**The Influence of the Blood Lipid-Lipoprotein Profile on Psychological Well Being**

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The Influence of the Blood Lipid-Lipoprotein Profile on Psychological Well Being

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**Table of Contents**

Chapter 1 Statement of the Problem- 1

Chapter 2 Literature Review- 8

Chapter 3 Methods- 28

Chapter 4 Results- 33

Chapter 5 Discussion- 38

References - 48

Appendices - 52

**Abstract**

 There are many discrepancies in the literature regarding the relationship among components of the blood lipid-lipoprotein profile and psychological well being. Therefore the purpose of this study was to examine the association between the blood lipid-lipoprotein profile and psychological well being in a population of healthy adults. This was a cross sectional study involving 440 healthy men and women over the age of 20 yr. All participants were recruited as part of a larger National Institute of Health (NIH) funded study (NIH R01HL081893-01A2) entitled “The Effects of Statins on Muscle Performance (STOMP)”. Volunteers were recruited equally into three different age groups (20-39, 40-54 and 55+ yr). At visit one their lipid-lipoprotein profile was assessed by measuring total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride levels. Psychological well being was measured using two self report questionnaires, The Beck Depression Inventory (BDI) and the Psychological General Well Being Index (PGWBI). Descriptive statistics were computed for all variables and were reported as the mean ± standard error of the mean (X±SEM). Pearson product moment correlation coefficients examined the relationship among components of the blood lipid-lipoprotein profile and psychological well being and linear regression analysis further evaluated these associations.

**Chapter 1 Statement of the Problem**

**Introduction**

 Cholesterol is a fatty substance made naturally by the body. It forms part of cell membranes and is a component of myelin which sheaths the axons of neurons in the nervous system. Additionally, cholesterol function­­s in the development and stability of synapses and may have secondary effects on the transmission of serotonin, which is a neurotransmitter in the brain that plays a role in mood Chattopadhyay et al., (2007).

Components of the blood lipid-lipoprotein profile include total cholesterol levels as well as its two components, low density lipoprotein (LDL) cholesterol and high density lipoprotein (HDL) cholesterol. The profile also includes blood triglyceride levels. This profile is used by the National Cholesterol Education Program (NCEP) to identify abnormal lipid levels, known as dyslipidemia. The blood lipid-lipoprotein fractions have been shown to be strong predictors in the development of cardiovascular disease (CVD) (National Heart Lung and Blood Institute (NHLBI) 2012).

Total cholesterol is made up of the combination of two different types which are distinguished by the kind of lipoprotein that carries them through the body. According to the NCEP, total cholesterol levels should be <200 mg/dL (See Table 1) however, elevated levels could be caused by high HDL cholesterol which is actually beneficial (NHLBI 2012).

 The negative effects associated with elevated cholesterol levels are not based solely on total cholesterol, but more so on LDL cholesterol levels instead. This “bad cholesterol” is more likely to lead to heart disease because, when present in large amounts, it causes the buildup of plaque which clogs the arteries. It is LDL levels that are taken into consideration when determining the need for treatment and targeted by lipid lowering medications. Optimal levels are <100 mg/dL, although it could be lower depending on the presence of additional risk factors for CVD (NHLBI 2012).

High density lipoproteins carry cholesterol away from the arteries to the liver for removal. Therefore, HDL cholesterol is generally referred to as the “good cholesterol” because it slows the buildup of plaques. Higher levels of HDL cholesterol are desirable because of its beneficial effects, and concentrations >60 mg/dL can counter the effects of other CVD risk factors (NHLBI 2012).

Triglyceride levels are significantly correlated with total, LDL and HDL cholesterol levels and have recently been deemed an independent risk factor of CVD which explains their inclusion in the lipid profile (NCEP ATP III). Triglycerides are a form of fat made in the body and often increase as a result of physical inactivity, being overweight or obese, cigarette smoking, excessive alcohol use, or high carbohydrate diets. Elevated levels of triglycerides are often seen in those with type 2 diabetes as well (NHLBI 2012). Very low density lipoproteins (VLDL) are LDL cholesterol precursors and are rich in triglycerides. Their remnants are thought to act similarly to LDL cholesterol and promote atherosclerosis which is why non-HDL cholesterol, including VLDLs and triglycerides, is the secondary target of lipid treatment (NCEP ATP III). According to the NCEP optimal triglyceride levels are <150 mg/dL (Table 1).

Table 1: Optimal and at Risk Lipid Concentrations

|  |  |  |
| --- | --- | --- |
| LDL Cholesterol  | Optimal Near/Above Optimal Borderline HighHigh Very High  | <100 mg/dL100-129 mg/dL130-159 mg/dL160-189 mg/dL≥190 mg/dL |
| Total Cholesterol | DesirableBorderline HighHigh | <200 mg/dL200-239 mg/dL≥240 mg/dL |
| HDL Cholesterol | LowHigh | <40 mg/dL≥60 mg/dL |
| Triglycerides  | Normal Borderline High High Very High  | <150 mg/dL150-199 mg/dL200-499 mg/dL≥500 mg/dL |

NCEP ATP III Guidelines

The NCEP was launched in 1985 by the National Institute of Health (NIH) with the goal of reducing the incidence of coronary heart disease (CHD). The third report of the Adult Treatment Panel (ATP III) was released in 2001 and the guidelines for lipid-lipoprotein levels are found in Table 1. The NCEP recommend a fasting assessment of the lipid profile every 5 years after age 20 in order to monitor the risk of developing CHD. Dyslipidemia can lead to atherosclerosis, an accumulation of plaque in the arteries due to the deposition of LDL cholesterol on the arterial walls. This accumulation can cause heart disease, blood clots, stroke or heart attack and can contribute to the development of many other cardiovascular diseases (NHLBI 2012).

In addition to components of the blood lipid-lipoprotein profile and other traditional CVD risk factors such as smoking, hypertension, physical inactivity, obesity, diabetes, age and gender, there is evidence that certain psychological factors may also contribute to the development of CVD (Suls & Bunde, 2005). Poor psychological well being, especially including depression, anxiety and aggression or hostility, have been shown to be predictors for CVD morbidity and mortality, through behavioral and physiological pathways. These mechanisms include a higher incidence of adverse health behaviors in individuals with negative psychological well being, such as smoking, medical incompliance, and sedentary lifestyle which can lead to the development of hypertension and diabetes and in turn can cause CVD. Additionally, stress and inflammatory reactions tend to be more common in those with worse psychological well being, and these mechanisms have been implicated in the promotion of atherosclerosis and risk of cardiovascular events (Suls & Bunde, 2005). Therefore the topic of psychological well being is of interest to researchers and health care professionals as it relates not only to the quality of life of their patients, but also to physical health, especially risk for CVD.

Psychological well being is a difficult term to define because it is composed of many different factors that all affect how a person thinks, feels and acts. Kramek et al., (2010) described emotional well being as, “the capacity to live a full and creative life and the flexibility to deal with the challenges of life”. Essentially, psychological well being is composed of the happiness or depression, anxiety, hostility, stress level, mood, and aggression of an individual (National Institute of Mental Health (NIMH) 2012). Depression is the most studied aspect of psychological well being in respect to its relationship with cholesterol levels. One reason being depression’s ability to be diagnosed based upon specific criteria. Psychological well being has also been defined as “an overall lack of depressive symptoms” (Kramek et al., 2010).

Much like physical disorders, mental disorders such as depression, can have a negative effect on one’s ability to function and quality of life, causing interference in daily activities and days missed from work (Kessler et al., 1997). The prevalence of depression has also been positively correlated with chronic diseases and health conditions such as high blood pressure, diabetes mellitus, arthritis, and several autoimmune diseases, indicating a need to address psychological well being when determining an individual's overall state of health (Kessler et al., 1997).

 Most research done on the topic of psychological well being uses questionnaires which rely on self report to assess the different aspects of well being including depression, anxiety and other symptoms related to quality of life (Suls & Bunde, 2005). This study uses two well known psychological measures to gauge psychological well being. One of the most commonly used and well tested measures for assessing severity of depression is the Beck Depression Index (BDI) (Beck et al., 1961). Another validated assessment of general well being is the Psychological General Well Being Inventory (PGWBI) which measures quality of life across 6 domains (Dupuy, 1984). Both of these tests have been used and validated in previous studies and provide a good overall view of the psychological well being of the participants (NIMH, 2012).

The link between cholesterol and psychological well being has yet to be clearly established as research thus far has been contradictory and inconclusive. Early research on the topic focused on the effects of total cholesterol and found that lowering total cholesterol was associated with increased risk of death unrelated to illness such as suicide or violence (Muldoon et al., 1990). The findings of Steegmans et al., (2000) support these results concluding a positive relationship between total cholesterol and psychological well being, however other studies have shown both a negative correlation between total cholesterol and well being (Ledochowski et al., 2003) or no correlation at all (Brown et al., 1994). Other studies went on to examine the effects of the different components of the blood lipid-lipoprotein profile including total, HDL and LDL cholesterol along with triglyceride levels and found varying relationships, both positive and negative, between all components of the lipid profile and well being. Strick et al., (2002) reported a positive relationship between LDL cholesterol and psychological well being. A few studies were able to show both negative (Olusi & Fido 1996) and positive (Lehto et al., 2008, Koponen et al., 2008) relationships between HDL cholesterol and psychological well being. Additionally, several studies found a negative relationship between triglyceride levels and psychological well being (Elovanio et al., 2010, Glueck et al., 1993, Fowkes et al., 1992).

It is hypothesized that low serum cholesterol levels cause an increase in the fluidity of the lipid membranes of serotonin receptors due to reduced free cholesterol surrounding the cell. This increase in fluidity has an effect on the brain's ability to metabolize serotonin (Engelberg, 1992). Low levels of serotonin have been associated with depression and increased risk of suicide and aggression (Steegmans et al., 2000). Thus, there appears to be possible mechanistic underpinnings for the reported associations among various components of the blood lipid lipoprotein profile and depression and aggression.

This study attempted to determine if there is an association between the blood lipid-lipoprotein profile and psychological well being using a large sample from a healthy population, 20-76 yr. The entire blood lipid-lipoprotein profile as well as a general representation of psychological well being, and a more specific assessment of depression were utilized to fully examine the relationship. If a connection is found, the results of this study may be able to contribute to the determination of the physiological mechanism which may help to further explain the relationship. The results of this study will provide researchers and clinicians with information that may be useful in the prevention, diagnosis and treatment of dyslipidemia and poor psychological well being.

**Chapter 2 Review of Literature**

 The purpose of this study was to examine the relationship between the blood lipid-lipoprotein profile and psychological well being as measured by the Beck Depression Inventory and the Psychological General Well Being Index in a healthy population of men and women over the age of 20 yr. The following literature review describes the current studies investigating this relationship.

**Psychological Well Being**

Psychological well being can most easily be described as the combination of the happiness or depression, anxiety, hostility, stress level, mood, and aggression of an individual (NIMH 2012), and is strongly related to quality of life (Kessler et al., 1997). Poor psychological well being, especially in the form of depression, anxiety and aggression, has been associated with increased risk of CVD, and therefore the determination of physiological mechanism relating two is of interest to researchers and clinicians (Suls & Bunde, 2005).

 Most studies examining the relationship between the blood lipid-lipoprotein profile and psychological well being have focused their investigation on the depression aspect of well being (Brown et al., 1994, Steegmans et al., 2000, Ledchowski et al., 2003, Strick et al., 2002, Olusi & Fido, 1996, Lehto et al., 2008, Koponen et al., 2008, Elovanio et al., 2010, Glueck et al., 1992). Depression is a serious mental illness, which ranges in severity from mild to major and can cause interference in daily life (NIMH 2012). Depression is diagnosed using specific criteria based upon the presence certain symptoms (eg. persistent sadness, irritability, loss of interest in pleasurable activities, fatigue, difficulty concentrating, insomnia or excessive sleepiness, changes in appetite, thoughts of suicide or feelings of hopelessness, guilt, worthlessness). Although a diagnosis is available, depression can also be easily measured using validated self report questionnaires, such as the BDI used in this study, which assess the presence of depressive symptoms.

 Other aspects of psychological well being explored by studies evaluating its relationship with the blood lipid-lipoprotein profile include aggression, hostility and suicidal behavior (Muldoon et al., 1990, Fowkes et al., 1992, Wilson et al., 2001) as well as anger, impulsivity (Steegmans et al., 2000), life stressors, a sense of control over ones health and cognitive functioning (Glueck et al., 1992). Each of these components contributes to quality of life and overall psychological well being, however they are often examined only one at a time. Suls & Bunde (2005) propose that there may be a clustering effect when it comes to psychological factors contributing to physical disorders. Therefore the current study assess overall psychological general well being using a self report questionnaire (PGWBI) to examine the influence of the blood lipid-lipoprotein profile across 6 domains of psychological well being.

*Beck Depression Inventory*

The Beck Depression Inventory (BDI) is a common tool used by researchers and clinicians to assess the depression aspect of psychological well being. The survey is a self report questionnaire assessing the severity of depressive symptoms. The BDI consists of 21 questions relating to symptoms and attitudes commonly associated with depression, each with a possible answer from 0 to 3. Scores from each item are added for the total score ranging from 0-63, with higher scores indicating greater depression (Beck, 1961). Across the population it has been found that depression is greater among women and tends to increase with age, although depressive symptoms and suicide are more common in elderly men than women. Sufficient information about the prevalence of depression among different ethnicities has not been determined due to cultural differences in language, experience of symptoms and access to mental health care (Harris, 2004).

Therefore, Contreras et al., (2004) examined the validity and reliability of the BDI along with the Beck Anxiety Inventory (BAI) across cultures. The researchers recruited 2,703 Caucasian Americans and 1,110 Latino college students (age 18-25 yr) who were asked to complete both the BDI and BAI.

Contreras et al., (2004) established the internal consistency of the BDI by calculating Cronbach’s alpha for the total sample, separately for each ethnicity and gender. In each case alpha was greater than 0.82, indicating that the BDI is a consistent measure of depressive symptoms. The results of this study showed that Latinos scored significantly higher than Caucasians on the BDI (p<0.001) and women scored significantly higher than men (p<0.001). The gender results are typical of what has been found thus far for the larger population which led Contreras et al., (2004) to conclude that the BDI is a valid measurement of depression. Therefore, the results of this validation study suggest the BDI is a tool that can be used by researchers and clinicians to accurately assess depression as an aspect of psychological well being in a population of healthy adults.

*Psychological General Well Being Index*

The Psychological General Well Being Index (PGWBI) is another tool used by researchers and clinicians to assess psychological well being. It is a self report questionnaire consisting of 22 questions regarding dimensions of psychological well being, rated from 0-5. Total score ranges from 0-110, with higher scores indicating greater psychological well being (Dupuy (1984)).

Wenger et al., (1984) established the reliability and validity of the PGWBI. They determined that the PGWBI is internally consistent with alpha coefficients averaging 0.92 across several earlier studies. Scores on the PGWBI were significantly correlated with items on the National Health Examination study including needs, utilization of mental health services and medical history and psychosocial items from the RAND Health Insurance Study (p<0.05). The PGWBI also correlates with indicators of general happiness (r=0.74), depression ratings (r= -0.47), and standard indices of mental health including Zung Depression Inventory(r= -0.75), Hopkins Symptoms Checklist (r= -0.77) and the Minnesota Multiphasic Personality Inventory (MMPI)(r= -0.55). These significant relationships led researchers to determine that the PGWBI is a reliable and valid assessment of general psychological well being (Wenger et al., 1984).

 Engelberg et al., (1992) suggests a hypothesis regarding the link between cholesterol levels and poor psychological well being. The researchers explain that serotonin, which is associated with feelings of well being and happiness, also plays a role in the suppression of harmful behaviors. Therefore alterations in the serotonin systems in the central nervous system (CNS) are associated poor impulse control, possible leading to suicide or aggression.

 The article goes on to say that cholesterol makes up the membranes of serotonin receptors, and membrane cholesterol freely exchanges with serum cholesterol. The fluidity of the lipid membrane affects the amount of serotonin that binds to receptors and higher levels of cholesterol increases the viscosity of the membrane leading to increased binding of serotonin (Engelberg, 1992). The researchers hypothesize that lowered cholesterol may cause to a decrease in psychological well being because it reduces the amount of serum cholesterol available to exchange with membrane cholesterol, therefore making the receptor membranes more fluid and unable to bind to serotonin. This decrease in brain serotonin contributes to the increase in depression and aggressive behavior seen in people with low cholesterol levels and may help to explain the relationship between the blood lipid-lipoprotein profile and psychological well being.

**Dyslipidemia**

The blood lipid-lipoprotein profile is made up of total cholesterol, HDL cholesterol, LDL cholesterol and triglyceride levels. Optimal levels established by the NCEP are seen in table 1. Individuals who have high or low cholesterol levels or a lipid disorder have a condition known as dyslipidemia. Total cholesterol is made up two types based on the type of lipoprotein that carries it throughout the body. Ideally it should remain below 200 mg/dL in order to reduce the risk of atherosclerosis, which can lead to CVD. LDL cholesterol level has been shown to be an independent risk factor of CVD and is the primary target of lipid lowering medication due to the tendency for these lipoproteins to deposit cholesterol on the artery walls. HDL cholesterol functions in reverse cholesterol transport from the arteries to the liver for removal, therefore higher levels are associated with reduced risk for CVD. Triglycerides are another independent risk factor for CVD and therefore the secondary target of lipid lowering medications, as they are carried by lipoproteins to the arteries and promote the development of atherosclerosis. While the correlation between components of the blood lipid-lipoprotein profile and CVD has been established, their relationship with psychological well being is controversial.

*Total Cholesterol*

Initial research on the relationship between the blood lipid-lipoprotein profile and psychological well being was prompted by the proposition that changing cholesterol levels may have neurochemical effects. Early research suggests that although lowering cholesterol decreases the risk of mortality due to heart disease, this may be offset by an increase in mortality due to other reasons including suicide as shown in a study done by Muldoon et al., (1990). Researchers performed a meta analysis examining causes of mortality of 24,842 men with an average age of 47 yr who had been involved in cholesterol lowering studies (Muldoon et al., (1990)).

At the time of follow up, 1147 deaths had occurred. Mortality due to heart disease seemed to be lower in men who had received an intervention to reduce cholesterol as compared to controls. However there was not a significant difference in total mortality between the two groups. Mortality that was not related to illness such as accidents, suicide and violence, was significantly higher in those who had been given treatment to lower cholesterol as compared to controls (p=0.04). These results led the researchers to conclude that there may be an association between lowering cholesterol with medication and deaths not related to illness (Muldoon et al., (1990)). These findings suggest a relationship between lowering cholesterol and increased depression. Whether this is a side effect of the medication or a result of low lipid levels must be further investigated.

Based on the ides proposed by Muldoon et al., (1990), Brown et al., (1994) investigated the relationship between low total cholesterol levels and severe depressive symptoms in elderly people. Participants were recruited via participation in an epidemiologic study of the health of people older than 65 yr conducted by the National Institute on Aging. The study included 3939 men and women, ≥71 yr, who were asked to answer questions about their general health, and depression was measured using the Centers for Epidemiologic Studies’ depression scale. The researchers split the participants into two age groups (70-79 yr. and ≥80 yr.) in order to further examine the effects of age on cholesterol levels and psychological well being. Correlations and multivariate regressions were used to assess the relationship between measures of psychological health and total cholesterol concentrations.

The results of this study found that the older group had a significantly higher incidence of severe depression (men p<0.001, women p<0.01) and a significantly lower total cholesterol level (men and women p<0.001) than the younger group. The researchers also found a significant negative correlation between total cholesterol and severe depression in the older group (p=0.03). This association was not seen in the younger group. The results of multivariate regressions accounting for age, self reported health, physical function number of drugs used and weight loss concluded that these associations were in fact not significant (p=0.61). Therefore, Brown et al., concluded that there is no relationship between low total cholesterol levels and severe depression in the elderly population.

Freedman et al., (1995) further explored the relationship between total cholesterol, HDL cholesterol and triglycerides and psychological well being. Participants included 3,490 male veterans of the US army, 31-45 yr. A fasted blood sample was used to determine total cholesterol, HDL cholesterol and triglyceride levels. Psychological well being was assessed using the Diagnostic Interview Schedule as per the Diagnostic and Statistical Manual of Mental Disorders (DSM-III), which is used to make psychiatric diagnoses, as well as the MMPI evaluating personality, emotional status and levels of psychopathology. Correlations and regression analysis were used to determine the relationship between the blood lipids-lipoproteins and measures of psychological well being (Freedman et al., (1995).

The results of this study found no significant correaltion between total cholesterol, HDL cholesterol or triglycerides and depression or anxiety (p>0.05). These findings contribute to the conclusions of Brown et al., (1994) that there is no relationship between the blood lipid-lipoprotein profile and psychological well being, and the researchers conclude that if there is a relationship between cholesterol levels and psychological well being, it is more complex than can be measured by a cross sectional study (Freedman et al., (1995).

 Steegmans et al., (2000) questioned whether middle aged men with chronically low cholesterol levels have a higher risk of depression. This study included 130 men, aged 40-70 yr with chronically low total cholesterol levels (≤4.5 mmol/L) and an age matched control group in a follow up to a population based cholesterol screening. Participants were asked to complete five psychological questionnaires. These included the BDI measuring depression, the Spielberger Anger Expression Scale (SECQ) and Spielberger State-Trait Anger scale (SAQ) measuring anger, the Buss-Durkee Hostility Inventory (BDHI) measuring hostility, and the Eysenck Impulsivity Questionnaire (IMP) measuring impulsivity. Total cholesterol levels were then correlated with the scores from the well being questionnaires (Steegmans et al., 2000).

 The researchers found men with low total cholesterol consistently had a higher prevalence of depressive symptoms (p<0.05), but no difference in anger (p>0.19), hostility (p>0.20) or impulsivity (p>0.30). Steegmans et al., (2000) predicted that low cholesterol levels may lead to depression due to changes in serotonin metabolism. The researchers suggest that low cholesterol is related to decreased availability of tryptophan, a serotonin precursor. This decrease in availability affects the capacity of the brain to metabolize serotonin which in turn is related to poor psychological well being. Steegmans et al., made a point to include only participants with chronically low, not lowered, cholesterol because it was predicted that there may be a difference in the presence of depressive symptoms due to naturally occurring low cholesterol as opposed to medically lowered cholesterol (Steegmans et al., (2000)).

On the other hand, Ledochowski et al., (2003) further examined the relationship between lipid levels and depression in a population of healthy patients, aged 15-85 yr. Researchers recruited 604 healthy men and women and compared cholesterol concentrations and depressive symptoms. Total cholesterol and triglyceride levels were obtained from a fasted blood sample at a medical health checkup, at which time the participants completed the BDI to assess depressive symptoms. The relationship between lipid levels and depression were then evaluated using correlations and ANOVA. (Ledochowski et al.,2003).

There was a significant positive correlation (p=0.0134) between total cholesterol level and BDI score, with 5.3% of the individuals with high total cholesterol (>200 mg/dl) scoring higher than 19 on the BDI indicating moderate to severe depression. BDI score was higher in those with cholesterol concentrations above the 75th percentile (p< .02). These findings indicate that those individuals with higher cholesterol had a higher susceptibility to depressive mood. Ledochowski et al., (2003) concluded that there is a relationship between high total cholesterol levels and depression, however it is unclear if high cholesterol is the cause of depression, or if lifestyle factors due to depression cause elevated cholesterol levels (Ledochowski et al., 2003).

*LDL Cholesterol*

 Many early studies looked only at the effects of total cholesterol on psychological well being, however important correlations may be associated with other components of the blood lipid-lipoprotein profile as well. LDL cholesterol makes up the majority of total cholesterol levels and both are strongly correlated to the risk of CVD. As LDL is the strongest independent predictor of CVD, researchers are interested in its effects on psychological well being.

 Strick et al., (2002) investigated the association between serum cholesterol as well as lipoproteins and depression after an acute myocardial infarction (AMI). Participants were 140 men and women, average 58 yr, who had suffered an AMI. Total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides were assessed 4 weeks after the AMI and again 3 months post-AMI. Depression was evaluated for all participants at both visits using a structured clinical interview as per the DSM-IV and the BDI.

 The results of this study showed no relationship between total cholesterol, HDL cholesterol, or triglycerides and diagnosis of depression or depressive symptoms. However, the results did find an inverse correlation between LDL cholesterol and diagnosis of depression (p=0.041) and depressive symptoms (p=0.002). Therefore, Strick et al., concluded that low LDL cholesterol is related to a greater occurrence of depression post-AMI. These findings are consistent with prior studies which found that lower LDL levels correlated with depression in those without AMI.

 The mechanism proposed by the researchers is similar to that suggested by Steegmans et al., (2000) as an explanation for the relationship between total cholesterol and depression. Strick et al., state that low LDL cholesterol levels often coincide with low total cholesterol levels which have an effect on tryptophan availability and fluidity of the serotonin receptor membranes. Therefore, low LDL cholesterol levels may be associated with depression due to a decrease in serotonin metabolism (Strick et al., 2002).

*HDL Cholesterol*

 HDL cholesterol is a less significant predictor of the development of CVD than total and LDL cholesterol, however it does play a role in the removal of plaques from the arteries and therefore higher levels are beneficial as it works to reverse the negative effects of LDL cholesterol.

Olusi & Fido (1996) were the first to look at the relationship between the entire blood lipid-lipoprotein profile and depression. The participants included 100 men and women, 20-79 yr, who had been admitted to the Psychological Medicine Hospital with a diagnosis of major depressive disorder (MDD), and 100 age and weight matched controls. Fasting blood samples were taken before and after treatment for MDD in order to assess the blood lipid-lipoprotein profile.

 The results of this study found that patients with MDD had significantly higher HDL cholesterol levels than the control group (p<0.05), however there was no change in HDL cholesterol level after treatment for MDD. The study also reported that those participants suffering from MDD had significantly lower total and LDL cholesterol levels (p<0.05) than those in the control group, which is consistent with the findings of Steegmans et al., (2000) and Strick et al., (2002). After treatment for MDD, both total and LDL cholesterol significantly increased from baseline (p<0.05), further indicating the relationship between low levels of these lipid-lipoprotein fractions and depression (Olusi & Fido 1996).

 The association between high HDL cholesterol and depression was unexpected and difficult to explain. Olusi & Fido (1996) concluded that further research should be done on this relationship as HDL is typically associated with good health and protection against CVD. The researchers were unable to propose a mechanism that could explain their findings, however the fact that HDL levels did not change post-treatment may indicate that HDL levels remain stable regardless of psychological well being (Olusi & Fido, 1996).

Lehto et al., (2008) also investigated the relationship between the entire blood lipid-lipoprotein profile and depression. A main goal of the study was to determine if long term depression has any effects on the risk of CVD as measured by lipid-lipoprotein levels. Participants included 124 men and women, 25-64 yr, taking part in a population based study on the mental health of the general population. The depressed group (n=63) had a recorded 7 year history of depression symptoms (n=63) as determined by BDI ≥ 10. The control group was made up of 61 participants with a recorded history of BDI ≤ 9.

 At the time of this study diagnosis of depression was verified using the Structured Clinical Interview for DSM-IV. A fasted blood sample was also taken in order to assess total cholesterol, HDL cholesterol, LDL cholesterol and triglyceride levels. Correlations and ANCOVAs were used to determine the relationship between the blood lipid-lipoprotein profile and depression.

 Unlike those of Olusi & Fido (1996), the results of this study show that those with long term depressive symptoms have a lower HDL cholesterol level than those in the control group (p=0.010). Lehto et al., found no significant relationship between depression and any other component of the blood lipid-lipoprotein profile. These findings indicate that HDL cholesterol may have a relationship with depression that is independent from other blood lipids-lipoproteins. The researchers suggest that there may be an underlying mechanism that links depression with HDL cholesterol and potentially atherosclerosis. This mechanism may be related to inflammation often seen in those with depression and its contribution to the development of atherosclerosis. HDL cholesterol is thought to reduce inflammation and therefore a dysregulation of inflammatory systems associated with depression may promote lower HDL cholesterol levels (Lehto et al., 2008).

Koponen et al., (2008) examined the link between metabolic syndrome and depressive symptoms by evaluating the risk of developing depression in patients diagnosed with metabolic syndrome. Metabolic syndrome is a combination of different disorders that contribute to risk of cardiovascular disease. It is identified by the NCEP as having 3 or more of several components including reduced HDL cholesterol (<40-50 mg/dL), elevated blood triglycerides (≥150 mg/dL), elevated waist circumference (men >40 in, women >35 in), elevated blood pressure (≥130/85 mmHg) and elevated fasting blood glucose (≥100 mg/dL).

The researchers followed 604 middle aged, Finnish men and women without depression over 7 yr (from 1998 to 2004/5). The participants completed the BDI at baseline and follow up, with the cutoff for depression set at 10. Metabolic syndrome was diagnosed based on the NCEP ATP III criteria (Koponen et al., 2008).

Patients without depression and who were diagnosed with metabolic syndrome at baseline were twice as likely to have depressive symptoms at follow up, independent of gender (p<0.05) (Koponen et al., 2008). The researchers also found that the lipid levels included in the diagnosis of metabolic syndrome (HDL cholesterol and triglycerides) were the largest contributors to the development of depression (p<0.05).

 Koponen et al., (2008) concluded that there is a relationship between metabolic syndrome and depression, and that relationship is mediated especially by low HDL cholesterol and high triglyceride levels. The researchers suggest that the physiological mechanisms that influence this relationship may be associated with cytokine mediated inflammation or HPA axis activation. HDL cholesterol plays a role in both of these functions, thus the relationship between low HDL concentrations and depression may have to do with malfunctioning of serotonin metabolism and transmission in the brain (Koponen et al., 2008).

*Triglycerides*

 The findings of Koponen et al., (2008) implicating high triglyceride levels as a major contributor to the development of depression in individuals with metabolic syndrome, indicate the need to include them in the analysis of the relationship between lipid-lipoprotein levels and psychological well being.

 Elovainio et al., (2010) performed a longitudinal study looking at the effects of lipid levels over time on the development of depression. Researchers enrolled 824, 3-9 yr olds involved in a cardiovascular risk assessment for young people. Lipid trajectories were determined by analyzing a fasted blood sample for all components of the blood lipid-lipoprotein profile 4 times over 21 years. At each visit depressive symptoms were assessed with a modified BDI.

Researchers found that across childhood into adulthood, triglyceride levels increased along one of two pathways; steeply increasing (17%) or moderately increasing (83%). The steeply increasing triglyceride trajectory correlated significantly with depressive symptoms (p<0.001). Results suggest that steeply increasing triglycerides across childhood may increase the risk of depression in adulthood. There was no association found between LDL or HDL trajectories with well being (p>0.05). Therefore, Elovainio et al., (2010) concluded there may be a link between high triglyceride levels and depression even without an association between other components of the blood lipid-lipoprotein profile and psychological well being. This study did not find a link between steeply increasing triglycerides and markers of childhood systemic inflammation, so the inflammatory dysregulation hypothesis proposed by Koponen et al., (2008) does not seem to extend to triglyceride levels. Elovainio et al., (2010) state that further research must been done on the relationship between triglycerides and psychological well being in order to determine the physiological mechanism involved.

Fowkes et al., (1992) examined the relationship between the blood lipid-lipoprotein profile and aggression and suicidal behavior in the general population. Subjets were 1592 men and women, 55-74 yr., participating in an artery study examining atherosclerotic disease. Participants were given the Bedford-Foulds Personality Questionnaire developed to measure hostile thoughts and denigratory attitudes towards others through questions about self confidence, dependence on others, hostile acts and social attitudes. The entire blood lipid-lipoprotein profile was assessed using a fasted blood sample. The relationship between lipids-lipoproteins and aggression was investigated using correlations, ANOVA and multivariate regressions.

The results of this study found a positive relationship between triglyceride levels and hostile acts in men (p<0.01) and denigratory attitudes towards others in women (p<0.01). There were no significant correlations found between any other component of the blood lipid-lipoprotein profile and hostility, indicating that triglyceride level may be an independent predictor of aggression and hostile acts.

The association between triglycerides and cholesterol levels as risk factors for CVD led researchers to believe that they may share the same physiological mechanisms related to poor psychological well being. Triglyceride levels may be involved in serotonin metabolism which moderates the suppression of aggressive behavior, however it is typically low levels of total cholesterol which are associated with low levels of serotonin, and the results of this study indicate that high triglyceride levels are coupled with greater aggression and hostility. Therefore it would seem that triglycerides are related to psychological well being via a different mechanism, lending to an independent association. Fowkes et al., (1992) state that high triglyceride levels have been linked with mental confusion and dementia which are reportedly associated with demyelination. Therefore triglyceride levels may affect psychological well being by disrupting myelination of neurons in the CNS (Fowkes et al., 1992). The researchers conclude that further investigations should be done on the relationship between triglycerides and psychological well being, especially with respect to potential effects of medication.

The effects of treatment for severe hypertriglyceridemia on symptoms of depression and life stressors were examined by Glueck et al., (1993). The main goal of this study was to determine if lowering triglyceride levels using diet and drug therapy had an effect on psychological well being over time. The study included 23 men and women with severe hypertriglyceridemia and assessed the blood lipid-lipoprotein profile 9 times over a 54 week treatment period. The risk of disease due to high triglyceride levels necessitated a single blind study in which the participants were asked to complete psychological questionnaires without being informed of their lipid response to treatment. These questionnaires included the BDI, the Hassles Scale and Hassles Index assessing an inventory of life stressors, the Health Locus of Control assessing individual sense of control over one’s own health, and the Folstein Mini-Mental Status Exam evaluating cognitive functioning. The study assessed the correlation of the changes in psychological and lipid-lipoprotein data from baseline.

The results of this study found that after treatment triglyceride levels were significantly reduced by 47% and HDL cholesterol levels were significantly increased by 19% (p≤0.001). Glueck et al., (1993) also found that BDI scores fell 43% (p≤0.001), with the greatest improvement seen at the first visit occurring after 6 weeks of therapy and a progressive decrease at each of the subsequent visits. Scores on the Hassles Scale was also significantly decreased after 6 weeks of therapy (p≤0.05), and remained lower than baseline throughout the study.

Glueck et al., found that a greater reduction in triglycerides was associated with a greater reduction in depressive symptoms, leading the researchers to conclude that treatment of high triglyceride levels plays a role in the alleviation and elimination of depression. This positive association was also seen between triglyceride levels and Hassles score, indicating that reduced triglycerides has an impact on life stressors as well. Physiologically, Glueck et al., (1993) suggest that high triglycerides are associated with increased blood fluidity which may hinder blood cell oxygenation and cerebral blood flow. This idea contrasts the previously stated theory that the increased blood viscosity seen with high lipid-lipoprotein levels is beneficial for serotonin metabolism and therefore aggression and depression, however, it may be further indicative of an independent relationship between triglyceride levels and psychological well being. Therefore, it is thought that reducing triglyceride levels may prevent depression of the CNS, reducing symptoms of depression and improving psychological well being (Glueck et al., 1993).

Newer research attempts to explain the inconsistencies in the literature regarding the association between the blood lipid-lipoprotein profile and psychological well being by proposing the existence of a U-shaped relationship. Wilson et al., (2001) hypothesized that the discrepancies in prior findings may be due to the attempt to determine a linear relationship when in fact, a U-shaped curve may be a more appropriate assessment as both high and low lipid-lipoprotein levels have been associated with negative health outcomes. In an attempt to better determine the relationship between lipid-lipoprotein levels and psychological well being, Wilson et al., (2001) investigated whether there was a U-shaped association between serum cholesterol levels and hostility. The researchers hypothesized that individuals with low serum lipid levels (<160 mg/dL) and those with high serum lipid levels (>200 mg/dL) would have higher hostility scores than those who exhibited optimal cholesterol levels.

Participants for this study included 2,306 men and women, 18-98 yr. and were recruited from a health survey assessing hypertension, CVD and healthcare practices of adults. Total and LDL cholesterol levels were determined following a fasted blood sample, and hostility was measured using the Cook-Medley Hostility Scale. Statistical analysis resulted in a significant quadratic association between hostility and both total and LDL cholesterol levels (p<0.01). The results found that individuals with both low and high serum cholesterol levels scored significantly higher on the hostility scale than those with normal levels (p<0.01). This association remained after controlling for a linear relationship and supports the hypothesis that a U-shaped relationship is present between hostility and total and LDL cholesterol (Wilson et al., 2001). The researchers conclude that it is more appropriate to assess the association between lipid levels and hostility using a curvilinear relation. However the entire blood lipid-lipoprotein profile as well as other measures of psychological well being in should be included in further studies in order to fully understand the curvilinear relationship (Wilsion et al., 2001).

The current study attempted to add to the literature by further investigating if there is a relationship between the blood lipid-lipoprotein profile and psychological well being in a large population of healthy adults, >20 yr. The large age span allows for assessment of the relationship across the lifespan and the general health of the population prevents confounding of the results by disease. Furthermore, this study explores the effects of the entire blood lipid-lipoprotein profile on measures of depression as well as general psychological well being.

The discovery of a relationship between lipid-lipoprotein levels and psychological well being, as well as the determination of a physiological mechanism for the relationship, would allow researchers and clinicians to better understand the link between depression and dyslipidemia. This understanding would allow for a more informed decision regarding the prescription of lipid lowering medication and the treatment of depression and poor psychological well being.

**Specific Aims and Hypotheses:**

1. To examine if there is a relationship between the blood lipid-lipoprotein profile and psychological well being measured by the BDI and PGWBI among healthy adults.

Hypothesis 1: We hypothesized there would be a negative association between total cholesterol, LDL cholesterol and triglyceride levels and psychological well being as measured with the Beck Depression Inventory (BDI) (Beck et al., 1961) and Psychological General Well Being (PGWBI) (Dupuy, 1984) questionnaires. Additionally we hypothesized that there would be a positive association between HDL cholesterol levels and psychological well being.

**Chapter 3 Methods**

 This sub-study is part of a larger NIH funded study titled “The Effects of Statins on Muscle Performance” (STOMP) (NIH R01HL081893-01A2). Data collection for STOMP took place at University of Massachusetts, Amherst, MA, University of Connecticut, Storrs, CT, and Hartford Hospital, Hartford, CT. The experimental design was approved by the institutional review boards of all three test sites. STOMP was a double-blind, study whose aim was to determine the effect of statins on skeletal muscle performance and any incidence of muscle pain due to the use of statins (Thompson et al., 2010).

The experimental group was assigned to take 80 mg of Atorvastatin (Lipitor) daily and the control group was given a placebo. The study consisted of six visits to the laboratory over a period of approximately 6 months. A physical examination, strength testing including handgrip as well as elbow and knee flexion isometric and isokinetic strength measured with a Biodex System 4 Pro isokinetic dynamometer (Biodex Medical Systems, Inc., Shirley, NY) and 2 measures of psychological well being were assessed among 440 healthy men and women > 20 yr (Thompson et al., 2010).

 This sub-study aims to assess the influence of the fasted blood lipid-lipoprotein profile on psychological well being measured at baseline prior to subjects receiving either Atorvastatin or placebo.

**Subjects:**

 STOMP participants were recruited using fliers, email announcements and radio and newspaper advertisements. Recruitment continued until equal age groups were filled. The study included 220 men and 220 women divided into equal age groups of 20-39, 40-54, and 55+ yr. Participants were healthy as determined by a set of inclusion/exclusion criteria. Individuals on antihypertensive medication were included as long as they had been on the medication for at least 3 months and had a stable blood pressure. Subjects were excluded if they had been diagnosed with cancer in the last 5 yr, coronary artery disease, peripheral vascular disease, hyperthyroidism, hypothyroidism, diabetes or renal disease. Any subject who was presently on or had previously been treated with lipid lowering medications was excluded. Exclusion criteria also extend to any subjects physically incapable of the muscle strength or aerobic testing. (Thompson et al., 2010).

**Study Procedures:**

 STOMP consisted of six visits to the lab for testing over approximately 6 months. On the first visit (V1), participants were asked to fast for 12 hr prior to the visit and a blood sample was taken for determination of blood lipids-lipoproteins. The participants were also asked to complete a physical activity survey, pain symptom questionnaire, the BDI, the PGWBI and undergo a physical examination. Isometric and isokinetic strength testing was done using a Biodex dynamometer and cardiorespiratory testing was done on a treadmill using a Bruce protocol.

*Sub-study Procedures:*

 **Lipid Profile:** Blood samples were drawn from the antecubital vein using a 21 gauge butterfly needle using a 4.0 mL lithium heparin tube for lipid-lipoprotein determinations.  Samples were spun in a centrifuge (VanGuard V6500, Hamilton Bell Co., Inc., Montvale, NJ, USA) at 3400 RPM for 15 minutes. Plasma was then aliquated into 1mL criovials and stored at -80 degrees until unbinding. Frozen samples were sent to Clinical Lab Partners (Hartford, CT) for analysis of total cholesterol, HDL cholesterol, and triglycerides. Low density lipoprotein (LDL) was later calculated with the Friedwald equation (Freidwald et al., 1972).

 **Beck Depression Inventory (BDI):** The BDI is one of the two questionnaires completed during V1 used to determine psychological well being The BDI is a 21 question, multiple choice assessment of severity of depression (Beck et al., (1961)). . Each item on the assessment relates to a different symptom of depression including hopelessness, cognition and physical symptoms. Possible answers for each item ranged in intensity from 0-3, and the scores for each question are added to obtain the final score. Total score ranges from 0-63, with higher scores indicating greater depression. A score of 0-9 indicates minimal depression, 10-18 indicates mild depression, 19-29 indicates moderate depression, and 30-63 indicates severe depression (Revicki et al., (1996)).

 **Psychological General Well Being Index (PGWBI):** The PGWBI is the second of the psychological well being questionnaires completed during V1. It is a 22 question, multiple choice assessment of the subject’s self representation of their emotional state reflecting a sense of well being or distress (Dupuy 1984). Items represent 6 dimensions of psychological well being, including freedom from bodily distress, life satisfaction, sense of vitality, cheerful vs. distressed, relaxed vs. anxious, and self-control, are scored on a scale of 0-5. Total score ranges from 0-110 with higher scores indicating greater psychological well being. Scores >85 indicate a general psychological well being, while scores <70 indicate psychological distress.

 The baseline lipid levels and scores on psychological questionnaires were used in this sub-study to examine the influence of components of the blood lipid-lipoprotein profile on psychological well being. All of the information used in this sub-study is based on data collected at V1.

Visit two (V2) of STOMP consisted of a 12 hr fast and occurred at least 72 hr after V1. Subjects participated in another round of strength and cardiorespriatory fitness testing. Subjects were then given an Actical accelerometer(Mini Mitter Company, Bend, OR, USA) and asked to wear it for four consecutive days (two week days and two weekend days).

 At visit three (V3), occurring at least 96 hours after V2, the subjects were randomized into the experimental and control groups. Participants were asked to once again to undergo strength testing with the Biodex. At the end of the visit the subjects were given a three month supply of either Atorvastatin or placebo. At visit four (V4) a non-fasted blood sample was taken and another three month supply of Atorvastatin or placebo was distributed. Visit 5 (V5) took place 3 months later and subjects were asked to provide another blood sample after fasting for 12 hr. Isometric and isokinetic strength was tested using the Biodex and cardiorespiratory fitness was measured on the treadmill. The participants were given the Actical accelerometer again and asked to wear it for another four consecutive days (two weekdays and two weekend days).

 The final visit six (V6) occurred at least 96 hr after V5. The final series of strength tests was performed using the Biodex dynamometer.

**Statistical Analysis:**

 STOMP data were compiled in an online database maintained by the study coordinator (BAP) at Hartford Hospital, but accessible to all three locations. Confidentiality was upheld by removing subject names from the data and using secure identification numbers instead. All analyses were done using the Statistical Package for the Social Sciences Base (SPSS) 14.0 for Windows (SPSS Inc, Chicago, IL) and statistical significance was set as p<0.05. Descriptive statistics were used to describe the data set, including the mean ±standard error of the mean (Mean±SEM) for all variables. The general characteristics between genders were compared with an independent sample *t* test. Pearson product moment correlation coefficients were calculated to examine the relationship between components of the blood lipid-lipoprotein profile (mg/dL) and scores on the BDI and PGWBI. Multivariate regressions were used to examine if age, gender, season, and waist circumference influenced the relationships among components of the blood lipid-lipoprotein profile and psychological well being.

**Chapter 4 Results**

**Subject Characteristics:**

Table 1 displays the subject’s physical and mental health characteristics. The sample of this sub-study (n=147) consisted of healthy men (n=74) and women (n=73). Subjects were slightly overweight, yet had near optimal total cholesterol and LDL cholesterol levels as well as optimal triglyceride levels. The population also exhibited a high HDL cholesterol level and. Women had a significantly higher total (p=0.0442) and HDL cholesterol (p<0.001) level than men. However, men had a larger waist circumference (p<0.001), higher BMI (p=0.016), triglyceride levels (p=0.007), Trig/HDL ratio (p<0.001), and SBP (p=0.016) than the women (Table 1). Average scores on the BDI remained in the minimal depression range for both men and women. Six participants scored in the mild range, one was labeled with moderate depression and one participant was severely depressed. PGWBI scores indicated a general state of well being among participants, although 11 participants had scores signifying psychological distress.

**Table 1: Subject Characteristics (Mean ±SEM)**

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics  | Total (N=147) | Men(N=74) | Women(N=73) |
| Age(yr) | 52.4±1.2 | 51.9±1.5 | 52.9±1.9 |
| Waist Circumference (cm) | 89.8±1.2*(N=143)* | 96.2±1.6\*\**(N=73)* | 83.1±1.4*(N=70)* |
| BMI | 26.9±0.7 | 27.9±0.6\* | 25.9±0.5 |
| Total Cholesterol (mg/dL) | 206.5±3.0 | 200.4±3.5\* | 212.6±4.8 |
| HDL (mg/dL) | 59.8±1.5 | 51.5±1.5\*\* | 68.3±2.1 |
| LDL (mg/dL) | 124.8±2.8 | 124.3±3.4 | 125.4±4.4 |
| Triglycerides (mg/dL) | 110.8±4.5 | 122.7±7.0\* | 98.8±5.2 |
| Trig/HDL (mg/dL) | 2.2±0.1 | 2.7±0.2\*\* | 1.7±0.1 |
| SBP (mmHg) | 120.4±1.1 | 123.1±1.5\* | 117.8±1.5 |
| DBP (mmHg) | 75.8±0.8 | 77.2±1.0 | 74.3±1.1 |
| VO2max (ml/kg/min) | 31.1±0.7 | 34.9±0.9\*\* | 27.3±0.9 |
| Beck Depression Inventory (BDI) | 4.4±0.5*(N=97)* | 3.9±0.7*(N=49)* | 5.0±0.7*(N=48)* |
| Psychological General Well Being Index (PGWBI) | 89.4±1.0 | 90.1±1.3 | 89.0±1.5 |

BMI = Body Mass Index; HDL = High Density Lipoprotein; LDL=Low Density Lipoprotein; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure

 \*p<0.05 \*\*p<0.005Men vs. Women

**Beck Depression Inventory:**

BDI data were collected on 98 participants during V1. Table 2 displays the relationship among components of the blood lipid-lipoprotein profile and score on the BDI. No significant correlation was found between the BDI and any of the blood lipid-lipoprotein profile components (Table 2). Gender (β =0.211, r2=0.043, p=0.038) and BDI (β =0.142, r2=0.020, p=0.158) were able to account for 5.1% of the variance in total cholesterol levels. In addition, gender (β =0.266, r2=0.078, p=0.007), waist circumference (β =0.404, r2=0.166, p<0.001) and BDI (β = -0.037, r2=0.002, p=0.671) accounted for 30% of the variance in HDL cholesterol levels. A small proportion of the variance in LDL cholesterol (4.7%) was explained by age (β =0.207, r2=0.043, p=0.040) and BDI (β =0.153, r2=0.023, p=0.128). Two factors, waist circumference (β =0.416, r2=0.174, p<0.001) and BDI (β =0.100, r2=0.012, p=0.291) accounted for 17% of the variance seen in triglycerides. The same two factors, waist circumference (β =0.469, r2=0.223, p<0.001) and BDI (β =0.081, r2=0.008, p=0.380), explained 21% of the variance in the triglyceride/HDL ratio. (Table 2).

**Table 2: Multivariate Regression Analysis of the Components of the Lipid-Lipoprotein Profile and the Beck Depression Inventory (N=98)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dependent Variable | Predictor | β | t | Partial R | Adjusted R2 | P value  |
| Total Cholesterol | GenderBDIModel Summary  | 0.2110.142 | 2.1061.424 | 0.2090.142 | 0.0440.0200.051 | 0.038\*0.1580.032\* |
| HDL Cholesterol  | GenderWCBDIModel Summary | 0.266-0.404-0.037 | 2.763-4.277-0.426 |  0.280-0.407-0.045 | 0.0780.1660.0020.298 | 0.007\*<0.001\*\*0.671<0.001\*\* |
| LDL Cholesterol  | AgeBDIModel Summary | 0.2070.153 | 2.0811.535 | 0.2070.153 | 0.0430.0230.047 | 0.040\*0.1280.039\* |
| Triglycerides | WCBDIModel Summary  | 0.4160.100 | 4.3921.061 | 0.4180.111 | 0.1750.0120.168 | <0.001\*\*0.291<0.001\*\* |
| TRIG/HDL | WCBDIModel Summary | 0.4690.081 | 5.0960.882 | 0.4710.092 | 0.2220.0080.213 | <0.001\*\*0.380<0.001\*\* |

BDI=Beck Depression Inventory; HDL=High Density Lipoprotein; LDL = Low Density Lipoproteins; WC=Waist Circumference

\*p<0.05, \*\*p<0.005

**Psychological General Well Being Index:**

Table 3 displays the relationship among components of the blood lipid-lipoprotein profile and score on the Psychological General Well Being Index. No significant correlation was found between the PGWBI and any of the blood lipid-lipoprotein profile components (Table 3). A small proportion of the variance in total cholesterol (8.4%) was explained by gender (β =0.161, r2=0.028, p=0.044), age (β =0.271, r2=0.076, p=0.001), and PGWBI score (β =0.042, r2=0.002, p=0.593). Three factors explained 28% of the variance in HDL cholesterol scores; gender (β =0.329, r2=0.106, p<0.001), waist circumference (β = -0.310, r2=0.075, p<0.001) and PGWBI (β =0.033, r2=0.002, p=0.648). Age (β =0.338, r2=0.114, p<0.001) and PGWBI (β =0.030, r2=0.001, p=0.703) accounted for 10% of the variance in LDL cholesterol. Waist circumference (β =0.392, r2=0.152, p<0.001) and PGWBI (β =0.004, r2=0.000, p=0.956) were able to explain 14% of the variance in triglyceride levels. The same two factors, waist circumference (β =0.399, r2=0.158, p<0.001) and PGWBI (β = -0.006, r2=0.000, p=0.941) accounted for 15% of the variance in the triglyceride/HDL ratio. (Table 3).

**Table 3: Multivariate Regression Analysis of the Components of the Lipid-Lipoprotein Profile and the Psychological General Well Being Index (N=147)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Dependent Variable | Predictor | β | t | Partial R | Adjusted R2 | P value  |
| Total Cholesterol | GenderAgePGWBIModel Summary  | 0.1610.2710.042 | 2.0293.4260.536 | 0.1670.2750.045 | 0.0280.0760.0020.084 | 0.044\*0.001\*\*0.5930.001\*\* |
| HDL Cholesterol  | GenderWCPGWBIModel Summary | 0.329-0.3100.033 | 4.094-3.8390.456 | 0.328-0.2730.039 | 0.1080.0750.0020.284 | <0.001\*\*<0.001\*\*0.648<0.001\*\* |
| LDL Cholesterol  | Age PGWBIModel Summary | 0.3380.030 | 4.3160.382 | 0.3380.030 | 0.1140.0010.103 | <0.001\*\*0.703<0.001\*\* |
| Triglycerides | WCPGWBIModel Summary  | 0.3920.004 | 5.0200.055 | 0.3900.004 | 0.1520.0000.142 | <0.001\*\*0.956<0.001\*\* |
| TRIG/HDL | WCPGWBIModel Summary | 0.399-0.006 | 5.126-0.074 | 0.397-0.006 | 0.1580.0000.148 | <0.001\*\*0.941<0.001\*\* |

PGWBI=Psychological General Well Being Index; HDL=High Density Lipoprotein; LDL = Low Density Lipoproteins; WC=Waist Circumference

\*p<0.05, \*\*p<0.005

**Chapter 5 Discussion**

 The current STOMP sub-study attempted to determine if there was a relationship between the blood lipid-lipoprotein profile and psychological well being as measured by the BDI and PGWBI among healthy men and women > 20 yr. Based on the evidence presented by Suls & Bunde (2005) stating that negative psychological factors contribute to the development of CVD, it was hypothesized that there would be a negative association between total cholesterol, LDL cholesterol, and triglyceride levels and psychological well being. Additionally, it was hypothesized that there would be a positive association between HDL cholesterol and psychological well being. Our findings indicated that there were no significant correlations among any component of the blood lipid-lipoprotein profile and measures of psychological well being. This lack of significance remained even in the presence of the following covariates; age, gender, waist circumference and season. Collectively, these predictors were only able to explain a small amount of variance in the measures of psychological well being.
 A proposed explanation for the variance seen in the measures of psychological well being involves the potential mechanistic underpinnings linking psychological well being to the blood lipid-lipoprotein profile. The NHLBI (2012) states that the use of statins has been shown to lower LDL cholesterol by up to 50% and increase HDL cholesterol by 15%. These improvements in lipoprotein levels can prevent and/or reduce the buildup of plaques in the arteries, thereby reducing the risk of CHD. Lowering levels of cholesterol in the population would contribute to public health by reducing the incidence of morbidity and mortality due to CHD. On the other hand, low lipid-lipoprotein levels may affect the fluidity of serotonin receptor membranes, causing reduced metabolism and binding of serotonin in the brain which could lead to depression and aggression (Engelberg (1992)). In a broader sense, blood lipid-lipoprotein levels may be indicative of poor lifestyle which in turn can have negative effects on well being. Depression has a profound impact on public health as it influences quality of life and is associated with morbidity and mortality due to other diseases such as high blood pressure, diabetes, thyroid disease and cancer (Kessler et al., 1997). Therefore, a possible mechanistic link between the blood lipid-lipoprotein profile and psychological well being would be clinically significant.

 The results of this study are consistent with some earlier studies in the literature which found no relationship between the blood lipid-lipoprotein profile and psychological well being. Brown et al. (1994) reported no relationship between total cholesterol and depressive symptoms in an elderly population of men and women (≥71 yr); however, the study did not investigate other components of the blood lipid-lipoprotein profile. Similarly to the current sub-study, Brown et al., (1994) utilized a cross sectional design and did not include a control group, which may have contributed to the negative results. Additionally, Freedman et al., (1995) reported no significant findings among men, 34-45 yr., suffering from generalized anxiety disorder, between total cholesterol, HDL cholesterol and triglyceride levels and measures of psychological well being that included depression and hostility. Again, this study utilized a cross sectional design, however it did include a control group and examined only men. This STOMP sub-study further contributed to the findings of Brown et al., (1994) and Freedman et al., (1995) by concluding no relationship between the entire blood lipid-lipoprotein profile and psychological well being among a population of both men and women spanning all ages.

However, the cross sectional investigation included in our study, as well as those of Brown et al. (1994) and Freedman et al. (1995), does not allow for assessment of changes in the lipid profile or psychological well being over time and prevents the determination of a causal relationship.

 Our findings are not consistent with other studies in the literature reporting significant relationships between different components of the blood lipid-lipoprotein profile and aspects of psychological well being. As we had hypothesized, Ledchowski et al. (2003) reported a positive correlation between total cholesterol and presence of depressive symptoms among a large sample of men and women, 15-85 yr. The study found that those participants with high cholesterol levels were more likely to exhibit greater depressive symptoms. As depression is often associated with higher intake of dietary fats and carbohydrates, it would seem that negative lifestyle factors may link higher cholesterol levels to poor psychological well being. Our study also assesses a large, healthy population in which lipid-lipoprotein levels remain only borderline high, which may indicate a healthy lifestyle and therefore less incidence of hyperlipidemia and depression.

 Contrary results are seen in a study by Steegmans et al. (2000) which found a significant positive relationship between total cholesterol and incidence of depression in a population of only men, 40-70 yr. with chronically low total cholesterol levels. The results concluded that those men who exhibited consistently low total cholesterol levels over a three year period were more likely to suffer from depression than those with normal cholesterol levels. The researchers explain their findings using the hypothesis proposed by Engleberg (1992). This hypothesis states that low cholesterol levels are associated with increased serotonin membrane fluidity and therefore increased depression. The discrepancies may be due to the fact that Steegmans et al. (2000) included a population with consistently low cholesterol, where as our study examined a population with healthy cholesterol levels. Therefore, we can assume that the amount of cholesterol present in the blood of our participants is sufficient for serotonin metabolism.

 An investigation of the associations between reductions in total cholesterol levels, increased depression and risk of mortality due to suicide, violence and aggression was conducted by Muldoon et al. (1990). This meta-analysis examined the effects of diet and drug interventions on several populations of males( 41-51 yr) with high total cholesterol. The results showed that reducing total cholesterol significantly increased the risk of morbidity and mortality due to suicide and violence, especially in trials utilizing medications such as statins. These causes of mortality not related to illness have been associated with depression and aggression. The association between low total cholesterol and psychological well being could be due to the reduction in cholesterol level or as a side effect of the medication rather than actual cholesterol levels, as this study assessed interventions and ours did not.

 Furthermore, the investigations of Steegmans et al. (2000) and Muldoon et al. (1990) included populations of only males with high or low total cholesterol and therefore the effects of gender on the entire blood-lipid lipoprotein profile could not be examined. The current sub-study included both males and females, with normal cholesterol levels, and investigated the relationship between all components of the blood lipid-lipoprotein profile on psychological well being; however no significant association was found when adjusted for gender.

 Additional studies have also found positive associations between LDL cholesterol and depression in a sample of men and women who had suffered from AMI (Strick et al., 2002). The researchers implicated low LDL cholesterol in decreased tryptophan availability and increased serotonin membrane fluidity, similar to Steegmans et al. (2000), However this does not explain why significant associations were found only for LDL cholesterol and not total cholesterol levels. The differences in findings may stem from the fact that Strick et al. (2002) examined a population who had suffered from AMI and therefore most likely had increased CVD risk factors. Again, the population investigated in the current study was healthy with optimal levels of blood lipids-lipoproteins and therefore the mechanisms leading to reduced serotonin and depression are not present, and the results are not confounded by the suffering from cardiovascular events.

 Our results were inconsistent with the findings of Lehto et al., (2008) who determined that the presence of long term depression in a population of men and women (25-64 yr) is associated with lower HDL cholesterol levels than those seen in a control group. Lehto et al. (2008) examined the entire blood lipid-lipoprotein profile, similar to our study, and only found a relationship between HDL cholesterol and depression. This indicates the possibility of an independent mechanism relating HDL cholesterol to psychological well being not seen in our study, perhaps because of the absence of long term depression in our population. Interestingly, Olusi & Fido (1996) found the opposite relationship between HDL cholesterol level and depression. The researchers concluded that a sample of men and women (20-79 yr) diagnosed with major depressive disorder (MDD) had higher levels of HDL cholesterol than those participants without MDD. No mechanism has been proposed as an explanation for this relationship, however stable levels of HDL cholesterol seen throughout treatment for depression show that HDL cholesterol may remain constant regardless of psychological well being. Therefore an association, positive or negative, between HDL cholesterol and psychological well being may not necessarily indicate a mechanistic relationship. Both Lehto et al. (2008) and Olusi & Fido (1996) utilized a control group in their studies which was absent in this sub-study and may have contributed to the ability to determine a relationship. Both studies also examined the relationship between the blood lipid-lipoprotein profile and psychological well being among depressed individuals, whereas our study included very few depressed subjects. Low HDL cholesterol levels indicate dysfunction of reverse cholesterol transport and are a risk factor for CVD (NHLBI 2012). The population included in this sub-study not only exhibited a high level of HDL cholesterol, but optimal levels of other components of the blood lipid-lipoprotein profile as well. These favorable lipid-lipoprotein levels may be associated with the relative physical and psychological wellness of the population therefore promoting an absence of depressive symptoms.

 Negative associations were also found in several studies between triglycerides and depression and aggression (Elovanio et al. 2010, Fowkes et al. 1992), which are contradictory to the lack of findings of this study. Elovanio et al. (2010) performed a longitudinal study which found that triglycerides that increase at a rapid rate from childhood into adulthood increased the risk of suffering from depression as an adult compared to triglyceride levels that increased at a moderate rate. A physiological mechanism could not be concluded, however a steeply increasing triglyceride trajectory may indicate poor lifestyle factors, such as increased dietary intake of fats that could contribute to the development of depression. The current sub-study was cross sectional and therefore unable to assess the change in blood lipids-lipoproteins over time which may contribute to the lack of relationship seen. Age may have also been a factor in the discrepancies as this sub-study examined the established lipid levels of adults rather than children investigated by Strick et al., (2002). This sub-study did account for age as a fixed factor in the population that was studied however, and no significant results were found. Fowkes et al. (1992) found positive correlations between triglyceride levels and aggression and hostility in a population of men and women(55-74 yr) independent of a relationship between other components of the blood lipid-lipoprotein profile and psychological well being. They hypothesized that the mechanism may have to do with the role of triglycerides in the myelination of neurons in the CNS, therefore low triglyceride levels disrupt the neural transmission which can affect aggression and hostility levels. In order to assess psychological well being Fowkes et al. (1992) utilized a self report questionnaire specifically measuring hostility and aggression. Therefore the conflicting results with our study may have to do with the fact that the questionnaire used did not account for the potential clustering effect of psychological risk factors on physical conditions. The current sub-study utilized two well known, reliable and valid questionnaires assessing depressive symptoms and overall psychological well being across several different domains.

 A potential explanation for the discrepancies in the literature is a U-shaped association between the blood lipid-lipoprotein profile and psychological well being. Wilson et al. (2001) explored this possibility and found a significant quadratic association between hostility and both total and LDL cholesterol among a large sample of men and women (18-98 yr). Although the study only investigated one aspect of psychological well being, there is potential for this association to extend to psychological well being in general. Wilson et al. (2001) concluded that it is more appropriate to assess the relationship between the blood lipid-lipoprotein profile and psychological well being for a U-shaped curve, stating that both low and high levels of lipids-lipoproteins may be related to negative psychological well being.

 There were several limitations to this study that include the inability of the cross sectional study design to determine a causal relationship between the blood lipid-lipoprotein profile and psychological well being. Another possible threat to internal validity exists among the consistency and reliability of data collection and reporting methods across various collection sites as there is potential for variations in procedure and equipment. To minimize this threat, the database and equipment were the same at all locations and mandatory monthly meetings were conducted among the three sites to ensure that the investigators at each site were accurately following the same study protocols (Thompson et al., 2010). Furthermore, STOMP was not specifically designed to measure the relationship between the blood lipid-lipoprotein profile and psychological well being. Finally, the measures of psychological well being used in this study are self report which can lead to incorrect results due to response bias (Koponen et al., (2008). Nonetheless, the BDI and PGWBI are widely used and have been proven reliable and valid to assess depression and general psychological well being respectively (Contreras et al., (2004),Wenger et al., (1984)).

 There were several strengths of this study however, beginning with the strong research team involved in STOMP, which included experts in the fields of cardiovascular and muscular physiology and physical activity assessment. Their experience in designing and carrying out clinical trials contributes to the accuracy of th­­­e results found in this study (Thompson et al. (2004), Angelopoulos et al. (2008)). The sample included in this sub-study consists only of healthy people over the age of 20 yr who had never taken a statin, which eliminates the potential confounding effects of age, disease and medication use. The large number of healthy adults across the lifespan included in this study makes these results applicable to the general population.

 High lipid-lipoprotein levels as well as several psychological factors have been associated with increased risk of atherosclerosis, CHD and other vascular diseases (NHLBI 2012, Suls & Bunde (2005)). A potential relationship between blood lipid-lipoprotein levels and psychological well being, could affect the diagnosis, treatment and prevention of cardiovascular and mental diseases. Future research should be performed with a longitudinal study design on a large healthy population, such as the population assessed in the current study, to investigate the effects of the blood lipid-lipoprotein profile on psychological well being over time and attempt to determine causality without the confounding effects of disease. Research should also explore the effects of lipid lowering medications, such as statins, on psychological well being to more conclusively determine if a relationship does or does not exist between the components of the blood lipid-lipoprotein profile and mental health. Additionally whether the relationship between the blood lipid-lipoprotein profile and psychological well being is due to medication use or baseline lipid-lipoprotein levels should be determined. Lastly, the possibility of a U-shaped association between lipid-lipoprotein levels and psychological well being reported by Wilson et al. (2001) should be further examined as it may explain the contradicting results shown in the literature and demonstrate that both low and high blood lipid-lipoprotein levels are associated with psychological well being.

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Appendix A

Beck Depression Inventory

Appendix B

Psychological General Well Being Index

Appendix C

Informed Consent