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# The Effects of Flaxseed SDG on Perimenopausal Women with Mild Hyperlipidemia

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# THE EFFECTS OF FLAXSEED SDG ON PERIMENOPAUSAL WOMEN WITH MILD HYPERLIPIDEMIA

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ABSTRACT

In 2001, the National Cholesterol Education Program (NCEP) expanded their guidelines for evaluation and treatment of hyperlipidemia which includes not only a low cholesterol diet and exercise, but also the use of plant stanols such as Flaxseed and Soluble fiber. According to the NCEP III guidelines, women with mild hyperlipidemia and low risk cardiac factors would not qualify for drug therapy to control their cholesterol. However, the use of plant stanols could be used as an alternative. As there are limited studies involving postmenopausal women in regards to treatment of heart disease, there is virtually no information or research on perimenopausal women who may be at increase risk for Coronary Artery Disease. This experimental pilot study evaluated the effects of Flaxseed SDG on perimenopausal women with mild hyperlipidemia to see if this could prevent advancement of hyperlipidemia.

11 perimenopausal women between the ages of 36-48 years with mild hyperlipidemia were involved in a 14 week randomized, double blind, experimental pilot study. Subjects were randomized into control Group 1 of Psyllium 11.7gm/day (n=5) and the experimental Group 2 of Flaxseed SDG (Brevail) 200mg/day (n=6). The study included an eight week period on the study product and this was followed by two washout periods at two weeks and then four weeks. Lipid levels and diet assessment were evaluated at each time point of the study.

Results showed the Brevail SDG group had significant findings for the VLDL Cholesterol-direct during all three time points of the study ($p=0.047, 0.031, 0.011$) and for Triglycerides at time point 1 vs. 2 and 2 vs. 3 ($p= 0.043, 0.047$). The Psyllium

group showed statistical significance for improvement of VLDL Cholesterol-direct levels between time point 1 vs. 3 (p=.021).

There was a trend for improvement of lipid values for LDL-C, Lp(a), and hsCRP while on the Brevail SDG and an improvement of Total Cholesterol, HDL-C, and Non-HDL-C at the six week washout period. The Psyllium group showed a trend for improvement of total Cholesterol, LDL-C, Non-HDL-C, and hsCRP while on the product and the HDL-C, Triglycerides, VLDL-C, and Lp(a) showed an improvement in values during the six week washout period.

In conclusion, due to the small sample size of the study, there was no statistically significant findings to support that Brevail SDG can improve lipid levels in perimenopausal women with mild hyperlipidemia. However, there was a favorable trend in improvement of LDL-c, Lp(a), and hsCRP values while taking Brevail SDG. Therefore, based on the findings of the study, it would be worthwhile to repeat this study on a larger basis to determine if there is significant data to support that flaxseed can improve cholesterol levels and prevent the risk of progressing to CHD in perimenopausal women with mild hyperlipidemia.

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## CHAPTER I

### Introduction

Coronary heart disease (CHD) has been considered the leading cause of mortality among men compared to women. However CHD is now the leading cause of death in women affecting 500,000 American women per year (Haan, 1999). Women's prognosis for heart disease is worse than for men and age mortality rate for CHD in women is four to six times higher than mortality from breast cancer (Bedinghaus, 2001). A woman's chance for CHD can progress at a higher rate after menopause. It is believed that endogenous estrogen acts as a protector against heart disease in premenopausal women (Knapp, 2002). During this time, women lag behind men by ten years for the risk of CHD, however with onset of menopause, their risk for heart disease can increase due to changes in lipid metabolism and atherosclerosis progressing at a faster rate compared to men. High total cholesterol and LDL-C (low-density lipoprotein) levels are considered to be a high risk factor for women compared to men (Knapp, 2002). In women, LDL-C and total cholesterol levels increase after age 55 and can peak between 55-65 years of age (Bedinghaus, 2002). Whereas, in the middle age population of women, low HDL-C (High-density lipoprotein) and elevated Triglyceride levels are the factors for increase risk of CHD (Knapp, 2002)

Other risk factors for CHD include age, hypertension, family history, obesity, diabetes, inactivity, and metabolic syndrome. Metabolic syndrome is defined as a

combination of conditions including diabetes, hypertension, hyperlipidemia, obesity, and clotting abnormalities that can put people at risk for CHD (Knapp, 2002).

With Coronary heart disease being so prevalent in postmenopausal women, there has been a history of limited studies involving women in regards to heart disease and treatment even though cardiac disease in women has a higher mortality rate than men.

As there are limited studies involving postmenopausal women in relation to heart disease and treatment there seems to be virtually no information or research done on perimenopausal women who may be at risk for CHD. The aim of this study is to evaluate alternative treatments for perimenopausal women who are considered borderline for hyperlipidemia and to see if this will benefit this particular population of women from progressing into CHD once they have entered menopause.

## *Background*

### *Historical Aspects of Omitting Women from Medical Research*

The statistics for women with CHD is increasing substantially. Since 1984, women in the United States have outnumbered men dying from cardiovascular disease. One in eight women between the ages of 45-54 years have shown clinical evidence of CHD and the number increases to one in three after the age of 65 years (Bedinghaus, 2001). A woman has a 42% chance of dying after a heart attack compared to 24% for men (AHRQ, 2003). A younger woman less than 50 years of age who had an Anterior Myocardial Infarction has a mortality rate twice that of men (Elfre, 2004). Regardless of these significant statistics, research on women with heart disease has been scarce. There has been a myth that "women don't get heart disease" and in 1908, heart disease surpassed childbirth as the largest health issue for women (Libov).

Historically, Medical and Biological research has been based on a patriarchal system where the male norm in research results was transferred as the norm for gender and race. Women were not included in medical research studies because it was believed that the female hormonal cycle would alter the research design and analysis (Greenberger, 2003). Another concern of using women in medical research was the increase risk of birth defects. An example of this is the use of thalidomide and DES in the 1960's and 1970's that caused serious birth defects (Greenberger, 2003).

The lack of women being utilized in research studies was illustrated quite well in the Harvard Physicians' Health Study that was published in 1989 (Greenberger, 2003). This federally-funded study evaluated the benefits of taking aspirin to help reduce the risk of having a myocardial infarction and its sample population included 22,000 men and no women.

The Framingham Study developed a tool to determine the risk of coronary heart disease. It uses five categories to assess risk including; age, total cholesterol levels, HDL-C, tobacco/smoking status, hypertension (and whether the hypertension is being treated) (Safeer, 2002). The assigned points for each of these five categories allow the clinician to determine a patient's risk of having a significant cardiac event over the next ten years. The initial Framingham study included men and women, however, it looked at middle-aged people and erroneously identified men more at risk for developing heart disease than women in early interpretations of the study (Libov). Women between the ages of 60-64 years old who are considered at high risk for CHD were at the top 10% of the Framingham scale and had only a 12% risk for developing CHD over a six year follow-up. It is believed that this low probability may be inaccurate for high risk women

because the earlier interpretations of the Framingham were taken from data on men and included into the design of the scale (Eastwood, 2005).

In 1985, the lack of women being included in medical research was brought to national attention through the Public Health Service Task Force on Women's Health issues. It stated that:

> "the historical lack of research focus on women's health concerns has compromised the quality of health information available to women as well as the health care they receive. Biomedical and behavioral research [should] be expanded to ensure emphasis on conditions and diseases unique to, or more prevalent in women in all age groups" (Greenberger, 2003, p. 2).

That same year, the National Institute of Health (NIH) developed new guidelines to encourage researchers to include women in clinical research. By 1993, the FDA reversed its policy of banning women with childbearing tendency from clinical research and allowed them to participate in early clinical drug trials. That same year, Congress passed the NIH Revitalization Act which established the Office of Research on Women's Health. It requires all studies funded by the NIH to include both sexes in sufficient numbers for a "valid analysis" (Greenberger, 2003, p.3).

*Gender Differences*

Current information addressing gender differences in CHD have shown that women display anatomical differences in the structure of their hearts compared to men. Women have smaller epicardial vessels and that the left main and anterior descending arteries are smaller in women (Eastwood, 2005). With smaller luminal diameter of the vessels, plaque rupture can increase risk of a total occlusion of the artery and cause a myocardial infarction. Also, there are theories regarding differences in plaque formation

in the coronary arteries. It is believed that women display more plaque erosion rather than rupture which is more common in men with a Sudden Cardiac Death event (Eastwood, 2005). Due to these differences, women present with atypical symptoms for a myocardial infarction (MI) that can be overlooked clinically. Men tend to complain of a crushing chest pain and show elevation in the ST segment on an Electrocardiogram during a MI. However, women will present with complaints of burning, squeezing, abdominal fullness, dyspnea, fatigue, nausea, dizziness, or weakness (Eastwood, 2005). Their symptoms reflect unstable angina and usually do not show an elevation of the ST-segment. Therefore, they have an increase risk of not being treated appropriately and can increase their risk of complications since they tend to have decrease collateral blood flow to the heart muscle (Eastwood, 2005).

Risk factors for CHD in women are similar for men in respect to hypertension, hyperlipidemia, diabetes, and inactivity. However, diabetes has been shown to be a three to seven-fold increase risk in women for CHD compared to men which is a two to three-fold elevated risk (Eastwood, 2005). Likewise, hyperlipidemia in women greater than 65 years of age is more of a risk for CHD compared to men. For men, the important factor that predicts risk for CHD with hyperlipidemia includes an elevated LDL-C. For women, high levels of Triglycerides and low levels of HDL-C are predictors for increase risk of CHD. It is believed that elevated Triglycerides can indirectly cause atherosclerosis by lowering HDL-C and promoting small dense LDL-C (Eastwood, 2005). Elevated Triglycerides in women can increase their risk of CHD by 75% compared to men at 30% (Umland, 2002).

Psychosocial factors in women have been found to increase their risk of CHD compared to men. Depression, anxiety, and social isolation can contribute to increase death after a MI in women. A study done in Alameda County showed that women with less social connections who suffered an MI were three times as likely to die compared to women who scored high on social ties (Eastwood, 2005).

Another risk factor for heart disease includes metabolic syndrome. This is defined as a combination of conditions including diabetes, hypertension, hyperlipidemia, obesity, and clotting abnormalities. Women are found to be more at risk for having the combination of factors that can lead to metabolic syndrome compared to men (Knapp, 2002)

*Theoretical Framework*

The National Cholesterol Education Program (NCEP) was developed in the 1980's to provide guidelines for cholesterol control *(Illingworth, 2003).* Since then, the NCEP guidelines have been updated with the most recent being in 2001 and referred to as NCEP III. The purpose of the guidelines is to bring about a connection between new trials in cholesterol management and application in the clinical setting. It is recommended that a complete lipid profile be completed on all patients who are twenty years or older every five years (Pasternak, 2003).

The NCEP III guidelines evaluate Total Cholesterol, Low density lipoproteins (LDL-C), High-density lipoproteins (HDL-C), and Triglycerides. Total Cholesterol is a sterol that is synthesized in the liver from dietary fat intake and endogenously in the cells. It is present in all body tissues and is mainly comprised of LDL, brain and nerve cells, cell membranes, and gallstones (Chernecky, 2004). Low density lipoproteins are

considered the "bad cholesterol". They carry cholesterol from the liver and deposit in the peripheral tissues, and in high levels, can be considered atherogenic (Chernecky, 2004). High density lipoproteins are considered the "good cholesterol" and is carried by alpha-lipoprotein (Chernecky, 2004). HDL-C helps protect against CHD. Triglycerides consist of fatty acid and glycerol ester that makes up "...(70%) of very-low-density lipoprotein (VLDL) and a small part (<10%) of low-density lipoprotein (LDL)" (Chernecky, 2004, p.1093). Triglycerides are transported through the bloodstream and the lymphatic system to adipose tissue where they are stored. They are also synthesized in the liver and stored in adipose tissue where they may later be formed into glucose to be used by the body (Chernecky, 2004).

LDL-C is optimal if less than 100mg/dL, HDL-C should be above 40mg/dL, and Triglycerides remain <150mg/dL. (See Table 1)

Table 1.

*ATP III classification of LDL, total Cholesterol, and HDL-C (mg/dl)* (Pasternak, 2003)

| Cholesterol type | mg/dl | Classification |
|---|---|---|
| **LDL** | <100 | Optimal |
| | 100-129 | Near of above optimal |
| | 130-159 | Borderline high |
| | 160-189 | High |
| | >190 | Very high |
| **Total** | <200 | Desirable |
| **Cholesterol** | 200-239 | Borderline high |
| | >240 | High |
| **HDL** | <40 | Low |
| | >60 | High |

The updated guidelines have also addressed those individuals who are at an increased risk for their first coronary event. The first high risk group are those individuals who have diabetes and a second high risk group are those individuals who have a 10-year CHD risk >20% according to the Framingham Heart Study risk scoring (Pasternak, 2003). (See Appendix A) The third high risk group include patients with metabolic syndrome. According to Pasternak (2003), 3 of 5 risk factors need to be included to identify metabolic syndrome. This includes abdominal obesity >102cm for men and >88cm for women, Triglyceride levels >150mg/dL, HDL-C <40mg/dL for men

and <50mg/dL for women, blood pressure >130/85mmHg, and a fasting glucose >110mg/dL.

Guidelines for women, according to NCEP III, suggest drug therapy if a woman has 2 or more risk factors for CHD and a 10-year risk of 10-20% according to the Framingham Risk tool. Women who have <10% risk over 10 years and a LDL-C level <130mg/dL are not candidates for cholesterol lowering prescription medicine unless their LDL-C is > 160mg/dL (Mosca, 2002).

The NCEP III guidelines have also expanded on their recommendations for healthy lifestyle changes to help reduce cholesterol. Along with weight management and physical activity, they have also included the use of plant stanols (2g/day) and soluble fiber (10-24g/day) as part of the dietary regimen (Pasternak, 2003).

*Plant Stanols*

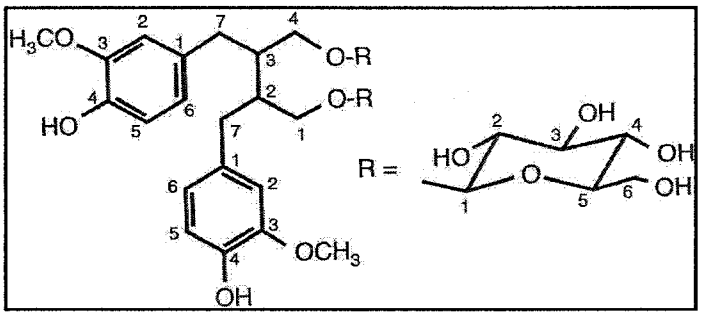
Plant stanols include Phytoestrogen which is a compound found in plants that are structurally similar to estrogen and bind to estrogen receptor sites (Kris-Etherton, 2002). Phytoestrogens display both an estrogen agonist and antagonist action and these factors are dependent upon dietary concentrations, endogenous estrogen levels, sex, and menopause (Kris-Etherton, 2002). Isoflavones, lignans, and coumestans are included as phytoestrogens.

Flaxseed, a lignan, primarily contains the lignan of secoisolariciresinol (SECO) which is considered a phenolic compound (Sterling, 2004). SECO consists of:

> "...ring structures bearing attached "hydroxyl" groups. Chemically it resembles endogenous steroid hormones. In flaxseed, SECO appears to exist as a complex attached to two glucose (sugar) molecules-SDG. After SDG enters the intestines, it has its two glucose molecules removed to form "aglycone" SECO" (Almada, 2003b) (See Figure 1).

SECO and SDG are not directly absorbed into the body but are acted upon by bacterial flora in the intestines and produces enterolactone (ENL) which then transforms into enterodiol (END) (Almada, 2003b). Initially, these two products are derived from plant sources, but since they are produced in the body, they are considered mammalian lignans (Almada, 2003b). Flaxseed, a mammalian lignan has a weak estrogenic and antiestrogenic activity comparable to isoflavones such as soy (D. J. A. Jenkins, Kendall, C.W.C., Vidgen, E., Agarwal, S., Rao, A.V., Roseberg, R.S., et al, 1999). It is comparable to Selective Estrogen Receptor Modulators (SERMS) by acting upon estrogen sites (Sterling, 2004). It is hypothesized that lignans may block the activity of progesterone receptors which would affect cardiovascular risk by changing HDL-C metabolism (Jenkins, 1999).

*Figure 1*- The Biochemical structure of SECO (Almada, 2003a)




Psyllium husk is derived from the plant Plantiago ovata that is native to Asia (*PDR for nonprescription drugs, dietary supplements, and herbs*, 2008). This is a natural fiber that has a bulking effect in the colon that retains water in undigested fiber and "...increased bacterial mass following partial fiber digestion" which decreases transit

time (*PDR for nonprescription drugs, dietary supplements, and herbs*, 2008, p. 642). In 1998 the U.S. Food and Drug Administration allowed the claim that 7gm of soluble fiber per day can help lower cholesterol (Gamble, 2008).

*Relevance to Nursing*

In the health care setting, Nurses have always been on the forefront in providing care and educating their patients. Nurses' strength has always been towards health promotion with their patients. Historically, Nurses have looked upon their patients as a biopsychosocial being and have tailored their approach to their patients' care as looking at the person as a whole. Nurses have encompassed not only assessing their patients and providing treatment for assorted disease processes, but also teaching their patients about preventing disease and promoting a healthy lifestyle.

With the majority of the Nursing profession being female-dominated, it makes sense that the area of preventing heart disease in women would be an area that Nurses would want to become involved and participate in . Nurses have the ability to relate to persons of the same gender and help guide other women to adapting healthy lifestyles. Also, Nurses would be able to educate women about alternative, acceptable treatments to help prevent the onset of heart disease that has been illustrated in the NCEP III guidelines.

As there are limited studies involving postmenopausal women in relation to heart disease and treatment, there seems to be virtually no information or research involving perimenopausal women who may be at risk for CHD. The aim of this study is to evaluate alternative treatments for perimenopausal women who are considered borderline

hyperlipidemia and to see if this will benefit this particular population of women from progressing into CHD once they have entered menopause.

# CHAPTER II

## Review of the Literature

### *Cholesterol Treatment and Women*

With CHD being so prevalent in postmenopausal women, there are limited studies involving women in regards to heart disease and treatment. Historically, women have either not been included in research studies for CHD or were included in small numbers in randomized control trials (RCT) that did not crossover well to the general population of women. Studies that were conducted to evaluate the effectiveness of the use of statins (cholesterol-lowering medications) in preventing heart disease has been limited in including women in their studies. (Ltd, 2005).

### *Women and Statins*

In a study done by Ansell, et al (2005), it was recognized that there is a disparity between men and women in regards to diagnosing and treating for early CHD. It was the opinion that both women and physicians were unaware of the prevalence and mortality of CHD in women (Ansell, 2006). Providers may have difficulty assessing a woman with CHD because women present with such subtle signs that may not be directly correlated to heart disease. This would include abdominal fullness, dyspnea, etc. Ansell, et al (2005) identify that one in three high risk women with CHD do receive treatment, however, physicians tend to down score the woman's risk factors to low.

The purpose of this study was to assess if there was a difference between men and women in regards to achieving NCEP III treatment goals for lipid management. The

study surveyed data from 376 physicians who were considered to be high volume prescribers for cholesterol-lowering treatments. Medical information, lab data, and therapies were included in the data that was being analyzed for the study. Of the 376 physicians, 90% were men and 42% were in Family Practice (Ansell, 2006).

The patient sample included an n=4,885 and of this number, 2,782 (51%) were men and 2,103 (43%) were women. The age range was between 20-75 years and the patients had been treated with a low fat/low cholesterol diet and/or medication for the last three months. Risk factors for the patients were determined by the NCEP III guidelines. High risk included a patient with established CHD, Diabetes, present smoker, Metabolic Syndrome, and/or an Acute Coronary Syndrome. For women, risk factors were based on the American Heart Association's guidelines and the Framingham Study Risk Factor. A woman at low risk had 0-1 risk factors and < 10% risk of CHD according to Framingham. Intermediate risk included 2+ risk factors and a 10-20% risk of CHD in the next ten years. High risk included known CHD and risk equivalents along with >20% risk of CHD in the next ten years (Ansell, 2006).

The results of the study showed that LDL-C achievement was equal between both men and women with low risk (89% & 88%) and intermediate risk factors (75% & 76%) (Ansell, 2006). However, women with high risk factors had a lower achievement of LDL-C goals compared to men in the same risk group (50% vs. 60%; $p<0.001$) (Ansell, 2006).

In regards to management by the physician, the study showed that fewer women were managed by a sub-specialist (Cardiologist or Endocrinologist) compared to men (22.6% vs. 26.8%; $p<0.001$) (Ansell, 2006). There was a statistically significant finding

in both men and women achieving cholesterol lowering goals when treated by their primary physician and a non-significant statistic when treated by the sub-specialist.

Women in the high risk category with known CHD and Risk Equivalents had a lower level of achieving desired LDL-C compared to men (17% vs. 18%) and also a lower referral to a specialist compared to men (18% vs. 28%) (Ansell, 2006).

This study did identify a sub-group of women who have a high risk of CHD, yet are not being managed as aggressively as their male counterparts in regards to referrals to specialists or utilizing cholesterol-lowering treatments. The study did utilize a very large percentage of male physicians (90%) and may have had a different outcome if more female physicians or female health care providers were included in the study.

Bazian Ltd. (Ltd, 2005) performed a meta-analysis of five large cholesterol studies to evaluate if the effectiveness of taking statin medications had a positive outcome on cardiovascular events for women without a diagnosis of CHD. The events that were being assessed included total mortality, CHD mortality, non-fatal MI, revascularization, or CHD events. Included in this meta-analysis was the AFCAPS/TexCAPS random control trials (RCT) that was performed between the years of 1998-2001. The study evaluated the statin Lovastatin (20mg-40mg/day) vs. placebo and a low-fat, low-cholesterol diet. Of the 6,605 participants, 997 were women. The results showed that women alone taking Lovastatin did not show any effect on total mortality (RR 1.53, 95% CI 0.62-3.81); CHD mortality (RR 2.99, 95% CI 0.12-73.3) non-fatal MI (RR 0.69, 95% CI 0.21-2.28); revascularization (RR 0.87, 95% CI 0.33-2.31); or CHD events (RR 0.55, 95% CI 0.22-1.34) (Ltd., 2005).

The ALLHAT-LLT RCT evaluated Pravastatin (40mg/day) vs. usual care over a 4.8 year period. The study included 10,355 participants with 5,051 of that number being women. For both men and women, there was no difference in mortality outcome between treatment and control groups. Yet, for women, Pravastatin did not have any effect on total mortality (RR 0.98, 95% CI 0.83-1.17) or CHD events (RR 1.10, 95% CI 0.57-2.12) (Ltd, 2005).

The ASCOT-LLA RCT evaluated Atorvastatin 10mg vs. placebo over a 3.3 year period. It included 10,305 participants with 1,942 being women. Results from this study showed a lower incidence of non-fatal MI and fatal CHD in the group that was taking the Atorvastatin ($p$=0.0005) (Ltd, 2005). For women who were taking the Atorvastatin, there was no effect on CHD events (RR 1.10, 95% CI 0.57-2.12) (Ltd, 2005).

The ACAPS trial was conducted between the years of 1992-1994 and had a factorial design with four interventional groups. This consisted of lovastatin-warfarin, lovastatin-warfarin placebo, lovastatin placebo-warfarin, and lovastatin placebo and warfarin placebo. The length of the study was 33-36 months. There were 919 participants between the ages of 40-79 years and 441 of those participants were women. For women alone, the lovastatin did not have any effect on total mortality (RR 0.09, 95% CI 0.01-1.70); CHD mortality (RR 0.35, 95% CI 0.01-8.47); or non-fatal MI (RR 0.35, 95% CI 0.04-3.31)

In the HPS study, 20,536 participants were included to compare the effect of treatment with Simvastatin 40mg/day with placebo. This study's length was five years and included 5,082 women. Findings showed that both men and women in the treatment groups did show significance in reduction of CHD events yet for women alone, only

reduction in CHD events was significant (RR 0.76, 95% CI 0.62-0.94; *p* value not given) (Ltd, 2005).

The meta-analysis statistics of all five studies combined showed that the use of statins did not have any effect on total mortality (RR 0.95, 95% CI 0.62-1.46); CHD mortality (RR 1.07, 95% CI 0.47-2.40); non-fatal MI (RR 0.61, 95% CI 0.22-1.68); revascularization (RR 0.87, 95% CI 0.33-2.31); or CHD events (RR 0.87, 95% CI 0.69-1.09) in women who have not been diagnosed clinically with CHD (Ltd, 2005).

In a review article titled "*Women may not achieve same cardiovascular benefits from statins as men*"(*"Women may not achieve same cardiovascular benefits from statins as men," May 2007),* a meta-analysis study was discussed that compared men and women in relation to the benefit of decreasing CHD risk by taking statin medication. 14 RCT's were evaluated that included a total of 54,160 men and 17,818 women. The inclusion criteria of the RCT's had to show a comparison between statin treatment with placebo or a routine diet with a follow-up period of 48 weeks. The meta-analysis evaluated incidences of death, unstable angina, revascularization, MI, or stroke. Evaluating risk factors of CHD, the results showed that a risk of greater than one of these events showed to be significantly reduced when using a statin drug for both men and women (Men- RR 0.76; 95% CI .070-0.81 & Women- RR 0.79, 95% CI 0.69-0.90) ("Women may not achieve same cardiovascular benefits from statins as men," May 2007). For men alone receiving treatment, there appeared to be significant results for decrease in MI (RR-0.72; 95% CI 0.64-0.81) and a trend towards reducing mortality (RR-0.84, 95% CI 0.69-1.02) and stroke (RR-0.91, 95% CI 0.71-1.17) ("Women may not achieve same cardiovascular benefits from statins as men," May 2007). For women, there was a trend towards

reduction in MI (RR-0.89, 95% CI 0.71-1.12) but no reduction in the risk of mortality (RR-1.00, 95% CI 0.85-1.18) or stroke (RR-1.14, 95% CI 0.82-1.59) ("Women may not achieve same cardiovascular benefits from statins as men," May 2007).

Overall, women did not show a benefit in reduction of stroke or risk of mortality when being treated with a statin medication compared to men who did generally show improvement. The limitation of this study was that it had a small sample size of women to compare with men.

*Research on Psyllium*

Soluble fiber, such as Psyllium, has also shown to be effective in lowering cholesterol. In the Scottish Heart Health study, dietary fiber was shown to reduce the risk of CHD and decreased mortality while The Nurse's health study showed that 10-g/day increase fiber intake was associated with a 20% reduction in CHD (Kris-Etherton, 2002). A daily intake of Pysllium of 10-g/day has been shown to decrease total cholesterol by 4% and LDL-C by 7% (Kris-Etherton, 2002).

The research study done by Anderson, et al (2000) evaluated the long-term effects and safety of taking Psyllium husk to lower cholesterol. The sample included both men and women who had a diagnosis of hyperlipdemia. They were placed on an eight week American Heart Association Step 1 diet and then randomized into the Psyllium (5.1gm twice/day) or microcrystalline cellulose (insoluble fiber taken twice/day) based on the inclusion criteria for LDL-C. Of the 459 initial participants, 200 completed the study with the sample size of the placebo group being 39 and the Psyllium group of 161. The treatment phase was 26 weeks.

Results from this study showed that during the dietary adaptation phase that included 248 participants, Cholesterol and LDL-C values decreased by 3.9% and 4.4% respectively (J. W. Anderson, Davidson, M.H., Blonde, L., Brown, W.V., Howard, W.J., Ginsberg, H., Allgood, L.D., & Weingand, K.W., 2000). During the treatment phase, Psyllium decreased total Cholesterol and LDL-C by 2.1% and 2.9% respectively while the placebo results showed an increase of these two values at 2.6% and 3.9% (J. W. Anderson, Davidson, M.H., Blonde, L., Brown, W.V., Howard, W.J., Ginsberg, H., Allgood, L.D., & Weingand, K.W., 2000). After six months of treatment, Psyllium showed a decrease in total Cholesterol and LDL-C compared to the placebo group (4.7% & 6.7%; $p<0.001$) (J. W. Anderson, Davidson, M.H., Blonde, L., Brown, W.V., Howard, W.J., Ginsberg, H., Allgood, L.D., & Weingand, K.W., 2000). The study showed no differences in cholesterol outcomes between men and women. Overall, both men and women benefited in lower total Cholesterol and LDL-C values on the Psyllium (J. W. Anderson, Davidson, M.H., Blonde, L., Brown, W.V., Howard, W.J., Ginsberg, H., Allgood, L.D., & Weingand, K.W., 2000).

The study did show that Psyllium was effective in lowering cholesterol over a long period of time. However, the final sample population appeared to be not evenly distributed in size with the placebo group being significantly smaller in number when compared with the Psyllium group.

Anderson, et al (2000) conducted a meta-analysis of eight studies to determine the size and consistency of Psyllium's effects on lowering cholesterol along with the safety of its use. The sample consisted of 656 adult subjects that had a diagnosis of mild to moderate hyperlipidemia. The participants were between the ages of 24-83 years with a

mean age of 55.2 in the Psyllium group and 54.5 in the Placebo group (J. W. Anderson, Allgood, L.D., Lawrence, A., Atringer, L.A., Jerdack, G.R., Hengehold, D.A., & Morel, J.G., 2000). There were 384 participants in the Psyllium group and 272 participants in the Placebo group. The design of the study included an eight week lead-in with a low-fat diet phase and then continued with either taking Psyllium 10.2gm/day along with a low fat diet vs. Placebo of taking cellulose $\geq$ eight weeks. The results showed that Psyllium decreased total Cholesterol by 4% ($p<0.0001$), LDL-C by 7% ($p<0.0001$), and the ratio of apoB to apo A-I by 6% ($p<0.05$) from baseline results compared to Placebo (J. W. Anderson, Allgood, L.D., Lawrence, A., Atringer, L.A., Jerdack, G.R., Hengehold, D.A., & Morel, J.G., 2000). However, Psyllium did show an increase from baseline with Triglycerides and apo A-I ($p<0.05$) (J. W. Anderson, Allgood, L.D., Lawrence, A., Atringer, L.A., Jerdack, G.R., Hengehold, D.A., & Morel, J.G., 2000). It did not show any effect on HDL-C concentrations and there were no significant differences of Triglyceride levels between the Psyllium and Placebo groups (J. W. Anderson, Allgood, L.D., Lawrence, A., Atringer, L.A., Jerdack, G.R., Hengehold, D.A., & Morel, J.G., 2000).

In regards to treatment outcome differences between men and women, the Psyllium showed a reduction of LDL-C over a eight week period for both men and women when compared to Placebo (J. W. Anderson, Allgood, L.D., Lawrence, A., Atringer, L.A., Jerdack, G.R., Hengehold, D.A., & Morel, J.G., 2000).

A study done by Jenkins, et al (2002) assessed the efficacy of the dose of fiber in reducing cholesterol values. The study consisted of 68 participants that included 37 men and 31 postmenopausal women. The mean age of the study participants was 60 ± 1 year

(33-82). The experimental group received a high fiber diet consisting of four servings per day of food containing β-glucan or Psyllium 8gm/day. The control group received a low fat/low cholesterol diet. The study was a randomized crossover study with a time component of four weeks for each experimental or control groups. Blood pressure was assessed as well at the baseline, two, and four week points of the study. Results showed that a high fiber diet decreased total Cholesterol ($p$=0.003), HDL-C ($p$=0.001), LDL:HDL ratio ($p$=0.015), and apo B: Apo AI ($p$=0.076) when compared to the control group (D. J. A. Jenkins, Kendall, C.W.C., Vuksan, V., Vidgen, E., Parker, T., Faulkner, D., et al, 2002). There appeared to be a reduction of cardiovascular risk according to the Framingham Study guidelines ($p$=0.003) and a small decrease in blood pressure for the Psyllium group compared to the control group (D. J. A. Jenkins, Kendall, C.W.C., Vuksan, V., Vidgen, E., Parker, T., Faulkner, D., et al, 2002).

The study supported the claim that a diet high in fiber can lower cholesterol and the risk of CHD. However, the study had a small sample size and for the female population, included only post-menopausal women. Also, the design of the study only allowed each group to be on their respective treatments for four weeks. In most cholesterol treatment studies, data is collected over an eight week period to be able to see significant changes.

*Flaxseed Research*

Lucas, et al (2001) conducted a study to examine the effects of flaxseed on lipid metabolism in postmenopausal women who were not taking hormone replacement medication. This double-blind randomized study included 58 women who were placed into two groups; those taking 40gm of ground flaxseed or a wheat-based comparative

regimen. The results of the study did show improvement of lipid levels for the women who were taking ground flaxseed. There was a significant decrease in total cholesterol and non-HDL-C by 6% and a non-statistical significant decrease of LDL-C by 4.7% and triglycerides by 12.8% (Lucas, 2001). Serum apolipoprotein A-l and B were significantly reduced by 6% and 7.5% respectively (Lucas, 2001).

Jenkins, et al (1999) research study also showed significant results in the use of flaxseed on lowering cholesterol values. 29 participants including both men and postmenopausal women were involved in a randomized crossover study comparing 50gm of partially defatted flaxseed and 20gm of wheat bran that were baked into muffins. The findings showed that partially defatted flaxseed did reduce total cholesterol (4.6%; $p$=0.001), LDL-C (7.6%; $p$<0.001), and apolipoprotein A-1 (5.8%; $p$=0.005) compared to the control group of wheat bran (D. J. A. Jenkins, Kendall, C.W.C., Vidgen, E., Agarwal, S., Rao, A.V., Roseberg, R.S., et al, 1999).

Both of these studies did show improvement in cholesterol values when using flaxseed. However, the sample sizes were not large and they included only post-menopausal women in the sample.

*Summary*

Overall, there are limited studies involving women with heart disease and treatment. The random controlled studies that evaluated the effects of statin drugs were not as favorable for women as they were for men. Women who are in a high risk category for CHD did not benefit from statin use in regards to lowering their total Cholesterol or LDL-C values and no significant decrease in risk for an unfavorable outcome related to CHD. Part of this may be attributed to women being scored lower for

risk of heart disease by their physicians due to either women not understanding signs and symptoms of heart disease or their physician being unenlightened on the subtle differences in presentation of symptoms of CHD between the two genders.

Psyllium and Flaxseed are both phytoestrogens and, according to the NCEP III guidelines, they can be effective in lowering cholesterol and decreasing the risk of heart disease. However, the studies that are available have included a smaller sample size when compared to the RCT's involving statin treatment and are only looking at postmenopausal women and not addressing the needs for perimenopausal women who have borderline hyperlipidemia. According to the NCEP III guidelines, perimenopausal women with borderline hyperlipidemia would not qualify for treatment with the statin drugs. According to the guidelines, stanols and soluble fiber would be an alternative to help lower cholesterol levels. Therefore, could the effects of Flaxseed SDG improve perimenopausal women's borderline hyperlipidemia when compared to Psyllium?

# CHAPTER III

## Method

### *Sample*

The sample size for this study included initially, twelve perimenopausal women between the ages of 35-48 years with defined mild hyperlipidemia (Total cholesterol 200-255mg/dL, HDL-C <50mg/dL, LDL-C 130-165mg/dL, Triglycerides 150-320mg/dL, and VLDL >30mg/dL). The study participants met the inclusion criteria of: (1) Two out of Five abnormal values of the lipid panel according to NCEP III guidelines, (2) a last menstrual period (LMP) within the month of the date of entry into the study, 3) a Body Mass Index (BMI) < 40, and (4) had a normal Complete Blood Count, Thyroid Stimulating Hormone level, and Basic Metabolic Panel. They also met the exclusion criteria by not having the following diseases: A diagnosis of cancer, liver disease, renal disease, uncontrolled hypothyroidism or hyperthyroidism, gastrointestinal disorders, Insulin Dependent Diabetes, uncontrolled Adult Onset Diabetes Mellitus Type II, a history of Coronary Artery disease, an Arrhythmia, or taking a cholesterol-lowering prescription medicine.

The participants were recruited from an ambulatory medical clinic in Southern California by evaluating the clinic's database for women between the age of 35-50 years who have an ICD-9 diagnosis of 272.4 (hyperlipidemia) on their medical charts, fit the inclusion and exclusion criteria of the study, and once identified, discussed with their

Provider about contacting the patient to volunteer for the study. Other methods of recruitment included a flyer that was posted in a local gym in the same area as the clinic.

Once a potential candidate for the study was identified, permission was verbally obtained from their Provider to contact the candidate about the study. The candidate was then contacted through the Providers' office staff to discuss interest in participating in the study. Once the candidate agreed, she was directed to contact the Principal Investigator (PI) and was informed further about the study. An appointment was then set up between the participant and the PI to enter into the study. Date, time, and location of the meeting were made at the convenience of the participant.

At the recruitment meeting, the participant was educated in more detail about the study in regards to the time frame of the study, the products the participant may be taking while on the study, and the lab work schedule. Risk and benefits of the study were discussed and written consent was obtained from the participant (See Appendix B). Also, the participant completed a Demographic questionnaire (See Appendix C ) and the Eating Pattern Assessment Tool (EPAT #1) (See Appendix D). The participant randomly drew a number from a container which indicated the study group the participant would be assigned. An odd number indicated the participant would be in the Control group of Psyllium (Group 1) and an even number indicated the Experimental group of Flaxseed SDG (Brevail SDG) (Group 2). The participant was then given their study product along with verbal and written instructions on how to take the product. Also, a folder packet was provided to the participant that included three more EPAT questionnaires to be completed at the time of their lab draws and a copy of their informed consent. The participants were contacted at the eight week period to meet the PI at a lab in the

Southern California area to have their first fasting lab draw completed. At that time, they were instructed to complete their EPAT #2 questionnaire and turn this in to the PI when they met at the lab. The participants were given their remaining lab requisitions for the remainder of the study and were directed to bring the appropriately marked lab requisition with them each time they returned to the lab. One week prior to the two week and six week washout periods, the participant was contacted by the PI by telephone to return to the lab in one week for their fasting lab draw. The participant was also instructed to complete EPAT #3 & EPAT #4, after each lab draw respectively, and to mail them in the self-addressed envelope provided in their packet back to the PI.

*Instruments*

Cholesterol values were tested by using the VAP-II cholesterol test (See Appendix E). The VAP measures total LDL-C-direct, total HDL-C-direct, total VLDL-C-direct, Total Cholesterol, Triglycerides-direct, and total Non-HDL-C (LDL + VLDL). It also measures Lp(a) and hsCRP. According to Atherotech, the designer of the VAP II, direct measurement of the LDL-C rather than the Friedewald equation which evaluated LDL-C based on measuring total cholesterol, HDL-C, and Triglycerides gives a much more accurate look at the cholesterol values and the risk of a patient having CHD (Paxton, 2002). It is believed that with the Friedewald cholesterol measurement, there was a larger chance of receiving a false low LDL if the triglyceride level was high (Paxton, 2002). VLDL-C is the main carrier for Triglycerides, and if elevated, can be a risk for CHD (Atherotech). Non-HDL Cholesterol is the combination of LDL + VLDL-C. It has shown to be a better predictor of CHD rather than LDL-C alone (Atherotech). Lp(a) reflects a genetic risk factor for heart disease and it does not respond to the usual

cholesterol lowering drugs (Atherotech). hsCRP is a marker for inflammatory reactions that are occurring during an acute phase of metabolic, immunologic, or infective processes in the body (Gotto Jr., 2006). Recent research has revealed that CRP may be expressed from atherosclerotic lesions, coronary artery smooth muscle cells, aortic endothelial cells, and adipocytes and CRP levels have been found to increase after a MI event (Gotto Jr., June 29, 2006). Chronic production of CRP from atheramatous tissue or coronary artery smooth muscle can be measured by the high-sensitive CRP assay and this can be used to predict risk factor for a coronary event (Gotto Jr., June 29, 2006).

The VAP-II uses a "non-segmented continuous flow (controlled-dispersion) analyzer for the enzymatic analysis of cholesterol in lipoprotein classes separated by a short spin (47 min) single vertical ultracentrifugation" (Kulkarni, 1994). A study comparing the Northwest Lipid Research Laboratories with the VAP-II showed a correlation of total and lipoprotein values as well as Lp(a) with an r=0.907 (Kulkarni, 1994). The reproducibility and accuracy of the VAP-II is within the guidelines set by the Centers for Disease Control-National Heart, Lung, and Blood Institute (Kulkarni, 1994).

Each phase of the study included an assessment of the participants' current diet using the Eating Pattern Assessment Tool (Peters JR, 1994). The tool was developed out of the University of Minnesota and permission to use the tool was given by the University. The EPAT is a self-administered food questionnaire that assesses foods high in fat and cholesterol content. It consists of two sections; the first section contains 12 questions that assesses intake of food that is considered high in fat and cholesterol.

Section two contains 11 questions that assesses diet intake of lower fat food groupings (See Appendix D). The goal of the tool is to:

> 1) Assess the overall intake of dietary fat and cholesterol; 2) assess the frequency with which a person eats foods within each food grouping, and 3) provide an educational message regarding types and amounts of foods that should be eaten to achieve a nutritious, low fat diet (Peters, 1994, p.1008).

Reliability and validity of the tool were done using repeated measures on 436 blue-collar and white-collar employees who were randomly selected and completed the EPAT on five visits. The test-retest reliability for Section 1 and Section 2 was $r>.70$ over 3 time periods except for Section 2 at four months apart which was .69 (Peters JR, 1994). The validity for Section 1 ranged from 0.55 to 0.56 across all five visits. Section 2 correlations were not as strong as Section 1 and this was believed because the food items in Section 1 were lower in fat and cholesterol (Peters JR, 1994).

The tool has a 1-4 scoring point method and in Section 1, consumption of the highest fat and cholesterol food items (found in column 1) is assigned a score of 4 points. Column 2 is 3 points, Column 3 is 2 points, and Column 4 receives 1 point. Ideally, a low score is acceptable for Section 1. Section 2, higher points are assigned to the column on the right and encourages a higher nutritional score (Peters JR, 1994).

*Data Collection Procedures*

The research study data was collected by the Principal Investigator and analyzed by a statistician. The study was a double-blind, randomized, experimental pilot study with test and control phases. Subjects were randomized into the control Group 1 of Psyllium 11.70gm/day and the experimental Group 2 of Brevail SDG 200mg/day. Compliance with the study medication was evaluated by distributing the correct amount of the product to the participants that covered the eight week period and the PI validated

with the participants via telephone that the entire product had been taken in its entirety as directed at the end of the eight week period. The VAP II lab was performed at week eight and at the end of two washout periods of two weeks and one month (See Table 2). The purpose of the washout time periods is to make sure there is no residual from the use of the Brevail SDG or the Psyllium in order to retest lipid levels off the experimental and control supplements. The lab work was drawn at a lab in Southern California and shipped to Atherotech in Alabama who analyzed the VAP-II lab and returned the results to the PI through electronic means.

Table 2

*Design of the Study*

| | **TIME 1** | **TIME 2** | **TIME 3** |
|---|---|---|---|
| **GROUPS** | **WEEKS** | **WASHOUT** | **WASHOUT** |
| | **1-8** | **2 WEEKS** | **4 WEEKS** |
| **Group 1** | Psyllium | | |
| | 11.70gm/day | | |
| **Group 2** | Brevail SDG | | |
| | 200mg/day | | |

*Human Subjects*

At all times during the research phases of the study, human subjects were protected under the guidelines for the expedited Investigational Review Board (IRB) as set forth by the University of San Diego (See Appendix F). The potential risk and

benefits of the study were discussed with the participants at the entry of the study and informed consent was obtained. The risks to the participants were minimal and included the potential for increase flatulence while on the study product or receiving a hematoma from a lab draw. None of these risks were reported during the entire time of the study. The benefit of the study was to collect data in order to identify if there was a benefit to taking Flaxseed SDG to prevent further development of hyperlipidemia and decrease the risk for coronary heart disease in the perimenopausal population. All information obtained about the participants was kept private and confidential except for the reporting of the final results.

Participation in the study was voluntary and all participants were aware that they could withdraw from the study at any time. The research proposal was submitted and approved prior to the initiation of the study by the University of San Diego's Human Subjects Committee.

*Data Analysis*

All eleven participants who received the study products and had an acceptable baseline measurement of Cholesterol, Complete blood count, Thyroid Stimulating Hormone, and a Mini-Chemistry-12 panel for entry into the study were included in efficacy analysis. The sample population was measured using descriptive frequencies to analyze the covariate variables of age, socioeconomic status (SES), race, and BMI. Lipid results that included a Total Cholesterol, Total HDL-Cholesterol-direct, Total LDL-Cholesterol-direct, Triglycerides-direct, Total Non-HDL Cholesterol, Total VLDL-Cholesterol-direct, Lp(a) Cholesterol, and hsCRP were analyzed at Time 1 (eight weeks on the study product), Time 2 (two weeks off the product) and Time 3 (six weeks off the

study product). The hypothesis that Brevail SDG will lower lipid levels in perimenopausal women when compared to Psyllium was tested by evaluating the continuous independent variables of Brevail SDG and Psyllium as well as the covariate variable including the EPAT scores along with the continuous dependent variable of the VAP-II lipid results.

This data was analyzed by the statistician using the SPSS version 15 program and evaluating correlated *t*- tests to compare both groups at Time 1 vs. 2, 1 vs. 3, and 2 vs. 3 for the VAP-II lab. The EPAT was evaluated by comparing sections 1 and 2 individually at Time 1 vs. 2, 1 vs.3, 1 vs. 4, 2 vs. 3, 2 vs. 4, and 3 vs. 4. The correlated *t*-test was used because it allows comparison between two groups over a period of time. It requires a continuous dependant variable in order to allow the two groups in the experimental design to be compared (Munro, 2005) . According to Munro (2005), "In the correlated *t*-test, a correction is made that has the effect of increasing *t*, thus making it more likely to find a significant difference if one exists" (p. 145). The purpose for using correlated *t*-test for this particular study was to be able to observe for any changes in cholesterol values during the study time points of the control and experimental groups and to be able to compare between the two groups. Results were reported at a 2-tailed $\alpha$=0.05 level.

# CHAPTER IV

## Results

### *Description of the Sample*

Of the twelve participants who entered into the study, only eleven women completed the study. The reason for attrition of the one participant from the study was the complaint about the taste of the product the participant was assigned to take.

The Control group (Group 1) consisted of five participants with an age range of 36-48 years with a mean of 40.65 (95%CI- 33.79/47.52) and the Experimental group (Group 2) consisted of six participants with an age range of 36-48 years with a mean of 43.61 (95% CI- 37.92/49.29) (See Table 3). There were four Caucasians (80 %) and one Asian (20%) in Group 1 and five Caucasians (83 %) and one Asian (17 %) in Group 2 (See Table 4). The income status in Group 1 included one participant with an annual income between $0-$30,000 per year (20 % ); two participants with an income of $75,001-100,000 per year (40 %); and two participants with an income >$100,00 per year (40% ) (See Table 4 ). Group 2 had one participant with an annual income of $30,001-$50,000 (17 %); two participants with an income of $50,001-$75,000 (33 %) per year; and three participants with an income >$100,000 (50 %) per year (See Table 4). The BMI for Group 1 was a mean of 29.30 (95% CI-24.52/34.08) (See Table 3). The BMI for Group 2 was a mean of 29.75 (95% CI- 24.84/34.66) (See Table 3). The *t*-test that was performed on both age and BMI did not show to be statistically significant between both groups (Age-p=0.396; BMI-p=0.868) (See Table 3).

Table 3
*Descriptive frequencies for Age & BMI*

| **AGE** | **GROUP 1** | **GROUP 2** | ***p*-VALUE** |
|---|---|---|---|
| | N=5 | N=6 | 0.396 |
| MEAN | 40.65 | 43.61 | |
| 95% CI | | | |
| UPPER BOUND | 33.79 | 37.92 | |
| LOWER BOUND | 47.52 | 49.29 | |
| MEDIAN | 38.42 | 46.43 | |
| STD. DEVIATION | 5.530 | 5.417 | |
| **BMI** | **GROUP 1** | **GROUP 2** | 0.868 |
| MEAN | 29.30 | 29.75 | |
| 95% CI | | | |
| UPPER BOUND | 24.52 | 24.84 | |
| LOWER BOUND | 34.08 | 34.66 | |
| MEDIAN | 28.50 | 28.75 | |
| STD. DEVIATION | 3.850 | 4.677 | |

Table 4
*Descriptive Frequencies for Race & SES*

| | **GROUP 1** | **PERCENTAGE %** | **GROUP 2** | **PERCENTAGE %** |
|---|---|---|---|---|
| **RACE:** | | | | |
| Caucasian | 4 | 80 | 5 | 83 |
| Asian | 1 | 20 | 1 | 17 |
| **SES:** | | | | |
| $0-$30,000/year | 1 | 20 | - | - |
| $30,001-$50,000/year | - | - | 1 | 17 |
| $50,001-$75,000/year | - | - | 2 | 33 |
| $75,001-$100,000/year | 2 | 40 | - | - |
| >$100,000/year | 2 | 40 | 3 | 50 |

*The Effect of Diet*

The EPAT questionnaire was analyzed showing time points (1-4) and divided between the two sections of the questionnaire. As described in the previous chapter, the EPAT's first section evaluates food intake that is high in fat. A lower score on this section reflects a lower fat diet. The second section reflects a diet where healthier choices are being made in regards to a lower fat diet. The desired results are a higher score.

When analyzing each group for each point in time the questionnaire was given, Section 1 showed a lower mean for time 1 & 3 (24.2/24.2) and a higher mean at point 2 & 4 (25.8/26.6) for Group 1. Group 2 had a higher mean (27/26.67) at time 1 & 2 and a lower mean (23.83/24.67) at time 3 & 4. Section 2 for Group 1 showed a higher mean (27.6) at time 1, but then the mean began to decrease by time 4(25.6) (See Table 5). Meanwhile, Group 2 showed a higher mean (28.83) at time 1 with a slight decrease in the mean value at time 2 (27.83). However, the mean value increased at both time 3 & 4 (26.67/29.33) (See Table 5).

In comparison of times, Group 1 showed an increase in negative mean differential value throughout all four time periods for Section 1, yet none of the values were statistically significant (See Table 6). Mean values for Section 2 also showed a decrease in mean differential for all time points and were not statistically significant except there was an improvement at time 3 vs. 4 with a mean differential of -0.600 and a *p*-value of 0.675 (See Table 6 ).

Group 2 showed an increase in differential mean values for Section 1 throughout the majority of time periods that were not statistically significant (See Table 6).

However, there was a decrease in the mean differential (-0.833) with a non-statistical *p*-value of 0.55 at time 3 vs. 4. Section 2 showed a decrease in differential mean value for time 1 vs. 2 (1) and 1 vs. 3 (0.167). However, there was an improvement in differential mean values for the remaining points in time. There was a statistically significant value at time 2 vs. 3 ($p$=0.042), however, the rest of the comparative values were non-statistically significant.

Table 5
*Descriptive Frequencies of EPAT*

| | Brevail SDG | | Psyllium | |
|---|---|---|---|---|
| | **Mean** | **95% CI** | **Mean** | **95% CI** |
| **EPAT Section 1** | | | | |
| Time 1 | 27 | 22.21 / 31.79 | 24.2 | 18.83 / 29.57 |
| Time 2 | 26.67 | 19.41 / 33.93 | 25.8 | 21.20 / 30.40 |
| Time 3 | 23.83 | 19.12 / 28.55 | 24.2 | 19.52 / 28.88 |
| Time 4 | 24.67 | 20.54 / 28.79 | 26.6 | 21.90 / 31.30 |
| **EPAT Section 2** | | | | |
| Time 1 | 28.83 | 25.23 / 32.43 | 27.6 | 23.16 / 32.04 |
| Time 2 | 27.83 | 23.94 / 31.73 | 25.6 | 19.94 / 31.26 |
| Time 3 | 28.67 | 24.70 / 32.63 | 25 | 19.45 / 30.55 |
| Time 4 | 29.33 | 24.61 | 25.6 | 21.16 / 30.04 |

Table 6
*Correlated t-tests of EPAT*

| | Brevail SDG | | | Psyllium | | |
|---|---|---|---|---|---|---|
| **EPAT Section 1** | **Mean Diff.** | **CI 95%** | **p-Value** | **Mean Diff.** | **CI 95%** | **p-Value** |
| Time 1 vs. 2 | 0.33 | (-7.137) / 7.803 | 0.913 | (-1.600) | (-7.594 / 4.395 | 0.5 |
| Time 1 vs. 3 | 3.167 | (-1.906) / 8.240 | 0.169 | 0 | (-4.390) / 4.390 | 1 |
| Time 1 vs. 4 | 2.333 | (-2.836) / 7.503 | 0.298 | (-2.40) | (-8.263) / 3.463 | 0.319 |
| Time 2 vs. 3 | 2.833 | (-2.240) / 7.906 | 0.211 | 1.6 | (-0.656) / 3.856 | 0.12 |
| Time 2 vs. 4 | 2 | (-4.537) / 8.537 | 0.467 | (-0.800) | (-4.014) / 2.414 | 0.528 |
| Time 3 vs. 4 | (-0.833) | (-4.179) / 2.513 | 0.55 | (-2.400) | (-5.977) / 1.177 | 0.136 |
| **EPAT Section 2** | | | | | | |
| Time 1 vs. 2 | 1 | (-1.737) / 3.737 | 0.391 | 2 | (-1.166) / 5.166 | 0.154 |
| Time 1 vs. 3 | 0.167 | (-2.905) / 3.238 | 0.895 | 2.6 | (-0.517) / 5.717 | 0.081 |
| Time 1 vs. 4 | (-0.500) | (-4.468) / 3.468 | 0.759 | 2 | (-2.118 / 6.118 | 0.249 |
| Time 2 vs. 3 | (-0.833) | (-1.623) / (-0.043) | 0.042* | 0.6 | (-0.816) / 2.016 | 0.305 |
| Time 2 vs. 4 | (-1.500) | (-3.676) / 0.676 | 0.137 | 0 | (-2.776) / 2.776 | 1 |
| Time 3 vs. 4 | (-0.667) | (-2.834) / 1.501 | 0.465 | (-0.600) | (-4.283) / 3.083 | 0.675 |

*VAP-II Results*

*Psyllium Group*

The descriptive frequencies of all the VAP-II results evaluate mean values in each time point on the study. Total Cholesterol, LDL-C, and Non-HDL-C showed an increase in mean value from Time 1 to Time 3 (See Table 7). Whereas, HDL-C, Triglycerides, VLDL-C, Lp(a), and hsCRP improved their mean values from Time 1 to Time 3 (See Table 7).

The comparison of time points evaluated the results from the different phases of the study. Total Cholesterol, LDL-C, Non-HDL-C, and hsCRP mean differential values became an increasingly negative value between Time points 1 vs. 2; 2 vs. 3; and 1 vs.3 However, there was no statistical significance (See Table 8). Whereas, HDL-C,

Triglycerides, VLDL-C, and Lp(a) showed improvements in the differential mean values between Time 2 vs. 3 and 1 vs. 3 (See Table 8 ). However, VLDL-C was statistically significant at Time 1 vs. 3 ($p$=0.021) and a very close statistically significant value for Triglycerides at Time 1 vs. 3 ($p$=.055). Otherwise, the other values were not statistically significant.

*Brevail SDG Group*

Evaluating the descriptive frequencies of individual time points for the Brevail SDG, Total Cholesterol and LDL-C had a slight increase in mean values between Time 1 & 3 (See Table 7). HDL-C showed a slight increase in mean value between Time 1 & 3 which reflects an improvement of HDL-C value (See Table 7). Triglycerides, VLDL-C, Non-HDL-C, Lp(a), and hsCRP showed an increase in mean value from Time 1 to Time 2, yet a decrease in mean value from Time 1 to Time 3 (See Table 7 ).

In the comparison of time points, hsCRP and Lp(a) showed an increase in negative differential mean values from Time 1 vs. 3 with an even greater increase in negative differential mean values from Time 2 vs. 3 though there was no statistical significance. LDL-C also showed an increase in negative differential means throughout all time points, yet, there was no statistical significance (See Table 8). Total Cholesterol, HDL-C, Triglycerides, VLDL-C, and Non-HDL-C showed an increase negative mean differential at Time 1 vs. 2 with an improvement in the differential mean values at Time 1 vs. 3 and 2 vs. 3. However, for Total Cholesterol, HDL-C, and Non-HDL-C there was no statistical significance (See Table 8).

Statistically significant values were observed with the Triglyceride level at Time 1 vs. 2 ($p$=0.043) and Time 2 vs. 3 ($p$=0.047). Also, the VLDL-C was statistically significant at all time comparison points ($p$=.047/0.031/0.011) (See Table 8).

Table 7

*Descriptive Frequencies of Brevail SDG & Psyllium VAP- II results*

| | Brevail SDG | | Psyllium | |
|---|---|---|---|---|
| | **Mean** | **95%CI** | **Mean** | **95%CI** |
| **Total Cholesterol** | | | | |
| Time 1 | 222.83 | 194.66 / 251 | 230.6 | 200.11 / 261.09 |
| Time 2 | 228.67 | 195.50 / 261.84 | 227.8 | 199.95 / 255.65 |
| Time 3 | 224.33 | 192.70 / 255.97 | 231.8 | 201.47 / 262.13 |
| **LDL-C** | | | | |
| Time 1 | 149 | 123.22 / 174.78 | 147.2 | 119.92 / 174.48 |
| Time 2 | 149.5 | 124.17 / 174.83 | 147.2 | 122.91 / 171.49 |
| Time 3 | 151.33 | 124.21 / 178.45 | 152 | 127.09 / 176.91 |
| **HDL-C** | | | | |
| Time 1 | 49.33 | 36.38 / 62.28 | 54.2 | 31.11 / 77.29 |
| Time 2 | 51 | 37.88 / 64.12 | 52.6 | 31.30 / 73.90 |
| Time 3 | 51.33 | 35.77 / 66.89 | 55.4 | 31.80 / 79.00 |
| **Triglycerides** | | | | |
| Time 1 | 151.33 | 90.23 / 212.44 | 177 | 96.48 / 257.52 |
| Time 2 | 166.5 | 104.10 / 228.90 | 175.6 | 51.94 / 299.26 |
| Time 3 | 130.83 | 81.19 / 180.48 | 155.4 | 73.73 / 237.07 |
| **VLDL** | | | | |
| Time 1 | 26.5 | 24.45 / 28.55 | 28.4 | 18.56 / 38.24 |
| Time 2 | 30 | 22.10 / 37.90 | 28.2 | 17.01 / 39.39 |
| Time 3 | 24 | 20.56 / 27.44 | 24.8 | 15.83 / 33.77 |
| **Non-HDL-C** | | | | |
| Time 1 | 174.17 | 145.80 / 202.53 | 175.6 | 155 / 196.20 |
| Time 2 | 178.17 | 146.53 / 209.80 | 175.4 | 155.44 / 195.36 |
| Time 3 | 173 | 142.30 / 203.70 | 176.8 | 154.84 / 198.76 |
| **Lp(a)** | | | | |
| Time 1 | 9.67 | 2.23 / 17.11 | 11.2 | 2.19 / 20.21 |
| Time 2 | 9.5 | 3.96 / 15.04 | 11.4 | (-0.63) / 23.43 |
| Time 3 | 10.33 | 4.83 / 15.83 | 9.4 | ( -0.75) / 19.55 |
| **hsCRP** | | | | |
| Time 1 | 4.433 | 1.015 / 7.852 | 4.94 | (-5.257) / 15.137 |
| Time 2 | 3.917 | 1.021 / 6.812 | 3.06 | (-2.32) / 8.441 |
| Time 3 | 11.367 | (-9.085) / 31.818 | 3.88 | ( -2.047) / 9.807 |

*$p<0.05$

Table 8
*Correlated t-tests for Brevail SDG & Psyllium VAP-II results*

| | Brevail SDG | | | Psyllium | | |
|---|---|---|---|---|---|---|
| | **Mean Differential** | **95% CI** | **p-Value** | **Mean Differential** | **95% CI** | **p-Value** |
| **Total Cholesterol** | | | | | | |
| Time 1 vs. 2 | -5.833 | (-26.349) /14.682 | 0.498 | 2.8 | (-11.259) / 16.859 | 0.61 |
| Time 1 vs. 3 | -1.5 | (-15.147) / 12.147 | 0.789 | -1.2 | (-24.386) / 21.986 | 0.893 |
| Time 2 vs. 3 | 4.33 | (-16.568) / 25.234 | 0.617 | -4 | (-21.183)/13.183 | 0.563 |
| **LDL-C** | | | | | | |
| Time 1 vs. 2 | -0.5 | (-21.179) / 20.179 | 0.953 | 0 | (-18.892) / 18.892 | 1 |
| Time 1 vs. 3 | -2.333 | (-12.215) / 7.548 | 0.57 | -4.8 | (-24.771) / 15.171 | 0.541 |
| Time 2 vs. 3 | -1.833 | (-17.727) / 14.060 | 0.779 | -4.8 | (-18.185) / 8.585 | 0.376 |
| **HDL-C** | | | | | | |
| Time 1 vs. 2 | -1.667 | (-6.297) / 2.964 | 0.397 | 1.6 | (-3.712) / 6.912 | 0.45 |
| Time 1 vs. 3 | -2 | (-7.473) / 3.473 | 0.391 | -1.2 | (-7.371) / 4.971 | 0.618 |
| Time 2 vs. 3 | -0.333 | (-8.121) / 7.454 | 0.917 | -2.8 | (-7.561) / 1.961 | 0.178 |
| **Triglycerides** | | | | | | |
| Time 1 vs. 2 | -15.167 | (-29.577) / (-0.756) | 0.043* | 1.4 | (-112.51) / 115.311 | 0.974 |
| Time 1 vs. 3 | 20.5 | (-12.824) / 53.824 | 0.175 | 21.6 | (-0.778) / 43.978 | 0.055 |
| Time 2 vs. 3 | 35.667 | 0.781 / 70.553 | 0.047* | 20.2 | (-85.529) / 125.929 | 0.625 |
| **VLDL** | | | | | | |
| Time 1 vs. 2 | -3.5 | (-6.933) / (-0.067 | 0.047* | 0.2 | (-8.856) / 9.256 | 0.954 |
| Time 1 vs. 3 | 3.5 | 0.477 / 6.523 | 0.031* | 3.6 | 0.880 / 6.320 | 0.021* |
| Time 2 vs. 3 | 7 | 2.450 / 11.550 | 0.011* | 3.4 | (-7.011) / 13.811 | 0.416 |
| **Non-HDL-C** | | | | | | |
| Time 1 vs. 2 | -4 | (-26.819) / 18.819 | 0.671 | 0.2 | (-11.295) / 11.695 | 0.964 |
| Time 1 vs. 3 | 1.167 | (-8.952) / 11.285 | 0.779 | -1.2 | (-21.591) / 19.191 | 0.878 |
| Time 2 vs. 3 | 5.167 | (-14.426) / 24.760 | 0.528 | -1.4 | (-16.898) / 14.098 | 0.814 |
| **Lp(a)** | | | | | | |
| Time 1 vs. 2 | 0.167 | (-3.045) / 3.378 | 0.899 | -0.2 | (-3.862) / 3.462 | 0.887 |
| Time 1 vs. 3 | -0.667 | (-3.963) / 2.630 | 0.625 | 1.8 | (-2.067) / 5.667 | 0.266 |
| Time 2 vs. 3 | -0.833 | (-2.870) / 1.203 | 0.341 | 2 | (-1.926) / 5.926 | 0.23 |
| **hsCRP** | | | | | | |
| Time 1 vs. 2 | 0.5167 | (-1.3051) / 2.3385 | 0.499 | 1.88 | (-2.9564 / 6.7164 | 0.341 |
| Time 1 vs. 3 | -6.9333 | (-26.5976) / 12.7309 | 0.406 | 1.06 | (-4.0615) / 6.1815 | 0.596 |
| Time 2 vs. 3 | -7.45 | (-25.8364) / 10.9364 | 0.345 | -0.82 | (-2.6372) / 0.9972 | 0.279 |

*$p<0.05$

# CHAPTER V

## Discussion

The purpose of this study is to determine if Flaxseed SDG would have an effect on lowering cholesterol levels in perimenopausal women with mild hyperlipidemia. An experimental, pilot, randomized, double-blind study of 11 perimenopausal women was utilized to determine the results. Though the sample size was small, and did not yield a robust study, there were some significant findings and trends for both groups.

### *Synopsis of Brevail SDG Results*

The Brevail SDG group did show significant findings for the VLDL cholesterol-direct during all three time points of the study. The VLDL-C did show a higher mean value at the two week washout period but then decreased in value by Time 3 and an overall improvement between the two and six week washout period. Likewise, the Triglyceride level was statistically significant showing an increase in Triglyceride at the two week washout period and then decreasing dramatically at the six week washout period when compared to the mean value of Time 2. Once again, the overall change in value improved six weeks off the product. According to Barlean's Organic Oils, Inc. the manufacturer of Brevail SDG, the half-life of Brevail SDG is ten hours. Therefore, it cannot be supported that the flaxseed product influenced the improvement of the VLDL cholesterol-direct and Triglyceride levels at the six week washout period when the participants had been off the product.

There was a trend for improvement of values for Total Cholesterol, HDL-C, and Non-HDL-C at the six week washout period when compared to the mean values of being on the Brevail SDG. LDL-C, Lp(a), and hsCRP appeared to have a more favorable differential mean value while on the Brevail SDG compared to being off the product at the six week washout period. In regards to the hsCRP, there was an outlier at the six week washout period. The participant's hsCRP at baseline was 29mg/L; time 1 was 5.80mg/L ; time 2 at 7.70mg/L. At the six week washout period, her hsCRP increased to 50.90mg/L. However, there was no statistical significance at all time points for hsCRP.

*Synopsis of Psyllium Results*

The Psyllium group showed statistical significance for improvement of VLDL-C levels between being on the Psyllium compared to six weeks off the product. The Total Cholesterol, LDL-C, Non-HDL-C, and hsCRP showed a trend for improvement in values when on the Psyllium compared to being off the product for six weeks. HDL-C, Triglycerides, VLDL-C, and Lp(a) appeared to have a trend of improvement six weeks off the product rather than being on the Psyllium.

*Brevail SDG vs. Psyllium*

Comparing Brevail SDG and Psyllium together, both of their values for HDL-C, Triglycerides, and VLDL-C seemed to improve at the six week washout period compared to being on their respective products. However, the VLDL-C was only statistically significant for the Brevail SDG during all time points and for the Psyllium at time 1 vs. 3. Ironically, Lp(a) increased in value off the Brevail SDG and decreased in value on the Psyllium at the six week washout period. Therefore, though non-statistically significant

for both, Lp(a) appeared to respond favorably when taking Brevail SDG rather than Psyllium.

The findings of the EPAT tool were non-significant for the Psyllium group and were statistically significant for the Brevail SDG group for Section 2 at time 2 vs. 3. Overall, according to the analysis, diet did not seem to influence the outcome of the cholesterol values for either group.

In the study performed by Lucas, et al (Lucas, 2001) involving 58 postmenopausal women who took grounded flaxseed, it showed a significant decrease in total cholesterol and non-HDL-C values which the present study did not repeat. However, with the present study, there were non-statistical significant changes with an improvement of the HDL-C at the six week washout period with the flaxseed. Also, Lucas, et al (2001) study showed non-statistical decreases in LDL-C, Triglycerides, and Serum apolipoprotein A-1 and B. The current study also repeated non-statistical findings for decreasing LDL-C and Lp(a) while on the Brevail SDG, yet showed significant values of changes over time with the Triglycerides for increasing at the second week washout period and then decreasing by the sixth week washout period.

Jenkins, et al study (1999) that included 29 participants of both men and postmenopausal women who were taking either 50gm of partially grounded flaxseed or 20gm of wheat bran showed with the flaxseed group significant findings for reduction of total Cholesterol, LDL-C, and Lp(a). As mentioned, there were non-significant statistics that showed lower values for these same components while on the Brevail SDG compared to the six week washout period.

While the original hypothesis that Flaxseed SDG would have an effect on lipid levels in perimenopausal women with mild hyperlipidemia was not supported, there were significant findings with the VLDL-C and Triglycerides that could have been affected indirectly by the flaxseed, though those mechanisms are unknown at this time. Also, even though non-statistically significant, there appeared to be a slight improvement of Total Cholesterol, LDL-C, and Lp(a) while on the Brevail SDG. Based on these findings, there seems to be sufficient evidence to support repeating this study on a larger basis to determine if there truly is an improvement of cholesterol values while taking Brevail SDG.

The limitations of this study included the small sample size, not including the element of exercise as a covariate that could potentially affect the cholesterol levels, and not utilizing the entry- into- study baseline lipid panel results for comparison with the lipid results throughout the study. The entry-into-study baseline labs were, for some participants, almost a year old before the study began and may or may not have reflected the true values of their cholesterol panel when the study began. When the data analysis was originally computed including the baseline lab, it tended to skew the results from the study and did not portray a realistic look at changes from being on the products and the two washout periods. Also, for most of the participants, their initial baseline lipid panels did not include all of the components found on the VAP-II lab that were included in the study, and therefore, it could not provide a true comparison of pre- and post-test results.

Recommendations for this study would include repeating the study using a larger sample size and extending the time phase of being on the study products. This would allow for a more robust study and to allow for a more realistic analysis of determining if

there was a significant difference of lowering cholesterol levels while taking Brevail SDG. Interestingly, both Brevail SDG and Psyllium showed significantly improved values of VLDL-C and Triglycerides at the six week washout point. It may be advantageous to evaluate urine metabolites throughout the study to determine absorption and excretion of the Brevail SDG in order to be able to explain why there was a trend for improvement in the majority of the cholesterol values at the six week washout period and to see if this product did influence its effect.

Also, exercise would be another independent variable to evaluate in the study. This was not included in the present study and could have shown to be a factor that may have influenced cholesterol results. Another recommendation would be to perform a VAP-II lab test at the onset of the study and to be able to compare pre-study cholesterol values with the experimental lab values as well as the two washout periods. This would allow for a more complete view of potential changes in cholesterol values during all time points of the study.

*Implications for Nursing*

Nursing, as a profession, contributes to health care by educating their patients about preventative health, and by doing this, allows their patients to choose behaviors that would lead to healthier lifestyles. This particular study fits in quite well with this philosophy of Nursing by focusing on prevention and evaluating alternative methods of treatment for hyperlipidemia in perimenopausal women in order to prevent them from progressing into CHD once they become menopausal.

It is very important that Nursing become more involved in research in the area of preventative health and evaluating alternative treatments for particular disease processes.

By becoming more proactive in this area of health care, Nurses can take their research findings, apply the findings, and continue to promote and educate their patients about disease prevention. In regards to women's health, it is also imperative that Nursing become more active in conducting research studies since the majority of Nurses are women. Historically, women have not been utilized in research studies. However, that trend has been changing since the 1990's where legislation has encouraged including more women in health care research. It would behoove Nurses to become more involved in developing and implementing research studies that focuses primarily on the unique health care needs of women. By doing this, Nurses can follow their underlying philosophy of caring for an individual as a biopsychosocial being and continue to promote preventative health care in order to decrease the number of individuals who end up with major disease processes.

# CONCLUSION

Heart disease is the number one cause of death in women and those numbers may be on the rise. 500,000 American women are dying from heart disease every year and have a higher incidence of metabolic syndrome and diabetes when compared to men. Scientific research is now acknowledging that women are anatomically different in structure of the coronary arteries and present with different symptoms of an MI when compared to men.

Historically, women were treated the same as men in regards to assessment and treatment of CHD. Earlier research for treatment of heart disease excluded women because it was believed that their hormonal changes may influence the outcome of the studies. Also, there was concern of utilizing women of childbearing years in the studies for fear of causing birth defects. Within the last 15 years, this philosophy has been reversed and we are now seeing more studies including women. However, in regards to treatment of women with statins for lowering cholesterol, there appears to be some question if women receive the same benefit as men in lowering their cholesterol.

The NCEP III guidelines addresses gender differences in their recommendations and are now including special circumstances for women who may be at risk for CHD in regards to treatment for hyperlipidemia. Women with a low-risk score and mild hyperlipidemia, who are not candidates for statin medications, may benefit not only from a low-fat diet and exercise, but also utilizing plant stanols or soluble fiber in the diet to help decrease cholesterol.

Flaxseed is part of the Phytoestrogen category of stanols and is a mammalian lignan that has a weak estrogenic and antiestrogenic activity. It has been compared to a

Selective Estrogen Receptor Modulators (SERMS). Studies that have been performed evaluating flaxseed for lowering cholesterol have been limited and included only postmenopausal women. There have been no studies identified in the literature that addresses perimenopausal women with mild hyperlipidemia in regards to prevention of developing CHD utilizing flaxseed.

This experimental, pilot study evaluated 11 perimenopausal women to determine if Flaxseed SDG (Brevail SDG) could lower cholesterol levels when compared to Psyllium. The results showed a significant value of improving VLDL-Cholesterol Direct over all 3 time points of the study and an improvement of the Triglyceride level at the six week washout period. Otherwise, there were favorable trends in improvement of LDL-C, hsCRP, and Lp(a) while on the Brevail SDG.

Based on these results, it could be supported that there is a need to repeat this study utilizing a larger sample size of perimenopausal women with mild hyperlipidemia in order to determine if flaxseed would benefit in lowering cholesterol. By repeating this study, hopefully, it can allow us to support the use of lignans as a preventative treatment in this particular population who may not qualify for standard cholesterol medication treatment. In time, it may help prevent women from furthering their risk of developing CHD and help to decrease the morbidity and mortality of this prevalent disease in women.

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APPENDICES

## APPENDIX A – *FRAMINGHAM GLOBAL RISK SCORING*

### Estimate of 10-Year Risk for Men

(Framingham Point Scores)

| Age, y | Points |
|---|---|
| 20-34 | –9 |
| 35-39 | –4 |
| 40-44 | 0 |
| 45-49 | 3 |
| 50-54 | 6 |
| 55-59 | 8 |
| 60-64 | 10 |
| 65-69 | 11 |
| 70-74 | 12 |
| 75-79 | 13 |

| Total Cholesterol, mg/dL | Points | | | | |
|---|---|---|---|---|---|
| | Age 20-39 y | Age 40-49 y | Age 50-59 y | Age 60-69 y | Age 70-79 y |
| <160 | 0 | 0 | 0 | 0 | 0 |
| 160-199 | 4 | 3 | 2 | 1 | 0 |
| 200-239 | 7 | 5 | 3 | 1 | 0 |
| 240-279 | 9 | 6 | 4 | 2 | 1 |
| ≥280 | 11 | 8 | 5 | 3 | 1 |

| | Points | | | | |
|---|---|---|---|---|---|
| | Age 20-39 y | Age 40-49 y | Age 50-59 y | Age 60-69 y | Age 70-79 y |
| Nonsmoker | 0 | 0 | 0 | 0 | 0 |
| Smoker | 8 | 5 | 3 | 1 | 1 |

| HDL, mg/dL | Points |
|---|---|
| ≥60 | –1 |
| 50-59 | 0 |
| 40-49 | 1 |
| <40 | 2 |

| Systolic BP, mm Hg | If Untreated | If Treated |
|---|---|---|
| <120 | 0 | 0 |
| 120-129 | 0 | 1 |
| 130-139 | 1 | 2 |
| 140-159 | 1 | 2 |
| ≥160 | 2 | 3 |

| Point Total | 10-Year Risk, % |
|---|---|
| <0 | <1 |
| 0 | 1 |
| 1 | 1 |
| 2 | 1 |
| 3 | 1 |
| 4 | 1 |
| 5 | 2 |
| 6 | 2 |
| 7 | 3 |
| 8 | 4 |
| 9 | 5 |
| 10 | 6 |
| 11 | 8 |
| 12 | 10 |
| 13 | 12 |
| 14 | 16 |
| 15 | 20 |
| 16 | 25 |
| ≥17 | ≥30 |

## Estimate of 10-Year Risk for Women

(Framingham Point Scores)

| Age, y | Points |
|---|---|
| 20-34 | −7 |
| 35-39 | −3 |
| 40-44 | 0 |
| 45-49 | 3 |
| 50-54 | 6 |
| 55-59 | 8 |
| 60-64 | 10 |
| 65-69 | 12 |
| 70-74 | 14 |
| 75-79 | 16 |

| Total Cholesterol, mg/dL | Points | | | | |
|---|---|---|---|---|---|
| | Age 20-39 y | Age 40-49 y | Age 50-59 y | Age 60-69 y | Age 70-79 y |
| <160 | 0 | 0 | 0 | 0 | 0 |
| 160-199 | 4 | 3 | 2 | 1 | 1 |
| 200-239 | 8 | 6 | 4 | 2 | 1 |
| 240-279 | 11 | 8 | 5 | 3 | 2 |
| ≥280 | 13 | 10 | 7 | 4 | 2 |

| | Points | | | | |
|---|---|---|---|---|---|
| | Age 20-39 y | Age 40-49 y | Age 50-59 y | Age 60-69 y | Age 70-79 y |
| Nonsmoker | 0 | 0 | 0 | 0 | 0 |
| Smoker | 9 | 7 | 4 | 2 | 1 |

| HDL, mg/dL | Points |
|---|---|
| ≥60 | −1 |
| 50-59 | 0 |
| 40-49 | 1 |
| <40 | 2 |

| Systolic BP, mm Hg | If Untreated | If Treated |
|---|---|---|
| <120 | 0 | 0 |
| 120-129 | 1 | 3 |
| 130-139 | 2 | 4 |
| 140-159 | 3 | 5 |
| ≥160 | 4 | 6 |

| Point Total | 10-Year Risk, % |
|---|---|
| <9 | <1 |
| 9 | 1 |
| 10 | 1 |
| 11 | 1 |
| 12 | 1 |
| 13 | 2 |
| 14 | 2 |
| 15 | 3 |
| 16 | 4 |
| 17 | 5 |
| 18 | 6 |
| 19 | 8 |
| 20 | 11 |
| 21 | 14 |
| 22 | 17 |
| 23 | 22 |
| 24 | 27 |
| ≥25 | ≥30 |

## APPENDIX B – *PARTICIPANT CONSENT*

RESEARCH PARTICIPANT CONSENT FORM

***The Effects of Flaxseed SDG on Lipid Levels in Perimenopausal Women with Mild Hyperlipidemia***

Bonnie Marblestone, RN, Ph.D-c, CFNP is a doctoral student in nursing at the Hahn School of Nursing and Health Science at the University of San Diego. You are invited to participate in a research project she is conducting to study the effects of eating Flaxseed SDG (a naturally occurring grain) on the levels of fats (like cholesterol) in your blood. If you decide to be in the study, here is what will happen:

After reading this consent form and asking Bonnie any questions you have, Bonnie will ask you to sign this form and keep a copy for yourself. Then she will ask you to pick a random number out of a hat. Depending on the number you pick, you will be given either a package of Flaxseed SDG OR a package of Psyllium. Both of these are naturally occurring grain fiber. You won't know which one you are getting. Bonnie wants to find out if the flaxseed works better than Psyllium in lowering your cholesterol levels. Both of these grain fibers have the potential to give you some side effects. The most common side effect of both of these grain fibers is that you may be passing more gas. If this becomes a problem for you, please contact Bonnie right away and she will give you some Beano, which is a naturally occurring substance that helps prevent gas formation. If at any time you notice distressing symptoms like abdominal pain or bloating, chest pain, or trouble breathing, ***stop taking the grain fiber and immediately seek medical help***. Bonnie will give you written instructions about how much grain fiber to take and when to take it. Depending on which kind of grain fiber you get, you will be taking about either a

tablespoon or a teaspoonful once a day, every day, for 8 weeks. Bonnie will then help you fill out a form that asks about your age, race, and annual income, and another form that asks you to circle the kinds of foods you've eaten in the past week. This first meeting with Bonnie will take about 60 minutes.

Bonnie will call you to set up 3 more meetings with you. The meetings will happen 8, 10, and 14 weeks after your first meeting. You don't have to worry about keeping track of these times, though, because Bonnie will call to remind you. At each meeting, you will meet Bonnie at a convenient time and place for you. Bonnie will be happy to spend time with you if you have any questions about the study. Then she will ask you to fill out a form asking about the foods you've eaten in the past week. She will then go with you to have your blood drawn. Each of these 3 meetings will take about 30 minutes.

About the blood sampling: You will be asked to provide a 10 ml blood sample (about a teaspoon) 3 separate times: these meetings with Bonnie will occur 8, 10, and 14 weeks later. A licensed person called a venipuncturist will draw your blood at the Pomerado Hospital lab service. The procedure will use all sterile equipment. You may feel a slight pinch as the blood is being drawn. This will last about 5 seconds. Most people have no problems with their blood being drawn, but in rare instances they do feel faint. Bonnie will be with you during it and will stay with you 10 minutes after it is done. If you feel dizzy or funny at all, please tell Bonnie right away. If you get a red, swollen place where the blood was drawn later in the day, call Bonnie right away.

Participation is in this study is entirely voluntary. You don't have to do this, and you can refuse to answer any question and/or quit at any time. Should you choose to

quit, no one will be upset with you and your information will be destroyed right away. If you decide to quit, nothing will change about the way doctors and nurses care for you.

The information you give will be analyzed and studied in a manner that protects your identity. That means that a code number will be used and that your real name will not appear on any of the study materials. All information you provide will remain confidential and locked in a file cabinet in the researcher's office for a minimum of five years before being destroyed.

The benefit to participating will be in knowing that you helped health care providers learn how to better help women lower their cholesterol levels.

If you have any questions about this research, please contact Bonnie Marblestone at 619-987-8098 or Dr. Jane Georges at the University of San Diego at 619-260-4548.

**I have read and understand this form, and consent to the research it describes to me. I have received a copy of this consent form for my records.**

_____ _____

Signature of Participant Date

_____

Name of Participant (**Printed**)

_____ _____

Signature of Investigator Date

APPENDIX C – *DEMOGRAPHIC QUESTIONAIRE*

**DEMOGRAPHIC DATA**

**AGE: _____** **CODE_____**

**RACE _____**

**INCOME PER YEAR**
**(Check appropriate line)**

**$0-$30,000 _____**

**$30,001-$50,000 _____**

**$50,001-$75,000 _____**

**$75,001-$100,000 _____**

**>$100,000 _____**

**BMI _____**

# APPENDIX D – *EATING PATTERN ASSESSMENT TOOL (EPAT)*

## DIRECTIONS

**How to complete EPAT:** For each of the 23 food groups on the chart, circle one box to the right of each food group that best describes your **usual** eating habits. The correct answer is what you actually eat. If you have trouble choosing between two boxes, circle the one that comes closest.

**How much is a serving?** Use the serving sizes listed next to the foods to determine the number of servings you eat. **Hint:** One "serving" is not necessarily the amount you eat at one sitting. If you eat a whole pizza, that's 4 servings, not 1.

**Adding it all up:** You probably eat a variety of foods within each food group. Include the listed foods you eat plus other similar items when you estimate the number of servings.

**For example:** In an average week, Joe might eat four pancakes for breakfast one weekend morning (4 pancakes = 2 servings). During the week, he has a doughnut at his coffee break about three times a week (3 doughnuts = 3 servings). He seldom eats desserts, but may snack on a large cookie about once a week (1 large cookie = 1 serving). That adds up to 6 servings in the Baked Goods group. (See the example below.)

FOOD GROUPS AND SERVING SIZES

| | Remember breakfast, snacks, and coffee breaks! | | | | |
|---|---|---|---|---|---|
| **Baked Goods** such as:<br>Doughnuts, sweet rolls, muffins 1 avg.<br>Cakes, coffee cakes 1 avg. piece<br>Cookies 2 avg. or 1 large<br>Pie 1 avg. wedge<br>Granola bars 1 bar<br>Granola cereals 1/2 cup<br>Pancakes 2 avg.<br>Waffles, french toast 1 avg. | **7 or more** servings per week | **5-6** servings per week | 3-4 servings per week | **2 or less** servings per week or Never eat | **BG** |

EXAMPLE

## SECTION 1

**PLEASE BEGIN HERE:**

| FOOD GROUPS AND SERVING SIZES | CIRCLE ONE BOX FOR EACH FOOD GROUP | | | | |
|---|---|---|---|---|---|
| **Convenience Foods** such as:<br>Fast-food meat sandwich 1 sandwich<br>All canned, packaged or frozen dinners (except lean, light or diet types) such as pizza, macaroni and cheese, pot pies, etc. 1/4 med. pizza<br>1 cup<br>1 avg. pot pie | **7 or more** servings per week | **3-6** servings per week | **1-2** servings per week | **Less than 1** serving per week or Never eat | **CF** |
| *(Most other meats are in Section II.)*<br>**Processed Meats and Untrimmed Red Meats** such as:<br>Bacon 4 slices<br>Bologna, lunch meat 2 slices<br>Hot dog, breakfast sausage 1 avg.<br>Bratwurst 1 link<br>Reg. or lean hamburger (not extra lean) 1/4-pound patty<br>Beef, pork, lamb, veal with visible fat 1 med. slice or 1 med. chop | **6 or more** servings per week | **3-5** servings per week | **1-2** servings per week | **Less than 1** serving per week or Never eat | **UN** |
| **Poultry Skin** | Always eat poultry with skin | Usually eat poultry with skin | Usually eat poultry without skin | Always eat poultry without skin or Never eat poultry | **PS** |
| FOR OFFICE USE ONLY | W-4 | X-3 | Y-2 | Z-1 | |



Version 3

repro w/out deletions

| FOOD GROUPS AND SERVING SIZES | CIRCLE ONE BOX FOR EACH FOOD GROUP | | | |
|---|---|---|---|---|
| **Eggs** (other than those used in baking) 1 whole egg | **6 or more** whole eggs per week | 4-5 eggs per week | 2-3 eggs per week | **Less than 2** whole eggs per week, and/ or eat only egg whites or egg substitutes, or Never eat eggs |
| *(Most other dairy desserts are in Section II.)* **Dairy Foods** such as: Ice cream 1/2 cup or 1 scoop | **3 or more** servings per week | 1-2 servings per week | **Less than 1** serving per week | Never eat |
| *(Most other milks and yogurts are in Section II.)* Whole milk, 2% milk, Regular yogurt 1 cup | **7 or more** servings per week | 3-6 servings per week | 1-2 servings per week | **Less than 1** serving per week or Never use |
| *(Most other cheeses are in Section II.)* **Cheeses** such as: Don't forget cheese contained in mixed dishes, e.g., sauces, cheeseburgers, pizza and blue cheese dressing. Cheddar, Colby 1 oz. slice; Swiss, Monterey Jack 1 oz. slice; American, processed cheese 1 oz. slice; Cream cheese, blue cheese 2 Tablespoons | **5 or more** servings per week | 2-4 servings per week | 1 serving per week | Never eat |
| **Types of Fats and Oils Used** (in cooking and at the table, but not in baked goods.) Include cream and fat used in casseroles as well as spreads on breads, etc. | Always use butter, lard, cream, and/or cream substitutes | Usually use butter, lard, cream, cream substitutes, and/or shortening | Usually use margarine, salad dressings, and/or oils | Always use margarine, salad dressings, and/or oils, or Never use any fats or oils |
| **Amount of Visible Fats and Oils** Do not include fats and oils used in cooking or baking here. Do include fats such as: Butter, margarine, lard (as a spread or on vegetables, etc.) 1 teaspoon (1 pat); Oils 1 teaspoon; Salad dressing (mayonnaise, french, etc.) 1 Tablespoon; Cream (whipped, sour, half and half, or cream substitutes) 1 Tablespoon; Peanut butter 1 Tablespoon; Nuts, seeds (shelled) 1 Tablespoon | **6 or more** servings per day | 5 servings per day | 4 servings per day | **3 or less** servings per day or Never use |
| | Note: These servings are <u>daily</u> amounts, not weekly. | | | |
| **Baked Goods** such as: Doughnuts, sweet rolls, muffins 1 avg.; Cakes, coffee cakes 1 avg. piece; Cookies 2 avg. or 1 large; Pie 1 avg. wedge; Granola bars 1 bar; Granola cereals 1/2 cup; Pancakes 2 avg.; Waffles, french toast 1 avg. | Remember breakfast, snacks, and coffee breaks! | | | |
| | **7 or more** servings per week | 5-6 servings per week | 3-4 servings per week | **2 or less** servings per week or Never eat |
| **Snacks** such as: Snack crackers 12 pieces; Chips 12 chips; French fries 1 small order | **7 or more** servings per week | 2-6 servings per week | 1 serving per week | Rarely or never eat |
| Chocolate candy 2 oz. or 1 avg. candy bar | **3 or more** servings per week | 2 servings per week | 1 serving per week | Rarely or never eat |
| FOR OFFICE USE ONLY | W-4 | X-3 | Y-2 | Z-1 |

## SECTION II

| FOOD GROUPS AND SERVING SIZES | CIRCLE ONE BOX FOR EACH FOOD GROUP | | | | |
|---|---|---|---|---|---|
| **Trimmed Red Meats** such as:<br>Low-fat lunch meat (e.g. 95% fat-free) 2 slices<br>Pork, beef, lamb, veal without visible fat 1 med. slice or 1 med. chop<br>Extra lean hamburger 1/4-pound patty | Less than 1 serving per week or Never eat<br>OR<br>8 or more servings per week | 1-2 servings per week | 3-5 servings per week | 6-7 servings per week | TR |
| **Poultry and Fish/Seafood** such as:<br>Chicken, turkey 1 med. slice, 1 avg. piece or 1/2 cup diced<br>Turkey lunch meat 2 slices<br>Fish fillet 1 med.<br>Tuna 1/2 cup or 1/2 avg. can<br>Crab 1/2 cup or 2 legs | 2 or less servings per week or Never eat<br>OR<br>10 or more servings per week | 3-4 servings per week | 5-6 servings per week | 7-9 servings per week | PF |
| **Dairy Foods** such as:<br>Ice milk 1/2 cup<br>Soft-serve or 1 scoop<br>Frozen yogurt | 4 or more servings per week | 3 servings per week | 2 servings per week | 1 or less servings per week or Never eat | IM |
| Skim milk<br>1% milk 1 cup<br>Low-fat or non-fat yogurt | 2 or less servings per week or Never use | 3-6 servings per week | 7-13 servings per week | 14 or more servings per week | SM |
| **Cheeses** such as:<br>Don't forget cheese contained in mixed dishes, e.g., sauces, pizza and salad.<br>Mozzarella, part-skim 1 oz. slice<br>"Diet" 1 oz. slice<br>"Lite" 1 oz. slice<br>Cottage cheese, ricotta 1/4 cup | Rarely or Never eat<br>OR<br>7 or more servings per week | 1-2 servings per week | 3-4 servings per week | 5-6 servings per week | CL |
| **Beans** such as:<br>Kidney beans, lima beans, split peas, or other dried beans or dried peas 1/2 cup cooked | Less than 1 serving per week or Never eat | 1-2 servings per week | 3-5 servings per week | 6 or more servings per week | BN |
| **Preparation Method for Meat, Fish and Poultry**<br>Fried or cooked with fat (butter, margarine, oil, shortening or lard) | Always prepared with fat or commercial breading | Usually prepared with fat or commercial breading | Usually prepared without fat or commercial breading | Always prepared without fat or commercial breading, or Never eat meat, fish or poultry | PM |
| **Preparation Method for Baked Goods** | Usually eat commercially prepared | Eat both commercially prepared and homemade from mixes | Usually eat homemade from mixes | Usually eat homemade from scratch | PB |
| FOR OFFICE USE ONLY | W-1 | X-2 | Y-3 | Z-4 | |

**Note: The servings below are daily amounts, not weekly.**

| FOOD GROUPS AND SERVING SIZES | | CIRCLE ONE BOX FOR EACH FOOD GROUP | | | | |
|---|---|---|---|---|---|---|
| **Breads and Other Starchy Foods** such as: | | | | | | |
| Bread | 1 avg. slice | 1 or less servings per day or Never eat | 2 servings per day | 3 servings per day | 4 or more servings per day | BR |
| Dinner roll, bagel | 1 avg. | | | | | |
| Cereal | 1 cup or 1 small package | | | | | |
| Rice, noodles, pasta | 1/2 cup cooked | | | | | |
| **Fruits and Vegetables** such as: | | | | | | |
| Fruit: fresh or frozen | 1 avg. piece | 1 or less servings per day or Never eat | 2-3 servings per day | 4-5 servings per day | 5 or more servings per day | FV |
| Canned fruit | 1/2 cup (1 avg. serving) | | | | | |
| Dried fruit | 2 Tablespoons or 2 avg. pieces | | | | | |
| Vegetable: fresh, frozen, or canned | 1/2 cup (1 avg. serving) | | | | | |
| Lettuce salad | 1 cup (1 small bowl) | | | | | |
| Potato (baked, mashed, or other) | 1 small or 1/2 cup | | | | | |
| Juice: fruit or vegetable | 1/2 cup (1 small glass) | | | | | |
| **Alcohol** such as: | | | | | | |
| Beer, regular or light | 1 can | 5 or more servings per day | 3-4 servings per day | 1-2 servings per day | Less than 1 serving per day or Never use | AL |
| Liquor | 1 cocktail or 1 jigger | | | | | |
| Wine | 1 small glass | | | | | |
| FOR OFFICE USE ONLY | | W-1 | X-2 | Y-3 | Z-4 | |

☐ Check here if you usually add salt at the table.

☐ Check here if you eat more than 5 meals per week in restaurants or fast-food chains.

If you are following a special diet or a vegetarian diet, enter name or type of diet here: _____

Please check that you have circled 23 answers and that you have filled in your name and the date.

**THANK YOU**

# EPAT SCORING INSTRUCTIONS

**NOTE:** Sections I and II are scored differently.
Please carefully read and follow the instructions below.

## SECTION I: Higher-Fat Foods

Section I contains foods that are higher in fat. Fat in your diet can lead to increased risk for heart disease. The Section I score is an estimate of the amount of fat in your diet. **For your health, the *lower* the score, the better.** (The highest score you can get is 48. The lowest is 12.)

To get your Section I score, look at the **"For Office Use Only"** strip at the end of Section I. For every box you circled in column W (left column) of Section I, give yourself 4 points. For every box circled in column X, 3 points. Column Y, 2 points. Column Z, 1 point. Add up your points, and write the total in the white box in the grid at the beginning of Section I.

**Remember, Column W = 4 points**
**Column X = 3 points**
**Column Y = 2 points**
**Column Z = 1 point**

**For example:** After filling out EPAT, Mary went down column W and found that she had circled 3 boxes. That gives her 12 points for column W (3 boxes X 4 points = 12 points). She counted 5 circled boxes in column X, so that is 15 points (5 X 3 = 15). For column Y, she counted 3 circles for 6 points (3 X 2 = 6). And for column Z, Mary had circled 1 box for 1 point (1 X 1 = 1). By adding her column scores, Mary got her Section I score: 34 points (12 + 15 + 6 + 1 = 34).

## SECTION II: A-OK Foods

Section II contains foods that are lower in fat. These foods are good substitutes for the higher-fat foods in Section I. The Section II score is an estimate of the quantity of health-promoting low-fat foods in your diet. **For your health, the *higher* the score, the better.** (The highest score you can get is 44. The lowest is 11.)

To get your Section II score, look at the **"For Office Use Only"** strip at the end of Section II. For every box you circled in column W (left column) of Section II, give yourself 1 point. For every box circled in column X, 2 points. Column Y, 3 points. Column Z, 4 points. Add up your points, and write the total in the white box in the grid at the beginning of Section II.

**Remember, Column W = 1 point**
**Column X = 2 points**
**Column Y = 3 points**
**Column Z = 4 points**

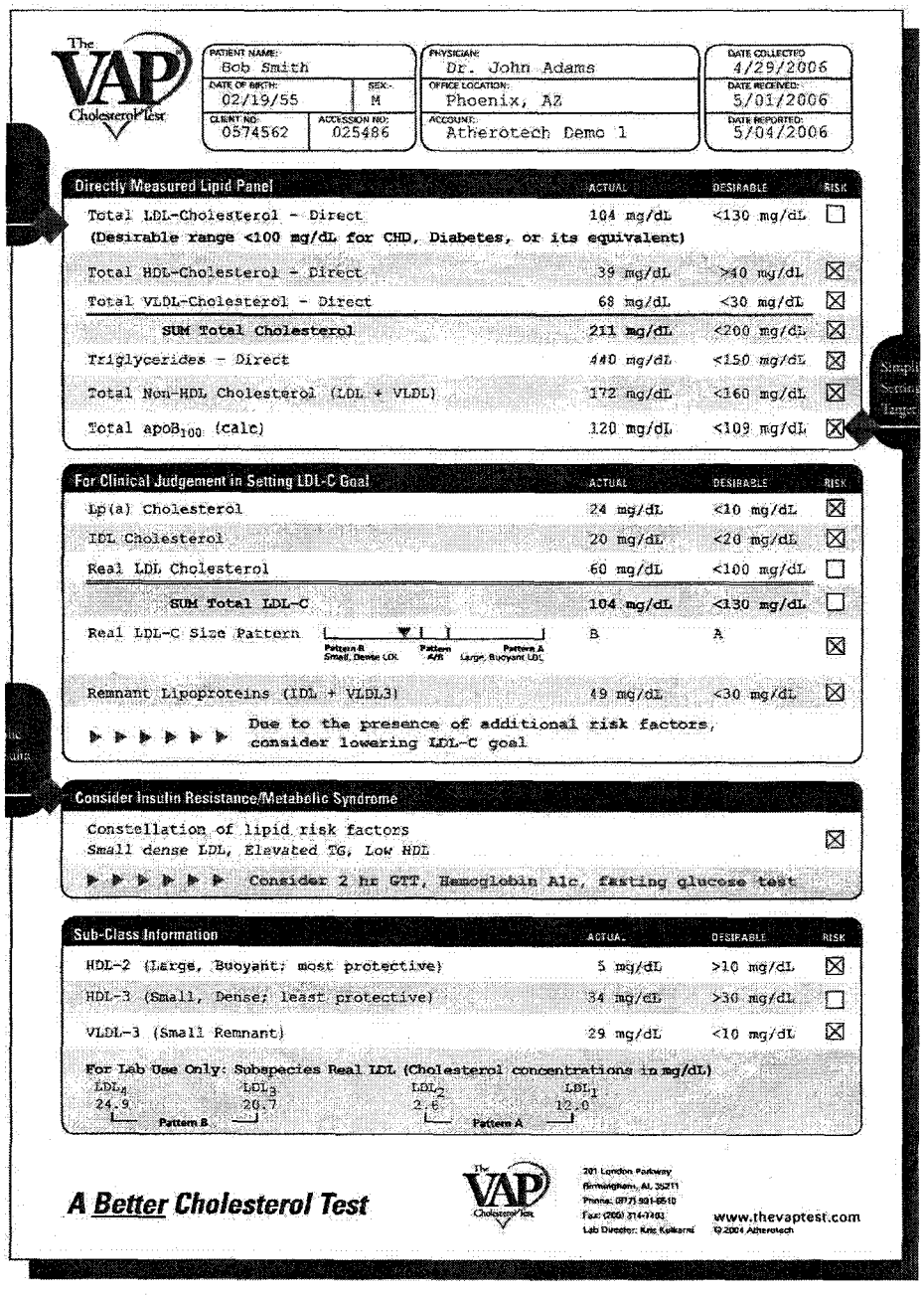
***(Notice that the columns get different points than in Section I.)***



**For Use With EPAT Version 3 Only**

Version 3 5/87

# APPENDIX E – *VAP-II RESULT SAMPLE SHEET*



The VAP Cholesterol Test

| PATIENT NAME: | | PHYSICIAN: | DATE COLLECTED |
|---|---|---|---|
| Bob Smith | | Dr. John Adams | 4/29/2006 |
| DATE OF BIRTH: 02/19/55 | SEX: M | OFFICE LOCATION: Phoenix, AZ | DATE RECEIVED: 5/01/2006 |
| CLIENT NO: 0574562 | ACCESSION NO: 025486 | ACCOUNT: Atherotech Demo 1 | DATE REPORTED: 5/04/2006 |

| Directly Measured Lipid Panel | ACTUAL | DESIRABLE | RISK |
|---|---|---|---|
| Total LDL-Cholesterol - Direct | 104 mg/dL | <130 mg/dL | ☐ |
| (Desirable range <100 mg/dL for CHD, Diabetes, or its equivalent) | | | |
| Total HDL-Cholesterol - Direct | 39 mg/dL | >40 mg/dL | ☒ |
| Total VLDL-Cholesterol - Direct | 68 mg/dL | <30 mg/dL | ☒ |
| SUM Total Cholesterol | 211 mg/dL | <200 mg/dL | ☒ |
| Triglycerides - Direct | 440 mg/dL | <150 mg/dL | ☒ |
| Total Non-HDL Cholesterol (LDL + VLDL) | 172 mg/dL | <160 mg/dL | ☒ |
| Total $apoB_{100}$ (Calc) | 120 mg/dL | <109 mg/dL | ☒ |

| For Clinical Judgement in Setting LDL-C Goal | ACTUAL | DESIRABLE | RISK |
|---|---|---|---|
| Lp(a) Cholesterol | 24 mg/dL | <10 mg/dL | ☒ |
| IDL Cholesterol | 20 mg/dL | <20 mg/dL | ☒ |
| Real LDL Cholesterol | 60 mg/dL | <100 mg/dL | ☐ |
| SUM Total LDL-C | 104 mg/dL | <130 mg/dL | ☐ |
| Real LDL-C Size Pattern (Pattern B Small, Dense LDL / Pattern A/B / Pattern A Large, Buoyant LDL) | B | A | ☒ |
| Remnant Lipoproteins (IDL + VLDL3) | 49 mg/dL | <30 mg/dL | ☒ |
| ▶ ▶ ▶ ▶ ▶ ▶ Due to the presence of additional risk factors, consider lowering LDL-C goal | | | |

| Consider Insulin Resistance/Metabolic Syndrome | |
|---|---|
| Constellation of lipid risk factors<br>Small dense LDL, Elevated TG, Low HDL | ☒ |
| ▶ ▶ ▶ ▶ ▶ ▶ Consider 2 hr GTT, Hemoglobin A1c, fasting glucose test | |

| Sub-Class Information | ACTUAL | DESIRABLE | RISK |
|---|---|---|---|
| HDL-2 (Large, Buoyant; most protective) | 5 mg/dL | >10 mg/dL | ☒ |
| HDL-3 (Small, Dense; least protective) | 34 mg/dL | >30 mg/dL | ☐ |
| VLDL-3 (Small Remnant) | 29 mg/dL | <10 mg/dL | ☒ |

For Lab Use Only: Subspecies Real LDL (Cholesterol concentrations in mg/dL)

| $LDL_4$ | $LDL_3$ | $LDL_2$ | $LDL_1$ |
|---|---|---|---|
| 24.9 | 20.7 | 2.6 | 12.0 |
| Pattern B | | Pattern A | |

*A Better Cholesterol Test*

The VAP Cholesterol Test

201 London Parkway
Birmingham, AL 35211
Phone: (877) 901-8510
Fax: (205) 314-7403
Lab Director: Kris Kulkarni

www.thevaptest.com
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The next deadline for submitting project proposals to the Provost's Office for full review is N/A. You may submit a project proposal for expedited review at any time.

Dr. Thomas R. Herrinton

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