depression, self-reported sadness, or self-reported thoughts of death. It was hypothesized that adults with altered mood (depression, self-reported sadness, or self-reported thoughts of death) would be more prone to misreporting energy intake compared to healthy adults. A secondary objective was to evaluate physiological and non-physiological characteristics that might affect the association between depression and under- or over-reporting in this population.

METHODS

Study Sample

The subjects were a nationally representative sample of males and females age 20-39 years old who participated in the 1999-2000 and 2001-2002 National Health and Nutrition Examination Survey (NHANES 99-02). These NHANES data were derived from a national probability sample of the civilian non-institutionalized US population from 1999-2002 using a 2-stage cluster design (NHANES ref manual[d,e]). The total eligible sample of subjects who completed both the Composite International Diagnostic Interview for Major Depression and the 24-Hour Dietary Recall consisted of 1554 individuals. The sample included subjects who identified themselves within the following race/ethnicities: Mexican-American, Other Hispanic, Non Hispanic White, Non Hispanic Black, African-American, and Other/Multiracial.

Measurements

Diet and Anthropometric Data: Energy measured as total kilocalories (kcal) was collected using an in-person 24-hour recall questionnaire administered by trained personnel. Extreme values were found in the kcal variable, therefore the 24 observations with values <500 kcal/day and >6000 kcal/day were recoded to missing. Energy in kcal was converted into megajoule (mjoule) measurement for use in the energy: basal metabolic ratio formulas (EI:$BMR_{est)}$.

Anthropometric data were collected at the mobile examination centers (MEC) during the NHANES data collection process and included body mass index (BMI), height, and weight. Based on standard BMI categories, a variable BMI group was created representing BMI cutpoints for *underweight* (BMI <18.5), *appropriate weight* (BMI =18.5 –24.9), *overweight* (BMI= 25.0-29.9), and *obese* (BMI >=30.0) (DHHS-CDC ref guide).

Total Mood/Altered Mood: The outcome variable *total mood* was derived to include subjects with a positive (*yes)* response to any one of the three indicator variables: *depression, sadness*, or *thoughts of death* as determined by The World Health Organization (WHO) Composite International Diagnostic Interview, Version 2.1 (CIDI) (NHANES ref manual[b,c]). The CIDI is a comprehensive and standardized interview used to assess and provide a diagnosis of major depression and is in accordance to the criteria and definitions of major depression by the ICD-10 (10th revision of the International Classification of Disease, World Health Organization 1992, 1993) and DSM IV (Fourth edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (1994). The three indicator variables, *depression score, sadness*, and

thoughts of death, were all dichotomous variables measured by a yes or no response. *Depression score* was the composite final score as determined by responses to the full CIDI questionnaire. *Sadness* was based on the first question on the CIDI questionnaire regarding sadness, emptiness, or depression reported over a two-week period. *Thoughts of death* was based on the first question in a series of questions in the CIDI questionnaire related to thoughts of death and suicide. The CIDI questionnaire assessed depressed and symptoms of depression within the previous 12 months prior to the interview.

Laboratory: Nutritional biochemistry data were collected at the MEC during the NHANES data collection. Detailed methodology of laboratory data collection can be found in the NHANES 1999-2002 documentation manuals for laboratory procedures (NHANES ref manual[d,e,f]). The laboratory data included in this analysis were consistently measured in the 1999-2000 and 2001-2002 NHANES collections.

Other Relevant Variables: Data from the NHANES 1999-2002 demographic questionnaires used in the current analysis included gender, age, race/ethnicity, poverty income ratio, education, marital status. The variable age was categorized into two groups: 20-29 years old and 30-39 years old. The variable marital status was collapsed into three groups: married and living with partner, previously married (widowed, divorced, separated), and never married. To determine smoking status, a cutpoint of >=15ng/mL serum cotinine was used to determine smokers and < 15ng/mL determined non-smokers (Bernert pers. comm., 2005; Caraballo pers. comm., 2005; SRNT, 2002). The variable appetite change included any subjects who reported an increase or decrease in their appetite from the CIDI questionnaire for major depression. The variable weight change

included any subject who reported an increase or decrease in weight from the CIDI questionnaire for major depression.

Study Design: Classifying misreporters and plausible reporter status.

Three categories were created to classify reporting of energy intake: plausible reporters (PR), underreporters (UR), and overreporters (OR). To determine misreporting, a ratio of reported energy intake (EI) to estimated basal metabolic rate (BMR_{est}) was calculated. Reported energy intake was derived from a single 24-hour dietary recall. Estimates of basal metabolic rate were calculated using age and gender specific formulas derived by Schofield (1985). The following formulas were used:

Males 20-29	0.063 * (weight) - 0.042 * (heightm) + 2.953
Males 30-39	0.048 * (weight) - 0.011 * (heightm) + 3.670
Females 20-29	0.057 * (weight) + 1.184 * (heightm) + 0.411
Females 30-39	0.034 * (weight) - 0.006 * (heightm) + 3.530

Misreporting was then defined by using Black's gender and age specific Goldberg and PAL cutoffs (Black, 2000; Goldberg et al., 1991):

a) *underreporters*
- Male 20-29 EI:BMR_{est} < 1.52
- Male 30-39 EI: BMR_{es} < 1.46
- Female 20-29 EI: BMR_{es} < 1.42
- Female 30-39 EI: BMR_{es} < 1.43

b) *plausible reporters*
- Male 20-29 EI:BMR_{est} ≥ 1.52-2.18
- Male 30-39 EI:BMR_{est} ≥ 1.46-2.08
- Female 20-29 EI:BMR_{est} ≥ 1.42-1.98
- Female 30-39 EI:BMR_{est} ≥ 1.43-1.93

c) *overreporters*
- Male 20-29 EI:BMR_{est} >2.18
- Male 30-39 EI:BMR_{est} >2.08
- Female 20-29 EI:BMR_{est} >1.98
- Female 30-39 EI:BMR_{est} >1.93

Statistical Analysis

Statistical differences between mean levels of energy and BMR were tested using two-sided *t*- tests. Mean ratios of energy intake to estimated basal metabolic rate ($EI:BMR_{est}$) were calculated separately for population subgroups based on age, gender, mood status and body mass index (BMI) level.

Stepwise multiple logistic regression models, stratified by gender, were used to examine the relationship of misreporting energy intake to altered mood. The following potential confounding variables were tested in the logistic regression models: age group, BMI group, reported weight change, reported appetite change, race/ethnicity, education, marital status, poverty level, smoking status, alcohol intake, serum cholesterol and plasma glycohemoglobin. Linear regression was used to assess the relationship between $EI:BMR_{est}$ and mood status. Linear regression was used to detect a trend across BMI groups (underweight, appropriate weight, overweight, obese). All continuous variables were examined for normality. Natural log transformations were performed for skewed data which including serum cholesterol and glycohemoglobin. All analyses were performed using weighted sample analysis following NHANES analytical guidelines.

Results were interpreted using a significance level of p-value < 0.05. All statistical analysis was performed using Intercooled Stata 8.0 (Stata Corporation, College Station, TX).

RESULTS:

Ratio of Energy Intake to Estimated Basal Metabolic Rate by Mood Status

Mean $EI:BMR_{est}$ was 1.47 (.02) overall, 1.34 (.03) for men and 1.59 (.03) women. Mean $EI:BMR_{est}$ decreased with age in males, but not in females. Overall, women had

significantly higher mean EI:BMR_{est} than males ($p < .001$). The mean EI:BMR_{est} was not significantly different between subjects with and without altered mood (Table 1). No differences were found in the mean EI:BMR_{est} stratified by mood status and age group. The mean EI:BMR_{est} was significantly higher in women compared to men with normal mood ($p< .001$), but no significant difference in the mean EI:BMR_{est} was found between genders in the altered mood group.

Ratio of Energy Intake to Estimated Basal Metabolic Rate by BMI Category

When stratified by BMI category, underweight (BMI<18.5), normal weight (BMI 18.5 to 24.9), overweight (BMI 25.0-29.9) and obese (BMI≥30.0), mean EI:BMR_{est} decreased as BMI increased, with the obese group having a slightly higher mean EI:BMR_{est} for all women with altered mood and males 30-39 years old with altered mood (Table 2-3). For the obese women, the mean EI:BMR_{est} was not significantly different from the mean EI:BMR_{est} of the overweight women.. The mean EI:BMR_{est} in the obese males age 30-39 years old was significantly higher than the same age overweight males ($p < .05$). There was a significant negative association for the mean EI:BMR_{est} for each BMI group. There was a significant linear trend in the normal mood group where the mean EI:BMR_{est} decreased as BMI increased for each gender, age group, with no increased mean EI:BMR_{est} in the obese group.

Misreporting of Diet: Summary Statistics

Thirty-six percent of women with altered mood and 41% of women with normal mood were classified as underreporters, using EI:$BMR_{est} < 1.42$ as the cutoff value

(Table 4-5). Thirty-eight percent of women with altered mood and 37% of women with normal mood were classified as overreporters, using EI:BMR_{est} >1.93 as the cutoff value. Fifty-three percent of men with altered mood and 57% of men with normal mood were classified as underreporters, using EI:BMR_{est} < 1.46 as the cutoff value. Twenty-three percent of men with altered mood and 20% of men with normal mood were classified as overreporters, using EI:BMR_{est} > 2.08 as the cutoff value. There were no significant differences between mood status groups for misreporting or plausible reporting based on marital status, poverty level, education status, or race/ethnicity (Table 5).

Compared to plausible reporters, a significantly higher proportion of males with altered and normal mood were underreporters (53%, $p < .001$ and 57%, $p < .001$, respectively). Compared to plausible reporters, and a significantly lower proportion of those with altered mood were smokers (33.5%, $p < .05$). No other significant differences were found between misreporting and plausible reporting among those with altered mood.

There were no significant differences in the proportion of those who misreported or gave plausible reports between the mood status groups for each BMI category (Tables 6-9). The highest proportion of underreporting in women age 20-29 years old occurred in the overweight and obese group, where 90.5% of overweight women with altered mood in this age group underreported. The proportion of underreporters was fairly consistent across BMI groups and mood status for women age 30-39 years old (26-46%). Among women who were underweight with normal mood, about 73% and 56% of those age 20-29 years old and 30-39 years old, respectively, overreported energy intake. While, 54%

of obese women age 30-39 years old also were overreporters. For men in both age groups the highest proportion of misreporting occurred as underreporting. Greater than 50% of males age 20-29 years old underreported energy intake in all BMI groups and mood status groups (52 –73 %), except males who were underweight with normal mood and normal weight with altered mood. Greater than 50% of males age 30-39 years old underreported energy intake in all BMI groups and all mood status groups (53- 81%), except males who were underweight in either mood status group.

Misreporting of Energy Intake and Altered Mood: Multivariate Approaches

Logistic Regression of Misreporting Status:

Logistic regression analyses were used to determine if those with altered mood misreport energy intake to a greater extent than those with normal mood after adjusting for confounding or factors found significant in bivariate analyses. Stepwise logistic regression was used in separate analyses for men and women. No significant associations were found between misreporting (either under- or over-reporting) and altered mood for males and females (Table 10). Non-significant odds ratios remained after adjusting for the confounding variables, poverty income ratio, appetite change, BMI status, education, and alcohol intake. Among women, a significant interaction was found between mood status and self -reported appetite change associated with underreporting compared to plausible and overreporting (interaction OR = .12, 95% CI= .02-.62, $p < .05$). Approximately 76% of women with normal mood and reported appetite change were classified as underreporters compared to 30% of women with altered mood and reported appetite change. The proportion of women with no appetite change did not differ by

mood status. No significant interaction terms between mood status and self-reported appetite change were found among men. No significant interaction of mood status and self-reported appetite change was found associated with overreporting in either gender. No other significant interactions were found with mood status.

Multiple Linear Regression of EI:BMR_{est} as a Continuous Variable

The relationship between altered mood status and the continuous ratio of EI:BMR_{est} was determined using a series of multiple linear regression models. The ratio of EI:BMR_{est} was not significantly associated with altered mood in either males or females and after adjusting for confounding variables. A significant negative association was found between the ratio of EI:BMR_{est} and BMI for both males (β = -.03, 95% CI= -.04-.-.02, p<.001) and females (β = -.04, 95% CI= -.04-.-.03, p<.001) with altered mood. Underreporting status was inversely associated with the ratio of EI:BMR_{est} (β = -1.05, 95% CI= -.1.10-.99, p<.001). Overreporting was significantly associated with the ratio of EI:BMR_{est} in both males (β = 1.28, 95% CI= .98-1.58, p<.001) and females (β = 1.12, 95% CI= .97-1.27, p<.001) with altered mood. There was a non-significant relationship between EI:BMR_{est} and the interaction of mood status by BMI group. The non-significant relationship was present when tested in the total sample and stratified by gender and age group. There was a significant interaction between mood status and self-reported appetite change associated with EI:BMR_{est} among women (β = .44, 95% CI= .09-.80, p<.001).

DISCUSSION

Regardless of mood status, considerable misreporting, particularly underreporting, of energy intake occurred among all subjects. From the total sample, 48% underreported, 29% overreported, and 23% reported plausible energy intake. Examination by gender revealed differences in reporting between women and men, such that a higher proportion of women overreported and a higher proportion of men underreported energy intake, with similar proportions of men and women reporting plausible energy intake. Similarly, women had higher mean EI:BMR_{est} compared to men. These results conflict with previous reports by Briefel et al. (1997) who examined misreporting in NHANES III and found higher mean EI:BMR_{est} in men. The finding that in men, the mean EI:BMR_{est} decreased with age was consistent with previous results from NHANES III misreporting studies (Briefel, 1997). It is possible that the conflicting results with NHANES III reports was due to use of higher cutoff values for classifying underreporting in this study and a younger population was used in this study.

Interestingly, among women with normal mood, reported appetite change had more effect on underreporting than among women with altered mood. Possibly women with normal mood and reported appetite change are more susceptible to misreporting because of perceived negative evaluation or social desirability than those with altered mood. For women with altered mood, appetite change may be a symptom of their mood status and not perceived as influential on dietary reporting.

The proportion of misreporting in this study appears to be higher than often reported in the literature. Comparisons with other reports of underreporting may vary as a

result of population characteristics, sample size, and differences in measurements of energy intake and/or energy expenditure. Furthermore, the accuracy of reporting is contingent upon many factors. Psychosocial factors that interfere with accuracy of dietary reporting include fear of negative evaluation, social desirability, and restrained or disinhibited eating behaviors (Tooze et al., 2004). Also, characteristics of the diet influence dietary reporting; such as the number of meals or snacks eaten, percentage of energy from fat, and eating out, which may contribute to misreporting. Lifestyle factors, such as smoking, and sociodemographic factors such as gender, age, and education, each play a role in the accuracy of reporting (Tooze et al., 2004). Among post-menopausal women age 50-79 years old, BMI was not associated with underreporting, but greater social desirability was associated with underreporting (Horner et al., 2002). Subar et al. (2003) classified underreporting in 21% of men and 22% women based on 24-hour recalls. However, the prevalence of underreporting among these same subjects was 50% of men and 49% of women based on food frequency questionnaire (Subar et al., 2003). Only 1% of women and 1.6% of men were classified as overreporters. In contrast, Novotny et al. (2003) reported high proportions of energy misreporting among healthy men and women age 25-73 years old from measurement of a 24-hour recall compared with energy expenditure measured by doubly labeled water or intake balance method. Eighty-five percent of women and 61% of men underreported their energy intake by an average of –621 kcal/day and –581 kcal/day, respectively (Novotny et al., 2003). Overreporting was identified in 15% of women and 39% of men (Novotny et al., 2003). Energy misreporting was significantly and negatively correlated with percent body fat

and significantly more women were classified as underreporters compared to men, but no other physical characteristics were correlated with misreporting. Among a highly educated sample, underreporting increased as BMI increased and as the total energy expenditure measured from doubly labeled water increased, so did underreporting of energy intake (Subar et al., 2003). For men, memory recall was a predictor of misreporting and among women; social desirability predicted misreporting (Novotny et al., 2003). The most important factors related to underreporting were differences in ideal body weight, memory, and attempted weight loss during the previous year (Novotny et al., 2003). Therefore, the high prevalence of misreporting from this NHANES study may have been related to factors that were not measured in the analysis, such as weight history, weight loss attempts, social desirability, and perceptions of body image. Poor memory as a consequence of altered mood may have played a role in misreporting, particularly among males, in this study as well.

As would be expected, both males and females who had a BMI that classified them as overweight or obese were found to have the lowest mean EI:BMR_{est} values. Interestingly, those with altered mood and obesity had a higher mean EI:BMR_{est} than those who were overweight. The increase in mean EI:BMR_{est} did not occur with obesity in the normal mood group. Yet, there was no significant interaction between BMI group and altered mood that would have supported the increased mean EI:BMR_{est} found in the obese plus altered mood group.

Additionally, in obese females with altered mood, the proportion of underreporting was lower than that of the overweight females. In obese males with

altered mood, the proportion of underreporting was lower than the overweight group only in those males age 30-39 years old. While there was underreporting among those with obesity and altered mood, there is question as to why they seemed to underreport less than the overweight group.

Since the relationship between diet and mood is reciprocal (Cohen et al., 2000; Allgöwer et al., 2001), it is possible that the group of obese adults with altered mood found the task of reporting accurate and honest dietary intake more challenging. Depression is common in people seeking treatment for obesity (Carpenter et al., 2000; McElroy et al., 2004). Overeating, decreased physical activity, and weight gain are common symptoms for both depression and obesity (McElroy 2004). Obesity plus depression may alter serotonin levels and therefore, affect appetite response (McElroy et al., 2004). Additionally, obesity is often associated with insulin resistance, which also can lead to an increase in feelings of hunger. Medications used in treating depression may cause an increase in appetite and subsequent weight gain (McElroy et al., 2004); therefore it is possible the obese group was overeating more than the overweight group so that the degree of underreporting was not as evident. Another possible explanation could be if the obese group used medications for weight loss, than the lower proportion of underreporting among the obese group compared to the overweight group would be understandable if the result was a true lower energy intake among the obese group. Without biomarkers to more accurately assess energy expenditure it is unclear if this group of obese plus altered mood possibly had lower or higher energy expenditure than was estimated (Macdiarmid and Blundell, 1998; Price et al., 1997). Furthermore, the

obese group with altered mood may have experienced more body weight cycling, which could affect the accuracy of the estimated basal metabolic rate.

It is possible that the lower proportion of underreporting by the obese group with altered mood was simply due to consumption of more food overall or higher caloric foods during the reported 24 hours of intake. Cohen et al. (2002) showed that having modest symptoms of depression was associated with unhealthful dietary practices, such as binge eating and unhealthful weight control practices. It could be speculated that the status of being obese coincided with more frequent attempts at dieting and in turn, contributed to a more distressful mood status as well (Needham and Crosnoe, 2005). Eating behaviors such as dietary restraint and disinhibition may be an underlying explanation for the differences in the proportions of underreporting between the obese and overweight groups. These behaviors were not measured in the present study, conjecture might suggest that if the overweight group engaged in more dietary restraint and the obese group practiced more dietary dishinbition, then the differences in the proportions of underreporting would seem reasonable. It may be that this group of obese adults with altered mood, more than other groups, misreported energy intake regarding foods with a negative health image (Macdiarmid and Blundell, 1998). For example, people with depression have been reported to more often skip breakfast, eat fish less often, and eat less fresh fruits and vegetables (Sarlio-Lahteenkorva et al., 2004; Allgöwer 2001). Also, it is possible that the obese group with altered mood had more "atypical depression" whereby they experienced an increased appetite and weight gain (McElroy et al., 2004). Therefore, it could be surmised that this group of adults with obesity and altered mood

may have poorer eating habits than their counterparts and opt to conceal their true dietary intake because of social desirability (Macdiarmid and Blundell, 1998; Taren et al., 1999). It appears in this study that the combination of obesity and altered mood presented a unique challenge and deserves further investigation.

Also noteworthy was the considerable underreporting among males 30-39 years old with normal weight. Contrary to our findings, other studies have demonstrated less underreporting among men than women and particularly younger men being less apt to under estimate intake than younger women (Johnson et al., 1994; Price et al., 1997). Since underreporting of energy intake by males included normal weight males, a higher BMI status alone cannot fully account for the underreporting among men in this study. The underreporting among men could be due to a variety of factors, such as weight status, ability to recall diet, appropriate application of cutoffs, and physical activity level, and smoking status. The use of a single 24-hour recall with this NHANES data set limits our ability to verify if males underreported due to 1) lack of knowledge regarding portion sizes or food preparation, 2) recall day not "typical", or 3) purposefully choosing to report perceived "appropriate" foods. A lower cutoff for classifying underreporting, as has been used in other NHANES studies (Briefel et al., 1997), may have yielded a lower proportion of underreporting from males in this study. Activity level was not measured or included in the estimation of energy expenditure. Depending on the amount of physical activity regularly performed, the true energy expenditure could have been greatly distorted as compared to what was estimated, thus contributing to bias in the degree of misreporting detected. Therefore, if this group of young males were more

physically active or had a large amount of muscle mass, their energy expenditure would be higher than what was estimated, in turn making a large proportion of normal weight males appear as if they were more prone to underreporting.

Regardless of mood status, both younger and older, underweight, women overreported energy intake. Much less overreporting occurred among the men across all BMI groups and regardless of mood status. There are several reasons for the large proportion of overreporters among the underweight women. It is possible that the women classified as overreporters, were physcially active and/or had more muscle mass, in which case they may have genuinely consumed larger quantities of food or higher caloric foods. Similar to the obese group, it may be that women who were underweight were attempting to give a record of foods consumed that was 1) perceived to be more healthful, 2) more socially desirable, and/or 3) less revealing of possible eating restraint or disordered eating habits. Interestingly, in women, the significant association between underreporting and the interaction between altered mood and self-reported appetite change likely played a role in the overall picture of misreporting and why a significant difference in the proportion of overreporting was found in women compared to men. The odds ratio of .12 for the interaction indicates that for women with altered mood and appetite change the likelihood of underreporting was quite low. Given the degree of misreporting that was found both among women and men, by BMI status, and no overall differences found by mood status, it appears that in this study the validity of self-reported energy intake was a limiting factor.

Accurate assessment of habitual intake and energy expenditure are fundamental in the ability to estimate the ratio of energy intake to basal metabolic rate and in determining reporting status. In this study, BMR was estimated based on standard age and gender calculations but it was not measured or validated by biomarkers, such as doubly labeled water or calorimetry measurements. In the present study, extreme values of reported energy intake (<500 kcal/day and >6000 kcal/day) were not included in the analysis as a concern that they would misrepresent the degree of under- or over -reporting found, that these values were not likely representative of habitual intake, and that these values were more likely measurement error or due to poor recall ability by these subjects. Furthermore, these extreme values were more than a 10% difference of the mean total energy, which has been shown to contribute to bias in misreporting (Black and Cole, 2001). Verification of these extreme values could not be established based on measuring dietary intake by a single 24-hour recall. However, the use of a 24-hour recall can be sufficient when comparing group differences to determine if medical, health, or disease state are associated with misreporting (Livingstone and Black, 2003), as was the objective of this study.

It has been suggested that a group of randomly selected, possibly less motivated sample, such as selected for NHANES, maybe more likely to overestimate the amount of underreporting compared to a group of self-selected subjects (Johnson et al., 1994). The accuracy of the dietary intake data is dependent on the subject's short-term memory and correct quantification of amounts of foods consumed (Buzzard, p.50-73, 1998; Willet, 1998). Poor concentration and motivation are common symptoms of depression, making

the task of dietary recall possibly more challenging in subjects with depressive symptoms or altered mood. If eating patterns are inconsistent due to altered mood, the ability to accurately recall food intake may also lead to measurement error. Yet, no differences in misreporting were found between those with and without altered mood. This suggests that young adults with depression, self-reported sadness, or self-reported thoughts of death were not impaired by their mood status and as likely to misreport energy intake, as were those adults without altered mood.

Estimates of misreporting vary across studies based on cutoff values used. The cutoffs used in this study were based on gender and age specific cutoffs assuming a sedentary lifestyle. The intent of this paper was to examine differences in energy reporting status between those with and without altered mood. Using alternative cutoffs may have generated more classification of misreporting by all subjects, but it does not appear that using a more conservative cutoff would have yielded significant differences in reporting status between the mood groups.

Understanding the relationship between dietary intake and mood has important public health and clinical implications. Change in appetite is a common symptom of depression, obesity and depression often occur concomitantly and planning or preparing meals could be affected by mood status. A corresponding increase or decrease of energy intake and/or weight change could negatively affect treatment outcomes for individuals with altered mood. Additionally, a change in dietary intake among those with altered mood could result in a decline in nutritional status thus, further compromising the overall

health of these individuals. Therefore, in order to ascertain how dietary intake is associated with mood, accurate measurement and assessment of dietary intake is needed.

Misreporting of energy intake is a concern in self-reported dietary intake studies, particularly when relying on a single 24-hour recall for dietary assessment, as was used in the present study. It is possible that among those individuals with altered mood, underreporting of energy intake in part may have occurred due to forgetfulness or poor concentration because of low mood, rather than deliberately reporting a reduction or modification of intake. However, in this study, without a repeated dietary collection measure, it was not possible to elucidate whether forgetfulness, poor concentration, or deliberate misreporting occurred in the subjects with altered mood. Only among women was underreporting associated with the interaction between altered mood and self-reported change in appetite. Furthermore, few other significant differences were found in reporting of dietary intake between those adults with and without altered mood. Overall, mean EI: BMR ratios were not significantly different based on mood status, therefore it appears adults with altered mood are similar to those without altered mood in ability to report energy intake related to their estimated energy expenditure. From a public health and clinical standpoint, the finding that young adults with altered mood are not more prone to dietary misreporting than healthy adults is important. This demonstrates that, while dietary misreporting is problematic, studying dietary intake, dietary habits, and nutritional status can be done with individuals who have altered mood with the same precision (or lack thereof) as can be done in a healthy population.

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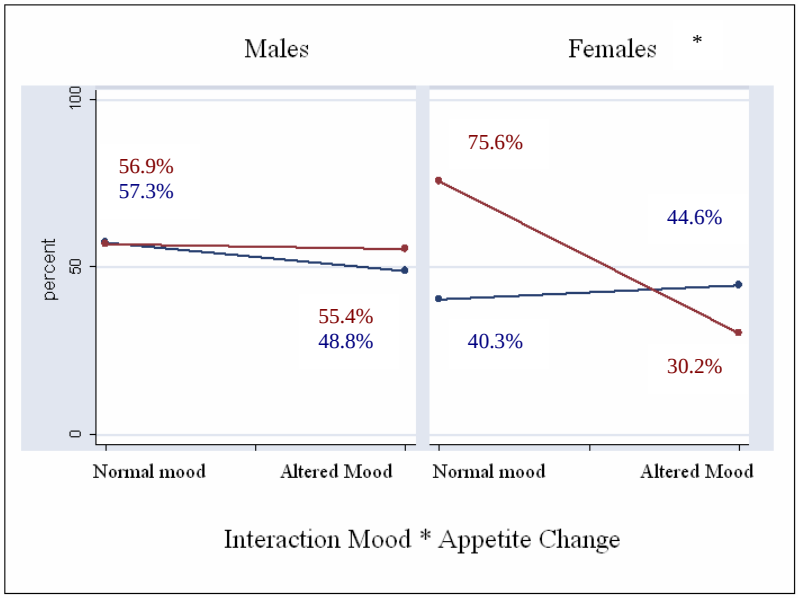
Graph 1. Interaction between mood status and appetite change effect on proportion of underreporting among males and females age 20-39 years old from NHANES 1999-2002.



Appetite Change (Yes)

Appetite Change (No)

* Significant interaction, p <. 05

Table 1. Mean (SE) ratio of energy intake to estimated basal metabolic rate ($EI:BMR_{est}$)

	Normal Mood	Altered Mood	p
Male			
20-29 years old	1.34 (.04)	1.46 (.12)	.35
30-39 years old	1.30 (.10)	1.43 (.10)	.24
Total	1.32 (.08)[a]	1.45 (.08)	.16
Female			
20-29 years old	1.58 (.06)	1.53 (.10)	.73
30-39 years old	1.62 (.09)	1.59 (.09)	.78
Total	1.60 (.04) [a]	1.56 (.06)	.67
Total Sample	1.46 (.03)	1.50 (.06)	.57

a. Significantly different p<. 001

Table 2. Mean (SE) ratio of energy intake to estimated basal metabolic rate ($EI:BMR_{est}$) among males stratified by age and BMI status

	Normal Mood	Altered Mood	p
Age 20-29			
Underweight	1.75 (.12)	2.02 (.35)	.47
Normal weight	1.56 (.09)	1.59 (.14)	.88
Overweight	1.19 (.07)	1.22 (.21)	.91
Obese	1.00 (.06)	.87 (.11)	.30
Age 30-39			
Underweight	1.74 (.15)	1.89 (.17)	.50
Normal weight	1.27 (.05)	1.26 (.09)	.89
Overweight	1.23 (.07)	1.07 (.18)	.40
Obese	1.12 (.07)	1.39 (.17)	.17

Table 3. Mean (SE) ratio of energy intake to estimated basal metabolic rate ($EI:BMR_{est}$) among females stratified by age and BMI status

	Normal Mood	Altered Mood	p
Age 20-29			
Underweight	2.46 (.13)	2.36 (.52)	.85
Normal weight	1.64 (.09)	1.69 (.18)	.83
Overweight	1.39 (.10)	1.19 (.13)	.18
Obese	1.17 (.06)	1.34 (.19)	.41
Age 30-39			
Underweight	2.03 (.17)	1.81 (.27)	.57
Normal weight	1.73 (.08)	1.62 (.20)	.65
Overweight	1.58 (.11)	1.46 (.09)	.34
Obese	1.35 (.10)	1.49 (.19)	.51

Table 4. Proportion (%) of misreporting by mood status, gender, and age*[ab]

Dietary Reporting Classification	Total		p	Females younger		p	Males younger		p
	Normal Mood	Altered Mood	.69	Normal Mood	Altered Mood	.46	Normal Mood	Altered Mood	.72
Under	49.0	45.0		42.6	41.2		57.8	51.7	
Plausible	22.5	25.2		21.5	31.5		22.6	26.8	
Over	28.6	29.8		35.9	27.4		19.6	21.5	
				Females older			Males older		
				Normal Mood	Altered Mood	.69	Normal Mood	Altered Mood	.81
Under				39.2	33.3		56.7	53.7	
Plausible				22.1	23.0		24.0	22.4	
Over				38.7	43.7		19.3	23.9	

*Proportions based on weighted analysis from sample of 1554 observations

a. Younger age represents 20-29 year olds; older age represents 30-39 year olds

b. p values shown for the comparison of misreporting and plausible reporting between mood status group

Table 5. Characterizing the proportion (%) of plausible and misreporting by mood status

Dietary Reporting Classification	Mood		p	Mood		p
	Normal	Altered		Normal	Altered	
	Younger			**Older**		
Under	50.2	47.7		47.7	43.0	
Plausible	22.0	28.5		23.0	22.7	
Over	27.7	23.7		29.3	34.3	
	Mood		**p**	**Mood**		**p**
	Normal	**Altered**		**Normal**	**Altered**	
	Males			**Females**		
			.75			.55
Under	57.2	52.7		40.8	36.0	
Plausible	23.3	24.6		21.8	25.9	
Over	19.5	22.8		37.4	38.4	
	Mood			**Mood**		
	Normal	**Altered**	**p**	**Normal**	**Altered**	**p**
	Decreased Appetite		.14	**Increased Appetite**		.54
Under	65.5	42.5		72.6	47.5	
Plausible	19.5	23.7		0.0	18.8	
Over	15.0	33.9		27.4	33.7	
	Mood			**Mood**		
	Normal	**Altered**	**p**	**Normal**	**Altered**	**p**
	Decreased Weight		.25	**Increased Weight**		.24
Under	44.3	44.8		78.4	44.9	
Plausible	47.8	20.1		0.0	26.3	
Over	7.8	35.1		21.7	28.8	
	Mood		**p**	**Mood**		**p**
	Normal	**Altered**		**Normal**	**Altered**	
	Smoker		.14	**Non-Smoker**		.72

Under	47.9	33.5		49.4	52.6	
Plausible	34.4	29.0		21.6	22.7	
Over	27.7	37.6		29.0	24.7	
	Mood			**Mood**		
	Normal	**Altered**	**p**	**Normal**	**Altered**	**p**
	Below Poverty			**Above Poverty**		
			.80			.54
Under	47.4	40.9		48.1	44.8	
Plausible	22.0	21.9		22.8	27.8	
Over	30.6	37.2		29.1	27.4	

	Mood			**Mood**			**Mood**		
	Normal	**Altered**	**p**	**Normal**	**Altered**	**p**	**Normal**	**Altered**	**p**
	Education			**Education**			**Education**		
	< High School		.86	**High School/GED**		.52	**> High School**		.51
Under	45.8	49.6		52.0	40.4		53.4	48.7	
Plausible	22.4	20.3		23.6	26.8		21.8	30.8	
Over	31.8	30.1		24.4	32.9		24.8	20.5	

	Mood			**Mood**			**Mood**		
	Normal	**Altered**	**p**	**Normal**	**Altered**	**p**	**Normal**	**Altered**	**p**
	Never Married			**Married/Living with Partner**			**Previously Married**		.03
			.04			.54			
Under	54.2	33.7		49.8	54.9		54.9	53.6	
Plausible	21.2	35.2		23.2	16.8		13.9	33.1	
Over	24.6	31.1		27.0	28.4		31.2	13.3	

	Mood			**Mood**			**Mood**			**Mood**			**Mood**		
	Normal	**Altered**	**p**	**Normal**	**Altered**	**p**	**Normal**	**Altered**	**p**	**Normal**	**Altered**	**p**	**Normal**	**Altered**	
	Non-Hispanic White		.73	**Non-Hispanic Black**		.61	**Mexican-American**		.85	**Other Hispanic**		.98	**Other/Multi-Racial**		
Under	50.3	47.0		47.4	39.5		44.2	49.8		61.6	61.9		41.6	10.7	
Plausible	21.5	26.5		26.4	27.1		22.0	19.0		17.6	16.6		28.8	35.1	
Over	28.2	26.5		26.2	33.5		33.8	31.2		20.8	21.4		29.7	54.3	

Table 6. Proportion (%) of misreporting among males age 20-29 years old by mood and BMI status*

Dietary Reporting Classification	Under Weight		p	Normal Weight		p	Over Weight		p	Obese		p
	Normal Mood	Altered Mood	.15	Normal Mood	Altered Mood	.17	Normal Mood	Altered Mood	.69	Normal Mood	Altered Mood	.32
Under	31.5	52.4		53.2	32.8		72.7	65.4		59.2	71.4	
Plausible	51.1	19.3		27.7	49.1		21.8	21.0		7.0	1.0	
Over	17.4	28.4		19.1	18.1		5.5	13.5		33.8	27.8	

*Significant differences in reporting among men age 20-29 years old by mood and BMI status. Normal mood (p<. 001), Altered mood (p<. 05).

Table 7. Proportions (%) of misreporting among males age 30-39 years old by mood and BMI status

Dietary Reporting Classification	Under Weight		p	Normal Weight		p	Over Weight		p	Obese		p
	Normal Mood	Altered Mood	.27	Normal Mood	Altered Mood	.43	Normal Mood	Altered Mood	.46	Normal Mood	Altered Mood	.99
Under	29.8	19.0		64.0	68.5		66.4	80.8		52.9	54.7	
Plausible	44.6	31.0		24.3	29.2		20.0	16.7		17.4	17.0	
Over	25.6	50.1		11.7	2.3		13.6	2.5		29.6	28.3	

*Significant differences in reporting among men age 30-39 years old by mood and BMI status. Normal mood (p<.01), altered mood (p<.05).

Table 8. Proportions (%) of misreporting among women age 20-29 years old by mood and BMI status*

Dietary Reporting Classification	Under Weight		p	Normal Weight		p	Over Weight		p	Obese		p
	Normal Mood	Altered Mood	.52	Normal Mood	Altered Mood	.69	Normal Mood	Altered Mood	.14	Normal Mood	Altered Mood	.46
Under	6.6	0.0		44.1	31.3		55.7	90.5		42.5	44.9	
Plausible	20.8	55.4		20.8	29.8		25.0	0.0		20.0	33.3	
Over	72.6	44.6		35.1	38.9		19.4	9.5		37.5	21.7	

*Significant differences in reporting among women age 20-29 years old with normal mood (p<. 05), Altered mood (p>.05)

Table 9. Proportions (%) of misreporting among females age 30-39 years old by mood and BMI status*

Dietary Reporting Classification	Under Weight		p	Normal Weight		p	Over Weight		p	Obese		p
	Normal Mood	Altered Mood	.75	Normal Mood	Altered Mood	.93	Normal Mood	Altered Mood	.26	Normal Mood	Altered Mood	.40
Under	26.6	39.3		34.0	35.2		42.0	40.2		45.5	30.3	
Plausible	18.9	12.9		31.8	27.1		25.8	47.4		10.8	15.3	
Over	55.6	47.8		34.2	37.7		32.2	12.4		43.7	54.4	

*No significant differences in reporting among women age 30-39 years old by mood. Normal mood (p>.05), altered mood (p>.05).

Table 10. Odds Ratios and 95% Confidence Intervals for comparison of under and over reporting to plausible reporting among altered mood stratified by gender

	Under Reporting				Over Reporting			
Females	**Crude OR**	**p**	**Adjusted OR**	**p**	**Crude OR**	**p**	**Adjusted OR**	**p**
Altered Mood	.74 (.49-1.11)	.15	.66 (.42-1.03) [a]	.07	.85 (.46-1.61)	.63	.43 (.15-1.22) [c]	.11
Males								
Altered Mood	.87 (.47-1.61)	.66	.71 (.35-1.46) [b]	.34	1.11 (.47-2.61)	.80	1.37 (.58-3.28) [d]	.46

a) Adjusted for confounding variables: PIR, interaction mood*appetite change
b) Adjusted for confounding variables: appetite change
c) Adjusted for confounding variables: BMI status, education, appetite change, alcohol intake
d) Adjusted for confounding variables: poverty and alcohol intake