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## The effects of exercise on homocysteine levels in men and women

Tracey Michelle Zuehlsdorff  
*University of Nevada, Las Vegas*

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THE EFFECTS OF EXERCISE ON HOMOCYSTEINE LEVELS IN  
MEN AND WOMEN

by

Tracey Michelle Zuehlsdorff

Bachelor of Science  
University of Nevada, Las Vegas  
1999

A thesis submitted in partial fulfillment  
of the requirements for the

**Master of Science Degree in Exercise Physiology  
Department of Kinesiology  
College of Health Sciences**

**Graduate College  
University of Nevada, Las Vegas  
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The Thesis prepared by

Tracey Michelle Zuehlisdorff

### Entitled


The Effects of Exercise on Homocysteine Levels in Men and Women

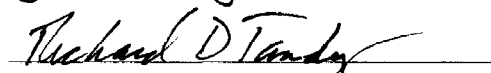
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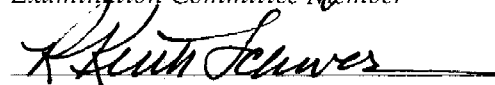
Masters of Science in Exercise Physiology

  
Examination Committee Chair

  
Dean of the Graduate College

  
Examination Committee Member

  
Examination Committee Member

  
Graduate College Faculty Representative

## ABSTRACT

### **The Effects of Exercise on Homocysteine Levels in Men and Women**

by

Tracey Michelle Zuehlsdorff

Dr. Lawrence Golding, Examination Committee Chair  
Professor of Kinesiology  
University of Nevada, Las Vegas

A recent coronary risk factor, and one believed to be an important biochemical marker of Coronary Heart Disease, is elevated levels of serum homocysteine (Boushley et al., 1995; Malinow et al., 1994; Malinow et al., 1999; Nygard et al., 1995; Stampfer et al., 1992). Serum homocysteine levels above 10  $\mu\text{mol/L}$  are considered elevated. There are several unalterable factors, which result in the elevation of homocysteine such as heredity, age, and gender. There are other factors that are alterable such as diet and possibly exercise. The purpose of the study was to determine if a 12-week daily progressive exercise program reduced homocysteine levels in men and women. Six men and four women between the ages of 32 and 50 years of age participated in the study. The subjects were all sedentary, business or professional individuals who joined the study to improve their physical fitness. Subjects' homocysteine levels were 10  $\mu\text{mol/L}$  or greater. The female subjects were all premenopausal. Homocysteine levels were assessed before and after the 12-week exercise program and a dependent t test evaluated the changes ( $\alpha = .05$ ). After the 12-week exercise program the analysis revealed a significant reduction in

homocysteine levels ( $t = 5.71, p < .05$ ) providing evidence that regular exercise reduces homocysteine levels in men and women.

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## CHAPTER 1

### INTRODUCTION

Cardiovascular disease is the major cause of death in the United States, and the American Heart Association has publicized the factors involved in the development of Coronary Heart Disease (CHD). These coronary risk factors include hypertension, elevated total cholesterol levels, cigarette smoking, sedentary living, obesity, uncontrolled diabetes, and others. One of the more recent factors, and one believed to be an important biochemical marker, of CHD is elevated levels of serum Homocysteine (Boushey et al., 1995; Malinow et al., 1994; Malinow et al., 1999; Nygard et al., 1995; Stampfer et al., 1992). Homocysteine (hcy) is derived from the metabolism of the amino acid methionine. Normal serum homocysteine levels are below 10  $\mu\text{mol/L}$ ; borderline elevated homocysteine is between 10 and 15  $\mu\text{mol/L}$ ; and elevated homocystiene is identified as 15  $\mu\text{mol/l}$  or greater (Spectra Cell Lab). Elevated homocysteine is termed hyperhomocystienemia. Even though most laboratories consider homocysteine levels between 5 and 15  $\mu\text{mol/L}$  as the normal range, studies (Segala et al., 2000) have shown that homocystiene levels above 6.3  $\mu\text{mol/L}$  result a progressive risk of coronary heart disease. Wilcken and colleagues in 1976 (Spectra Cell laboratories) first demonstrated a relationship between elevated homocystiene levels and cardiovascular disease. They showed that patients with premature atherosclerosis had elevated hcy levels in comparison to control subjects. Since 1976, several studies have shown high

homocystiene levels with the increased incidence of heart disease (Boushey et al., 1995; Malinow et al., 1994; Nygard et al., 1995; Stampfer et al., 1992; Kang et al., 1986). Blood homocystiene levels tend to increase with age (Nygard et al., 1995). However, hyperhomocysteinemia is observed in 30% of patients with known coronary artery disease and 42% of patients with cerebrovascular disease (Stein et al., 1998). The American Heart Association has reported that moderate and intermediate hyperhomocysteinemia is present in 47% of patients with coronary, cerebral, or peripheral arterial occlusive diseases (Malinow et al., 1999). The Physician's Health Study (Stampfer et al., 1992) studied 14,916 apparently healthy male physicians for five years, of which 271 subsequently developed myocardial infarctions. The homocysteine levels were significantly higher in the physicians who suffered the myocardial infarctions. Malinow et al. (1989) followed 47 patients with peripheral arterial occlusive disease and in all cases plasma homocysteine was elevated. In another study Malinow et al. (1996) found elevated homocysteine levels in 40% of patients with coronary heart disease. There is considerable evidence to link elevated homocysteine levels and heart disease (Malinow et al., 1989; Malinow et al., 1996; Stampfer et al., 1992).

There are several factors resulting in elevated homocysteine levels: heredity, age, and gender. These factors are unalterable, however, some factors, such as diet, are alterable (Nygard et al., 1995; Malinow et al., 1996; Genest et al., 1991; William et al., 1990; Malinow et al., 1999; Moustapha et al., 1999). Heredity is considered one of the greatest reasons for elevated homocystiene. Several studies (Malinow et al., 1996; Genest et al., 1991; Williams et al., 1990) have linked heredity to elevated homocysteine levels. An autosomal recessive genetic disorder called Homocysteinuria effects 1:200,

000 births. This condition is caused by inherited errors of metabolism and can cause skeletal abnormalities, mental retardation, and a high incidence of heart disease (Malinow et al., 1999). Age and gender are two other unalterable factors in elevated homocysteine levels. homocysteine levels tend to increase with age, and males tend to have higher homocysteine levels than females (Nygard et al., 1995). In females homocysteine levels tends to increase after menopause and decrease during pregnancy. However, postmenopausal women can control the increase in homocysteine by using estrogen replacement therapy (Nygard et al., 1995; Moustapha et al., 1999).

One important factor often resulting in elevated homocysteine levels is diet. Diet, and in particular the amount and kind of vitamins consumed, can be controlled and these tend to effect the homocysteine level. Consuming or supplementing the RDA for Vitamin B6, B12, and folic acid normally prevents elevated homocysteine levels. The RDA for folic acid is 400 ug/day, the RDA for B6 is 2.0 mg/day, and the RDA for B12 is 3.0 ug/day (Malinow et al., 1999). Due to poorer absorption in older adults, maintaining adequate vitamin intake is especially important. If the recommended amount of these vitamins is not being met by diet alone, then supplementation is recommended.

One of the most accepted coronary risk factors is elevated serum cholesterol levels. Several studies have shown that exercise lowers total cholesterol levels and increases HDL cholesterol, which decreases the risk for cardiovascular disease (Gordon et al., 1994; Lennon et al., 1983; Crouse et al., 1997; Hubinger et al., 1992). Lennon and associates (1983) showed that 40 minutes of exercise increases HDL cholesterol, decreases total and LDL cholesterol. Hubinger and colleagues (1992) demonstrated that 30 minutes of moderate exercise made a significant increase in HDL cholesterol. Gordon

et al. (1994) demonstrated the importance of the intensity of exercise: a moderately trained male working at 75% of VO<sub>2</sub> max increased HDL cholesterol levels significantly. It was suggested that those with higher baseline levels of HDL cholesterol might require longer duration exercise to achieve the same affect. Crouse and colleagues (1997) demonstrated that a single bout of exercise had a significant affect on lipid concentration in hypercholesterolemic men: it increased HDL cholesterol and decreased total cholesterol and with continued training there was a significant decrease in LDL cholesterol.

The evidence indicating that exercise reduces total cholesterol suggests that exercise may also beneficially affect homocysteine levels. Since elevated homocysteine levels are an important risk factor for cardiovascular disease, the effects of exercise on homocysteine levels needs to be investigated. Nygard et al. (1995) demonstrated a linear relationship between total homocysteine levels and total and LDL cholesterol levels. Therefore, it could be hypothesized that when high LDL cholesterol levels persist, high homocysteine levels may be expected. Since exercise has been shown to lower cholesterol, it is also possible that exercise may lower elevated homocysteine levels.

To date, only two studies have examined the effect of exercise on homocysteine levels. The Norwegian Hordaland Homocysteine Study (Nygard et al., 1995) studied 8,585 women and 7,591 men, between the ages 40 to 67 years. The purpose of this study was to investigate the relationship between homocysteine levels and other cardiovascular risk factors. The investigators determined that homocysteine levels were inversely related to physical activity. The men that participated in exercise had an average of a 1.08 umol/L lower total homocysteine levels than their sedentary counterparts and the

women had an average of a .65  $\mu\text{mol/L}$  lower level than sedentary subjects. However, in another study, Wright et al. (1998) found that the one bout of acute exercise had no effect on homocysteine levels. In their study 20 healthy young males ran on a treadmill at 70% of their max heart rate for 30 minutes.

### Statement of the Problem

The purpose of the present study was to investigate the effects of a 12-week daily exercise program on homocysteine levels in men and women aged 32 to 50 years. The hypothesis was that regular, progressive exercise significantly lowers elevated homocysteine levels. The research question was: Does persistent regular exercise reduce homocysteine levels?

### Need for the Study

Since homocysteine has been determined to be an important biochemical marker of coronary heart disease, it was desirable to know if regular, daily exercise positively effects homocysteine levels.

### Limitations and Assumptions

#### Limitations:

1. The financial laboratory cost of determining homocysteine levels and the limited age range of the subjects, limited the number of subjects. Since females needed to be premenopausal, women over 50 years of age were not used.

2. A 12-week exercise program was used. A longer program of exercise may produce different results.
3. Some dietary information was obtained from the subjects, but it was not possible to rigorously control diet or supplementation use even though they were asked not to change or modify their diets and not to begin any diet supplementation during the study.
4. Since heredity is an unalterable factor involved in elevated homocysteine, it was not possible to know the level homocysteine due to heredity.
5. Although women were screened for menopausal status, it was not possible to be completely assured that all the women involved were premenopausal.
6. Study was limited to those that had serum homocysteine levels of 10  $\mu\text{mol/L}$  or greater.

Assumptions:

1. Subjects were asked to attend at least 3 of the 5 days of exercise each week.  
Attendance was taken, and it was assumed that individuals worked diligently while in the exercise sessions.
2. Subjects were asked to not change their diets and not begin taking any supplements.  
It was assumed that they followed those requests
3. Subjects were asked if they were sedentary before the study. All reported that they were sedentary. Therefore it was assumed that they were sedentary previous to beginning the exercise program.



4. Subjects all reported and signed consent forms that indicated that they were free of any heart disease or other major health complications.
5. It was assumed that all women that participated were premenopausal at the time of the study.
6. It was assumed that the Homocysteine levels were accurately assessed.

## CHAPTER 2

### LITERATURE REVIEW

#### Medical Discovery

The interest in homocysteine started in 1933 when an eight-year-old boy was admitted to the Massachusetts General Hospital with symptoms of headaches, drowsiness, and vomiting, he also had signs of mental retardation and the lenses of both eyes were detached. The boy had indications of a stroke and died a few days later. The cause of death was recorded as arteriosclerosis of the carotid artery with a cerebral infarct, even though this was usually a condition reserved for older adults (McCully, 1997). This case was basically ignored for thirty-two years, and then in 1965, a young girl was evaluated at the same hospital for retarded mental development and had similar symptoms of the boy thirty -two years previous. The eight-year-old boy that had died 32 years earlier was the young girl's uncle (McCully, 1997). This was later determined to be a result of elevated homocysteine levels. In 1962 in Belfast, Ireland doctors studying the composition of urine in mentally retarded individuals found elevated homocysteine levels and the term homocysturinia was used (McCully, 1997). Homocysteine was analyzed in the urine as an amino acid formed from the normal breakdown of the proteins. The symptoms of the young girl and boy mentioned above were similar to those discovered in homocysturinia. The young girl was tested for elevated homocysteine, and was diagnosed with homocysturinia. After elevated homocystiene and homocystinuria

became more diagnosable, research in the United States on elevated homocysteine began being published (McCully, 1997).

### Metabolism

Homocysteine (hcy) is an amino acid formed from methionine. Excess methionine in the diet is converted to homocysteine. The RDA for methionine is .9 g/day; however, the average American diet usually contains approximately 2 g/day of methionine (Stein et al., 1998). Methionine is found in all proteins and animal foods such as meat, eggs, milk, and cheese which contain more protein than most foods of plant origin. The RDA for protein based on weight is approximately 60 grams for adult men and 50 grams for adult women (McCully, 1997). The metabolism of homocysteine starts when methionine is introduced into the digestive tract. Methionine combines with an ATP molecule and forms S-adenosylmethionine (SAM), an intermediate, which then gives up a methyl group and becomes homocysteine. Homocysteine can then either be further metabolized by the transulfuration pathway to cystathionine and cysteine with the excretion of sulfur in the urine or it is remethylated by one of two pathways back into methionine (Carmel R & Jacobsen D, 2001).

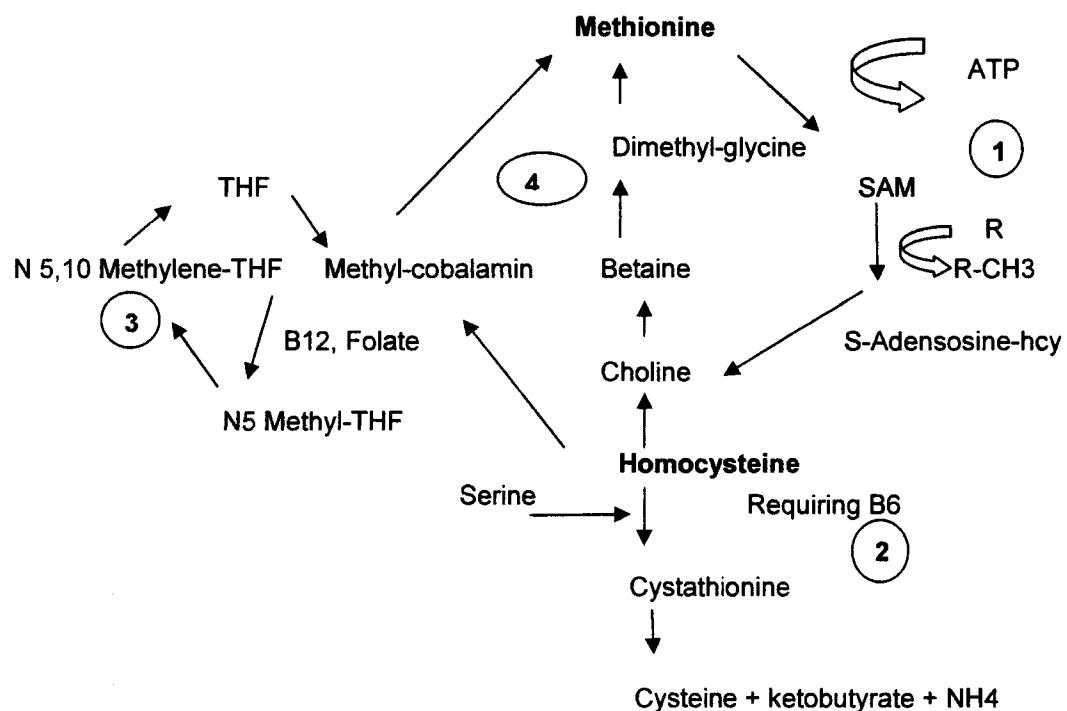
In transsulfuration, homocysteine, in the presence of vitamin B6 and the enzyme cystathionine B-synthase combines with serine to form cystathionine from which cysteine,  $\alpha$ -ketobutyrate, and ammonium are formed. This process produces the secretion of sulfur in the urine. Homocysteine can then be remethylated back into methionine by one of two pathways. One of the two pathways requires Vitamin B12 and allows homocysteine to pick up a methyl group from methyltetrahydrofolate, a folic acid

derivative, catalyzed by homocysteine methyltransferase (FHMT), forming methionine. The remaining tetrahydrofolate then forms 5, 10 methylene-tetrahydrofolate and continues through the metabolic pathway. In the other remethylation pathway, betaine donates a methyl group to homocysteine and forms methionine, and dimethylglycine. The two metabolic pathways tend to compete for the available homocysteine. Figure 1 on the next page illustrates the process.

Studies have demonstrated that in young adult men fed a diet adequate in methionine (14mmol/day), about 38% of homocysteine is remethylated to methionine and 62% is catabolized by transsulfuration (Shils et al., 1999). Elevations in homocysteine levels occur primarily through a genetic deficiency of cystathionine B synthase (CBS). With a deficiency in CBS, the transsulfuration pathway for homocysteine metabolism is not possible. Other possible causes of elevated homocysteine levels occur with deficiencies in Vitamins B6, B12, and folic acid. Without these vitamins, the transsulfuration and transmethylation pathways are not effective. Therefore, homocysteine cannot be excreted nor can it be reformed back into methionine. Although, these are the most common causes of elevated homocysteine levels, any error that does not allow homocysteine to either be excreted or remethylated into methionine has the potential to cause elevated homocysteine levels.

Total plasma homocysteine is the sum of all free homocysteine and protein-bound homocysteine. According to Spectra Cell Laboratories, mean value for normal total homocysteine is 10 umol/L and generally 10% higher in men than women and increases with age. Some research (Malinow et al., 1999) has indicated in the fasting patient, normal levels of plasma homocysteine are between 5 and 15 umol/L. However, according

to McCully (1997) if blood homocysteine levels can be kept below 10  $\mu\text{mol/L}$  a significant measure of protection against development and progression of arteriosclerosis is assured. Even though some laboratories find homocysteine levels between 5 and 15  $\mu\text{mol/L}$  to be in a normal range, studies (Segala, 2001) have shown that homocysteine levels above 6.3  $\mu\text{mol/L}$  cause a steep and progressive risk of heart attack.



### Figure 1: Methionine Metabolism

1. Methionine combines with ATP and forms S-adenosylmethionine (SAM), which forms Homocysteine.
2. Transulfuration pathway of homocysteine requiring Vitamin B6.
3. One remethylation pathway requiring Vitamin B12 and folate.
4. The second remethylation pathway requires betaine as a methyl donor to form methionine.

Homocystinuria is a genetic disease that affects the metabolism of homocysteine. This is a rare autosomal recessive genetic disorder that approximately affects 1:200,000 births (Malinow et al., 1999). Homocystinuria results from severe hyperhomocysteinemia caused by abnormality of the metabolism of homocysteine. There are three possible mechanisms for the abnormality of hcy metabolism; the first and most common cause is a lack of cystathionine B-synthase activity that can cause plasma homocysteine levels as high as 200  $\mu\text{mol/L}$  in untreated patients (Shils et al., 1999). The second common cause is a lack of N-methylenetetrahydrofolate reductase activity, which affects folate metabolism. The third possible cause of homocystinuria is an error in the synthesis of methylcobalamin (Shils et al., 1999). Overall, those with homocystinuria have a high incidence of vascular pathology that can lead to myocardial infarction, stroke, or pulmonary embolism (Malinow et al, 1999). Homocystinuria that is caused by a cystathionine B synthase deficiency can lead to dislocation of optic lenses, skeletal abnormalities, mental retardation, and neurological disorders (Shils et al, 1999). Fortunately, newborn screening for homocystinuria detects a CBS deficiency by primary screening for hypermethioninemia and secondary screening for elevated urine and/or plasma homocysteine levels (Shils et al, 1999).

### Homocysteine and Heart Disease

Elevated homocysteine level is presently an important biochemical marker for coronary heart disease. Several studies have shown a positive correlation between elevated hcy levels and the incidence of coronary heart disease (CHD). In 1992 Stampfer and his colleagues did one of the first prospective studies on homocysteine and CHD and

was entitled The Physicians Health Study. These researchers followed 14, 916 male physicians between the ages of 40 and 84 years of age who, prior to the study, had not had any known myocardial infarctions or strokes. The homocysteine levels of the physicians were analyzed, compared and matched to their controls for five years. Two hundred seventy one of the physicians developed a myocardial infarction, and these had elevated homocysteine levels above 11  $\mu\text{mol/L}$ . Thirty one of the cases had homocysteine levels greater than 15.8  $\mu\text{mol/L}$ , which was found to be significant. This proportion would probably be higher in the general population, which is presumably less well nourished than US physicians. Selub and others (1995) showed a significant relationship between Carotid Artery Stenosis and elevated total homocysteine levels and low concentrations of folate and vitamin B6. They studied 1,041 men and women between the ages of 67 and 97 years from the Framingham Heart Study, which was a study done with a group of patients from Framingham, Massachusetts with coronary heart disease. The relationship between the maximal degree of stenosis of the extracranial carotid arteries and plasma homocysteine along with concentrations and intakes of folate, Vitamin B6, and B12 were examined. The study showed that high plasma homocysteine concentrations and low concentrations of folate and Vitamin B6 were associated with an increased risk of extracranial carotid-artery stenosis in the subjects.

Although the precise mechanisms by which elevated homocysteine can causes vascular damage is not completely understood, it is hypothesized that endothelial injury is a probable factor (Berwanger et al., 1995). It is speculated by researchers (McCully, 1997; Malinow et al., 1993; Graham et al., 1997) that elevated homocysteine levels cause endothelial dysfunction and aggregation of platlets by promoting oxidation at the cellular

level. This oxidation process increases LDL accumulation and enhances foam cell formation which leads to the progression of occlusive arterial diseases. Studies have also correlated elevated homocystiene levels with peripheral arterial occlusive disease (PAOD) (Boers et al., 1985; Clarke et a., 1991; Malinow et al., 1989). Malinow et al. (1989) studied 47 patients with PAOD, 35 cases had carotid arterial involvement and 32 subjects also had ileo femoral lesions, therefore, occlusion was found in both arterial areas in the about 80 % of the subjects. The results of the study showed that plasma homocysteine levels were elevated in the patients with PAOD when compared to their controls. Malinow et al., (1993) showed a correlation of elevated homocysteine to carotid arterial wall intimal-medial thickness in 287 case-controlled pairs of individuals free of clinical athersclerosis. Subjects for the study were selected from a sample of 15,800 men and women between the ages of 45 and 64 years of age. The study revealed that the subjects with thickened carotid wall or occlusive arterial disease are more likely to have elevated homocysteine levels that their controls. Elevated homocystiene levels have also been noted in patients with cerebrovascular disease (Boers et al., 1985; Brattstrom et al., 1990; Clarke et al., 1991; Malinow et al., 1996). Brattstrom et al. (1992) matched 142 stroke survivors with 66 control subjects that were free of cerebrovascular disease. They found hyperhomocysteinemia present in 40% of stroke patients and only 6% of control subjects.

### Vitamin Deficiency and Supplementation

Besides genetic factors, vitamin deficiency is the most common cause of elevated homocysteine levels. Inadequate plasma concentrations of vitamin B6, B12, and/or folate



contribute to 67% of cases of hyperhomocysteinemia (Spectra Cell Lab). The RDA for vitamin B6 is 2.0 mg/day and foods include fortified cereals, noncitrus fruits, poultry, beef, and vegetables such as artichokes, beans, cabbage, and asparagus. The RDA for vitamin B12 is 3.0 mcg/day and food sources include beef, poultry, and fortified cereals. Lastly, the RDA for folic acid is 400 mcg and foods containing folic acid include fortified cereals, leafy green vegetables, fruits, and legumes (Malinow et al., 1999). However, the majority of the population does not meet the RDA requirements for these vitamins, and in addition, due to reduced absorption with age, this is most prominent in those over the age of 50 (Malinow et al., 1999). Therefore, supplementation of these three vitamins is recommended. Both folate and vitamin B12 are cofactors for methionine synthase and are needed to remove homocysteine.

In Vitamin B6, B12 and folate deficiency homocysteine is not metabolized and its concentration in the blood rises (Pancharuniti et al., 1994). Of the three vitamins involved in homocysteine metabolism, supplementation with folate seems to be the most successful in lowering high homocysteine levels (Franklin et al., 1998). Stein et al. (1998) have shown that folic acid supplementation of 400 mcg or more a day can decrease total Hcy levels up to 42%. However, supplementation with a combination of all three vitamins (Vitamin B6, B12, and Folate) results in a 72% reduction in total homocysteine. The American Heart Association recommends a folic acid dose between .2 and 15 mg/day to lower hcy levels. In addition, the AHA showed that the daily intake of fortified cereals, which contain 499 to 650 ug of folic acid per serving, and the RDA of the vitamin B6 and B12, can reduce homocysteine by 14%. However, there is a small danger with folic acid supplementation. A high folate intake may mask the development

of megaloblastic anemia characteristics of older patients with vitamin B12 deficiency (Moustapha et al., 1999). Therefore, it is important to screen older adults for vitamin B12 deficiency before beginning treatment for elevated hcy. Research (Boushley et al., 1995) has demonstrated that large doses of folic acid (5000 ug) are not necessary to reduce hyperhomocysteinemia. A folic acid dose of 650 ug reduced homocysteine concentrations by 42% in subjects. Boushley and others showed that there was no additional lowering of hcy after six weeks of treatment with 1000 mcg folic acid per day, 0.4 mg/day of B12, and 12.2 mg/day of B6 when twice these amounts were given. This suggests that there may be an upper limit in supplementation as it relates to homocysteine reduction.

Although, folic acid is very effective in reducing homocysteine, combination therapy with vitamin B6 and B12 is suggested (Boushley et al., 1995). Cobalamin (B12) supplementation alone is only successful in reducing total homocysteine levels in cases of overt B12 deficiency (Boushley et al., 1995). Boushley and associates (1995) showed that pyridoxine (B6) is not effective in reducing elevated fasting total homocysteine levels when used alone. A few other vitamins that may affect homocysteine levels include riboflavin and nicotinic acid. Riboflavin can function as a cofactor for methylenetetrahydrofolate reductase (MTHFR), which is the enzyme that regulates the metabolic pathway for homocysteine. A .6 mg/day food intake of riboflavin can slightly reduce total homocysteine. On the other hand supplementations of 3000 + mg/day of nicotinic acid may elevate homocysteine levels. Research reported by the American Heart Association, (Malinow et al., 1999) has shown that users of multivitamin supplements have lower homocysteine levels than nonusers. McKay et al. (2000)

reported lower homocysteine levels and improved vitamin B status with multivitamin/mineral supplementation. The study involved 80 men and women between 50 and 87 years of age with homocysteine levels of  $\geq 8$   $\mu\text{mol/L}$ . Each subject received a multivitamin/mineral supplement or a placebo for 56 days while consuming their normal diets. The results showed plasma folate, pyridoxal phosphate, and vitamin B-12 concentrations were increased 41.6, 36.5, and 13.8 %, respectively and no changes were observed in the placebo group. Mean homocysteine concentrations decreased 9.6% in the supplementation group, as well.

### Heredity

Several studies have studied the heritability of plasma homocysteine in families. Malinow et al. (1996) reported various studies (Genest et al., 1991; Reed et al., 1991; Berg et al., 1992) that have shown hyperhomocysteinemia can be an inherited abnormality and possibly explains cases of early familial coronary artery disease. Genest and colleagues (1991) studied families of patients with premature CAD (coronary artery disease) to determine whether the hyperhomocysteinemia was familial. Subjects consisted of 176 men less than 60 years of age that had been diagnosed with CAD. Two hundred and fifty-five control subjects were also examined. The families of 71 of the subjects were also examined. Family included spouses and first generation relatives, resulting in a total of 370 subjects. The results showed that 20 families had elevated hcy levels compared to controls and that 14% of the CAD patients did have familial hyperhomocysteinemia. Therefore, elevated homocysteine levels are partially genetically determined in individuals with CAD. Williams et al. (1990) measured homocysteine

levels in 37 men and women with CAD and in 30 male and 18 female control participants who were matched for age and sex. Participants of the study were selected to include 13 male sibling pairs with CAD, 13 male sibling pairs as control subjects and 13 spouse pairs as control subjects. The results showed significantly higher hcy levels in CAD patients, among 26 male sibling pairs, a strong familial correlation of homocysteine was observed. The above studies suggest that hyperhomocysteinemia was an inherited abnormality and may explain certain cases of early familial CAD (Malinow et al., 1996).

### Age

Advancing age is a contributing factor in elevated homocysteine levels. There is a high correlation between homocysteine and age indicating that total homocysteine levels increase in older individuals with or without cardiovascular disease. Nygard and others (1995) revealed higher total homocysteine levels in men and women as their age increased. Their study examined 7,591 Norwegian men and 8,585 Norwegian women between the ages of 40 and 67 years. There are several causes for increasing hcy levels with age. The production of Cystathionine B synthase and other enzymes involved in homocysteine metabolism tend to decline with age (Moustapha et al., 1999). Due to a decrease in the absorption of folate, vitamin B12 and B6 with age, an increase in homocysteine can occur (Moustapha et al., 1999). The amount of food consumed also tends to decline with age, which causes a decline in the dietary intake of Vitamin B6, B12, and folic acid. One study (vonEckardstein et al., 1999) found that elevated homocysteine levels are significantly correlated with age, among other factors such as fibrinogen and plasma viscosity in CAD patients. Overall, age is an unalterable factor,

which, can lead to elevated homocysteine levels. Therefore it is advisable to become aware of the alterable factors such as diet.

### Gender and Menopause

Nygard et al. (1995) indicated that because of a larger muscle mass and creatine synthesis, men tend to have higher homocysteine levels than women. In females, premenopausal women have lower homocysteine levels than postmenopausal women. However, postmenopausal women on estrogen replacement therapy tend not to have elevated homocysteine levels (Nygard et al., 1995; Malinow et al., 1994). This finding suggests that premenopausal women remethylate homocysteine to methionine better or that their transulfuration rate or renal excretion differs from postmenopausal women (Carmel, Jacobsen, 2001). Nygard et al. (1995) also indicated that increased levels of plasma estrogens may account for lower hcy levels in pregnant women. However, Henderson (2000) showed no correlation between estrogen and homocysteine. He measured homocysteine levels before and after six months of estrogen replacement therapy and found no significant changes in homocysteine levels.

### Homocysteine and Cholesterol

Elevation in plasma homocysteine levels are found with increased levels of cholesterol and triglycerides (Karmin et al., 1998; Glueck et al., 1995). Nygard and associates (1995) found a positive correlation between total homocysteine and total cholesterol and LDL cholesterol when examining the relationship between cardiovascular risk factors and total homocysteine in plasma. According to Karmin et al. (1998)

homocysteine stimulates the production and secretion of cholesterol in hepatic cells. In his study, hepatic cells were incubated with 4mM of homocysteine. This amount (4mM) is considerably higher than that found in the plasma of homocysteinemic patients because the chronic process of homocysteine in patients cannot be readily produced when using a cell culture model. The results showed that homocysteine produced an elevated cholesterol level in the hepatic cell and stimulated the secretion of cholesterol by the cells. Glueck and others (1995) studied 482 patients with hyperlipidemia. Homocysteine levels were measured in all subjects and 18 of the 482 patients had elevated homocysteine levels ( $> 16.2 \mu\text{mol/L}$ ). However, of the 18 with elevated homocysteine, 13 had atherosclerotic vascular disease. Zulli and others (1998) found a positive effect among cholesterol, homocystiene, and triglyceride levels. The study used rats and fed them a control diet which consisted of a high cholesterol supplemented diet, a high methionine supplemented diet, and a combination of the two, a high cholesterol plus a high methionine supplemented diet. The results of the study showed that excess methionine and cholesterol feeding act positively to increase plasma homocysteine, cholesterol, and triglyceride levels. The methionine only diet showed an increase in homocysteine and the cholesterol only diet showed an increase in homocysteine, but the combined diet had the greatest effect and showed the greatest increase in homocysteine. Zulli and associates believed that humans show the same effect, therefore indicating that elevated levels of cholesterol increase homocystiene levels.

Elevated HDL cholesterol levels have been known to reduce overall risk of coronary heart disease. In contrast to the above studies Superko et al. (1997), reports that despite the protective effects that elevated HDL cholesterol has, atherosclerosis can still

occur in the setting of hyperhomocysteinemia. In his study, he reported an 82 year old women with elevated HDL cholesterol and normal LDL cholesterol levels with coronary artery disease. However, the patient did have elevated homocysteine levels. Therefore, there is a conflict in the research. However, Superko's study only looked at one subject.

### Homocystiene and Ethnicity

There is not total agreement on the effect of ethnicity and elevated hcy levels. Gerhard et al. (1999) concluded that premenopausal black women tend to have two to three times the incidence of CHD than similar white women. In addition, black women had higher levels of homocysteine levels than white premenopausal women. The study was conducted using 89 black women and 90 white women between the ages of 18 and 45. The result showed that total homocysteine levels were significantly higher and plasma folate levels were significantly lower in the black women compared to their white counterparts. In contrast, Giles et al. (1999) concluded that there is no difference in homocysteine levels among different ethnic groups. The study examined data from the Third National Health and Nutrition Examination Survey. This was a survey that was used to examine the relationship between total homocysteine levels in 3,173 patients with acute myocardial infartions among whites, blacks, and Mexican Americans over 40 years of age. The study revealed that there is an increase in the likelihood of myocardial infarction among those with elevated homocysteine levels ( $>15$   $\mu\text{mol/L}$ ), but homocysteine levels did not differ among blacks, whites, and Mexican Americans. Due to the inconsistent results of the two studies, further research is needed to determine the relationship between homocysteine levels and ethnicity.

## Diabetes and Kidney Disease

Diabetes mellitus has been associated with heart disease (McCully, 1997; Bostom et al., 1994; Chauveau et al., 1993; Freidman et al., 1995). Diabetics often suffer from heart attack, stroke, kidney failure, blindness, and gangrene. A few of these ailments are a result of atherosclerosis. An adverse effect of kidney failure, whether it is from diabetes or other causes, is a large build up of homocysteine in the blood. The levels of homocysteine can become extremely high, sometimes reaching two to three times the normal values (McCully, 1997). According to Bostom et al. (1994), who examined a group of 24 patients between the ages of 35 and 70 years with End-Stage Renal Disease (ESRD) on maintenance dialysis. Subjects were matched with controls. Plasma homocysteine levels were higher in ESRD patients than in controls. Vitamin B concentrations were also examined in the above patients and elevated homocysteine levels were also apparent in the ESRD patients with normal and above normal vitamin B levels, suggesting that vitamin status is an independent factor. Chauveau et al. (1993) examined 118 adults with end stage renal disease (ESRD), 79 of the patients were not on dialysis and 39 patients were on maintenance dialysis. All subjects were matched for controls. The 79 nondialyzed patients did not receive any vitamin supplementation and had homocysteine levels two to four times greater than their controls. Of the 39 patients on maintenance dialysis all received adequate levels of Vitamin B12 and folate and still had elevated postdialysis homocysteine levels. Overall, the study showed that as renal function decreased, homocysteine levels increased. Therefore there is evidence that patients with renal failure have high homocysteine levels. Individuals receiving dialysis treatment, either hemodialysis or continuous peritoneal dialysis still may show elevated



hcy levels, although homocysteine levels tend to be even more elevated in untreated patients (Freidman et al., 1995). The above research also indicates that vitamin therapy does not decrease those levels of homocysteine in patients with renal disease.

### Homocysteine and Alzheimer's Disease

Alzheimer's disease and dementia has been related to atherosclerosis and vascular disease (Perry et al., 1999; Bell et al., 1992; Clarke et al., 1998; McCadden et al., 1998). The relationship between the two began in the late 1980's with The Oxford Project to Investigate Memory and Aging (OPTIMA). OPTIMA is an ongoing study that was established in 1988 to study Alzheimer's disease and all factors that affect it. The projects found research to link elevated levels of homocysteine causing damage to the blood vessels in the brain resulting in the development of Alzheimer's disease (Perry, 1999). McCaddon et al. (1998) studied 30 subjects 65 years or older with Alzheimer's disease and found a significant relationship between homocysteine levels and scores of the Cambridge Cognitive Examination (CAMCOG), which is the cognitive assessment for elderly individuals with mental disorders. The test assesses retention skills and short-term memory skills. Clarke et al. (1998) found a significant relationship between homocysteine levels and scores on the Cambridge Cognitive Exam and a Mini-Mental State Exam (MMSE). The MMSE assesses a combination of orientation skills, ability to follow directions, and attention skills. Homocysteine levels, serum folate and vitamin B12 levels were also examined. The study showed lower levels of vitamin B12 and folate in the Alzheimer's patients with elevated homocysteine levels. The study by Clarke et al. (1998) also suggests that adequate amounts of folate and B12 may reduce

the risk of Alzheimer's disease. Research has found that Alzheimer's patients as well as those with dementia tend to have lower levels of the two vitamins than those with normal brain function (Tufts University Health & Nutrition Letter, 1999). Higher levels of homocysteine have been shown to reduce the ability to learn and remember, especially with the association of low levels of folate and Vitamin B12 (Miller et al., 1999). Riggs et al. (1996) demonstrated this by giving a battery of cognitive tests to 70 male subjects between the ages of 54 and 81 years. As a result, lower levels of both vitamins correlated with a high concentration of homocysteine, which produced a poor memory response. The higher levels of folate and B12 improved the outcomes of the cognitive exams on two measures of memory.

The correlation between elevated homocysteine levels and individuals with Alzheimer's type dementia is not fully understood, however, scientist have reported that people with Alzheimer's disease have no S-adenosylmethionine (SAdMe) in their brains, which is required for maintenance and repair of the brain cells (Segala, 2001).

### Summary

The discovery of homocysteine dates back to the 1933 with the death of a young boy with symptoms normally associated with older adults. It was not until the 1965 when the cause of death was determined to be homocysturinia. From the time of discovery until now, research involving homocysteine has been extensive and continues to expand.

Elevated homocysteine levels have become an important biochemical marker for coronary heart disease (CHD). Several studies (Stampfer et al., 1992; Selub et al., 1995; Malinow et al., 1995; Malinow et al., 1989; Berwanger et al., 1995) have shown a strong

correlation between elevated homocysteine levels and CHD, cerebrovascular disease, and peripheral arterial occlusive disease.

There are several factors leading to the causes of elevated homocysteine levels such as heredity, age, and gender. These factors are unalterable, there are some factors that are alterable such as diet and possibly exercise (Nygard et al., 1995; Malinow et al., 1996; Genest et al., 1991; William et al., 1990). Elevated homocysteine is more common in those that demonstrate an inherited factor; as well elevated homocysteine is more common in older adults rather than younger adults. Homocysteine levels are commonly higher in men than in women. However, postmenopausal women tend to have higher levels than premenopausal women due to the related estrogen status.

Elevated homocysteine levels have been associated with increased levels of cholesterol and triglycerides (Karmin et al., 1998; Glueck et al., 1995). However, more research is needed in this area. Due to inconsistent results (Gerhard et al., 1999; Giles et al., 1999) research is needed to determine the relationship between homocysteine levels and ethnicity. Other areas of research related to elevated homocysteine levels include diabetes, kidney disease, and Alzheimer's disease. These also show a correlation with elevated homocysteine levels.

Homocysteine has been widely researched and related heart disease. Both unalterable risk factors and alterable risk factors have been examined. However, more research is needed to determine the effect exercise has on homocysteine levels.

## CHAPTER 3

### METHODOLOGY

There are several unalterable factors in elevated serum homocysteine levels such as heredity, age, and gender. However, there are other factors that are or maybe alterable: these are diet and exercise. The purpose of the study was to determine if a 12-week progressive exercise program, which met five days a week for 45 minutes would significantly effect serum homocysteine levels in men and women.

#### Participants

Ten men and women between the ages of 32 and 50 years of age participated in the study. The female subjects were all premenopausal. Subject's homocysteine levels were 10  $\mu\text{mol/L}$  or greater. The subjects were all sedentary, business or professional individuals who joined the study to improve their physical fitness.

#### Subject Selection

Homocysteine has been widely researched and related to heart disease. The University of Nevada, Las Vegas exercise physiology laboratory conducts an experimental exercise program, which studies the effect of daily exercise on the aging process and on coronary risk factors. This program has been conducted for the past 26 years. The exercise program meets Monday through Friday for 45 minutes of exercise each day. The program is a formally lead, progressive exercise program consisting of

flexibility and stretching exercises, strength and muscular endurance exercises, and cardio-respiratory exercises. (see Appendix A for exercise class details) In the fall of 2001 all 22 of the new exercise participants were recruited to participate in the present study. In addition to the normal physical fitness test battery (see Appendix B for test battery) and the usual blood profile, all new participants were also tested for homocysteine levels. Of the 22 new participants 11 had homocysteine levels 10  $\mu\text{mol/L}$  or greater and these 11 were identified to be in the study. One subject whose homocysteine levels were extremely high was later eliminated as an outlier. The exercise program is a year-long program. However, for the present study the new participants were tested before and after 12 weeks. Previous results had shown that the major changes in physical fitness occurred during the first 12 weeks. Those who participated in the 12-week homocysteine study attended at least 75% of the exercise sessions. Table 1 presents the subjects physical characteristics.

**Table 1 Physical Characteristics of Subjects**

<b>Subjects</b>	<b>Height (In)</b>	<b>Weight (Lbs)</b>	<b>%Fat</b>
<b>MALES</b>			
<b>1</b>	<b>70</b>	<b>177</b>	<b>26</b>
<b>2</b>	<b>74</b>	<b>225</b>	<b>36</b>
<b>3</b>	<b>70</b>	<b>177</b>	<b>26</b>
<b>4</b>	<b>69</b>	<b>170</b>	<b>23</b>
<b>5</b>	<b>70</b>	<b>180</b>	<b>26</b>
<b>6</b>	<b>73</b>	<b>185</b>	<b>29</b>
<b>Mean for males</b>	<b>71</b>	<b>186</b>	<b>28</b>
<b>FEMALES</b>			
<b>7</b>	<b>53</b>	<b>125</b>	<b>28</b>
<b>8</b>	<b>52</b>	<b>120</b>	<b>32</b>
<b>9</b>	<b>51</b>	<b>118</b>	<b>29</b>
<b>10</b>	<b>53</b>	<b>175</b>	<b>38</b>
<b>Mean for females</b>	<b>52</b>	<b>135</b>	<b>32</b>

### Pre-exercise Physical Fitness Assessment

Prior to the exercise program starting, the participant's physical fitness was assessed using a standard physical fitness test battery. The physical fitness test battery consisted of items to evaluate flexibility, strength and muscular endurance, cardio-respiratory fitness, and body composition. (see appendix B for complete test battery) Participants were asked to not change their diets or physical activity levels and not to begin any diet supplementation, so that the only factor affecting any possible change in their homocystiene levels would be the daily exercise.

### The Exercise Program

After the physical fitness assessment was completed, the 12- week exercise program was started. Participants met Monday through Friday and participated in a progressive general exercise class. Attendance was taken daily. The class started at an intensity of approximately 35-50% of V02 max and increased intensity weekly so that at the end of the 12-week period, participants were working at an intensity of approximately 85% of maximum oxygen uptake. The exercises stressed warm-up and stretching, muscular strength and endurance, cardio-respiratory exercises and a cool down period (See Appendix A for exercise class details).

### Post-Experimental Period

At the end of the 12 weeks of exercise all physical fitness tests were repeated and homocystiene levels were again determined.

### Homocysteine Determination

Homocysteine levels were determined at a local medical laboratory. Subjects were asked to report to the medical laboratory after a 14 hour fast during which no food or drink, other than a reasonable quantity of water for thirst. Subjects were asked not to exercise 12 hours before reporting to the laboratory and were asked to get at least 8 hours of sleep the previous night. Three 10ml syringes of blood were drawn from the antecubital vein. The blood was centrifuged and 10 cc were used to determine serum homocysteine. Homocysteine ultraquant was determined by a micro particle enzyme immunoassay procedure.

### Statistical Analysis

The purpose of the study was to investigate the effects of a daily 12-week exercise program on homocysteine levels.

Ho: Exercise has no effect on Homocysteine levels.

H1: Exercise reduces Homocysteine levels.

A dependent one tailed t test was performed to evaluate the changes in mean homocysteine values, before and after the 12-week exercise program. ( $\alpha = .05$ )

## CHAPTER 4

### RESULTS AND DISCUSSION

The purpose of the present study was to investigate the effects of a 12-week exercise program on homocysteine levels in men and women. The research question was: Does regular exercise reduce homocysteine levels? Homocysteine levels were determined prior to the 12-week exercise program and again at the end of the 12-week period. The homocysteine levels were then evaluated for any significant changes.

#### Subjects

Subjects in the study were business or professional men and women ranging from 32 to 50 years of age. All subjects were sedentary prior to the program and joined the program to improve their physical fitness level. All subjects attended at least 75% of the exercise sessions. Table 1 in chapter 3 presents the physical characteristics of the subjects prior to the 12 week exercise program beginning. The females had a mean weight of 128 lbs and a mean height of 64 inches. Their body composition was not unusual for the average female, namely 29.8% body fat. The males were likewise normal for the adult population with an average height and weight of 70.5 inches and 181 lbs. The males' percent body fat was 26.2%. The average attendance during the 12-weeks of exercise was 79.2%. During the physical fitness testing following the 12 weeks of exercise all tests items improved although weight and body composition did not



change dramatically (see Appendix E for fitness test scores). Figure 2 and 3, and 4 present the changes in body composition, strength, and cardio-respiratory fitness levels.

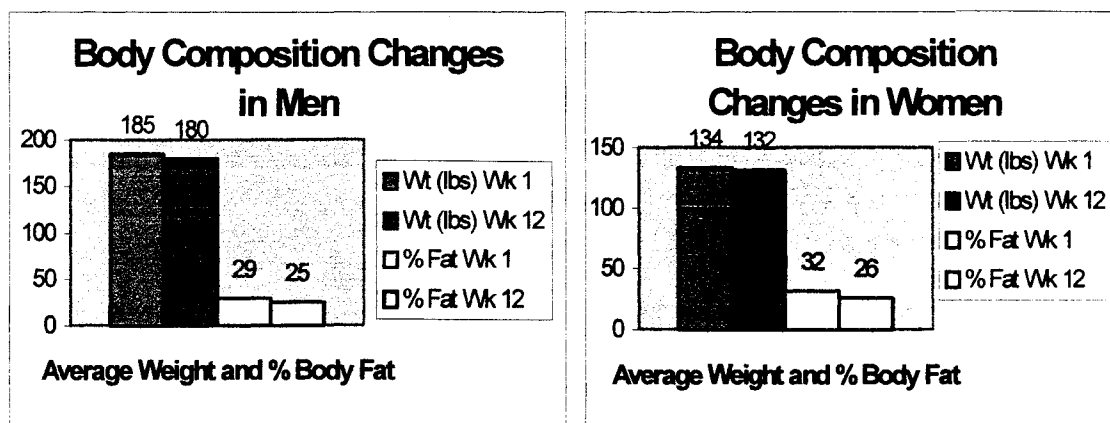


Figure 2. Changes in Body Composition in Men and Women.

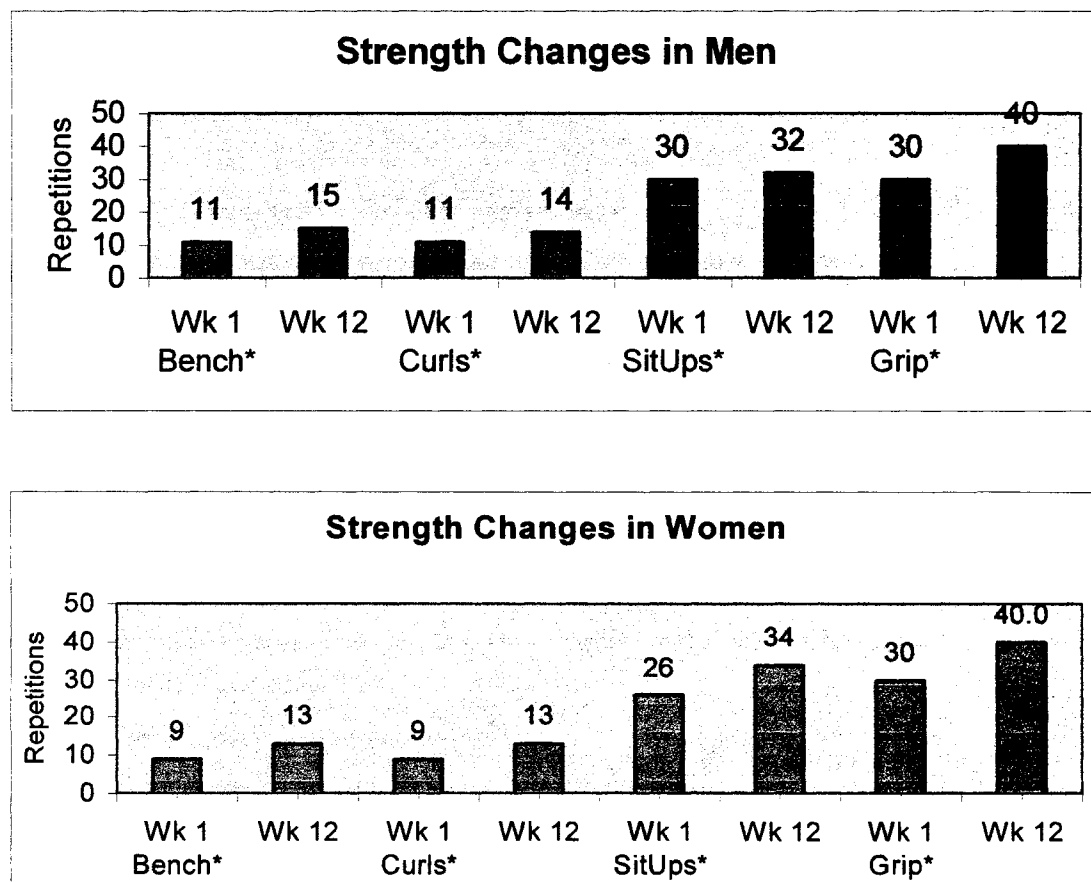


Figure 3. Strength Changes in Men and Women

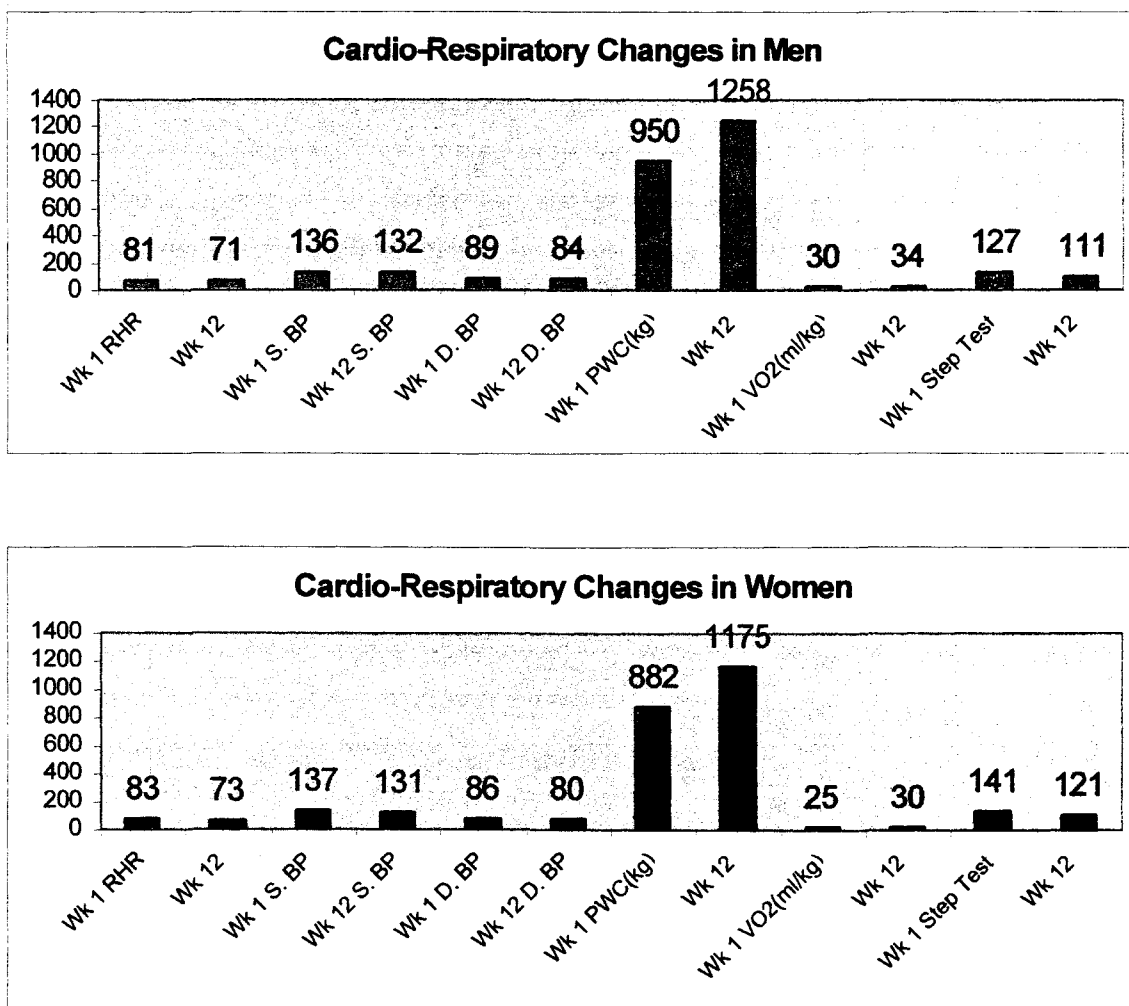


Figure 4. Cardio-Respiratory Changes in Men and Women

#### Data Analysis

A dependent t test was performed to evaluate the changes in homocysteine levels following the exercise program ( $\alpha = .05$ ). The mean homocysteine level prior to the exercise program was 12.47  $\mu\text{mol/L}$  and the mean homocysteine level after the 12-week period was 11.18  $\mu\text{mol/L}$ . The mean difference was 1.29 from week 1 to week 12. Table 2 shows the individual values and the mean values of homocysteine.

**Table 2 Changes in Homocysteine**

<b>Subject</b>	<b>Hcy T1</b>	<b>Hcy T2</b>	<b>diff. T1 &amp; T2</b>	<b>%attendance</b>
1	10.3	10.1	0.2	80
2	12.6	11	1.6	82
3	12.6	11	1.6	78
4	11.1	10	1.1	81
5	12.7	12.6	0.1	76
6	14.9	13.7	1.2	75
7	15.1	12.7	2.4	83
8	10.5	9.1	1.4	84
9	11.6	10.3	1.3	77
10	13.3	11.3	2	76
<b>Total</b>	<b>124.7</b>	<b>111.8</b>	<b>12.9</b>	<b>792</b>
<b>Mean</b>	<b>12.47</b>	<b>11.18</b>	<b>1.29</b>	<b>79.2</b>
<b>Standard Deviation</b>	<b>1.66</b>	<b>1.43</b>	<b>.714</b>	
<b>Standard Error</b>	<b>0.53</b>	<b>0.45</b>	<b>0.23</b>	

Due to his extremely high levels of homocysteine subject 11 was considered an outlier and was eliminated from the statistical analysis because he was not representative of the population.

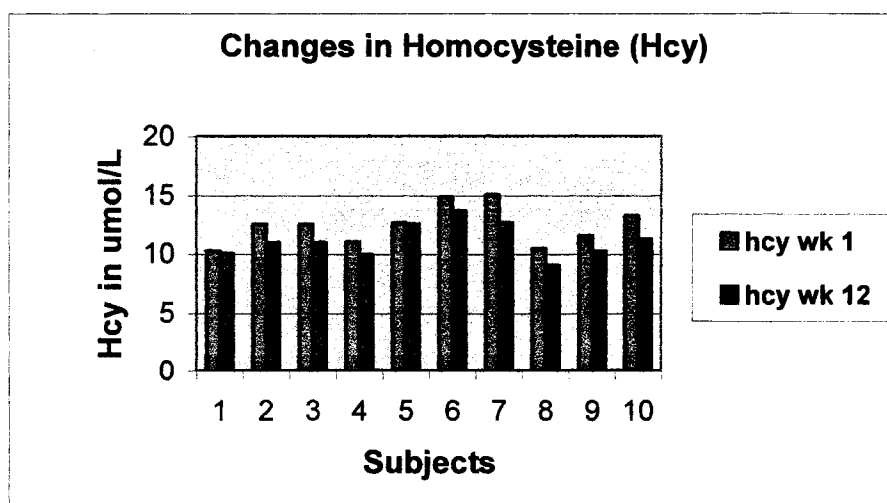


Figure 5. Illustrates the changes in homocysteine over 12 weeks.

The analysis revealed a significant difference in homocysteine levels after the 12-week exercise program ( $t = 5.71$ ,  $p < .05$ ). The result of the statistical analysis provides evidence that regular exercise does reduce homocysteine levels in men and women.

**Table 3 Paired T test for changes in homocysteine**

t-Test: Paired Two Sample for Means

	<i>Variable 1</i>	<i>Variable 2</i>
Mean	12.47	11.18
Observations	10	10
Hypothesized Mean Difference	0	
df	9	
t Stat	5.712838	
P(T<=t) one-tail	0.000145	
t Critical one-tail	1.833114	

### Discussion

The present study revealed a statistically significant change in homocysteine levels after a 12-week exercise program. Six men and four women participated in the study to improve their physical fitness. It was assumed that all women were premenopausal based on the ages of the subjects ranged from 32 to 50 years of age. All subjects reported that they were free of any known heart disease or any other major medical condition. Subjects reported being sedentary prior to the exercise program and were asked to refrain from changing their diet or to begin taking any supplements other than their multivitamin.

The exercise program consisted of stretching, muscular strength and endurance, cardio-respiratory exercise and a cool down. Attendance was taken and subjects attended a minimum of 3 out of 5 days per week for the 12-week period.

A large volume of research has been published about homocysteine in the last decade; however, to date little research has been published on the specific effects of regular exercise and homocysteine levels. Nygard et al. (1995) showed a correlation between exercise and homocysteine levels in the Norwegian Hordaland Homocysteine study. However, Wright et al. (1998) showed that one bout of 30 minutes of acute exercise has no effect on homocysteine levels.

It is an accepted fact in the medical population that elevated cholesterol levels are a major risk factor for heart disease and that cholesterol can be lowered by regular exercise and diet. Normal levels of cholesterol should be below 200 for total cholesterol with LDL levels below 130 and HDL above 35. Exercise can increase HDL cholesterol and lower total cholesterol. But there is only limited information about the effect of regular exercise on serum homocysteine levels (Malinow et al., 1999; Spectra Cell Lab; Franklin, 1998; Stein et al. 1998; Boushley et al., 1995). The present study gives evidence that regular exercise lowered homocysteine levels.

Overall there was a 10% reduction in homocysteine levels over the 12 weeks and while this is statistically significant there is a question whether, from a practical preventive standpoint, this is a significant reduction. There is little research to indicate the magnitude of homocysteine reduction necessary to significantly reduce the risk of a cardiovascular accident. It is possible that exercise for a longer period of time might reduce homocysteine levels enough to show that homocysteine has been reduced enough

to lessen the chance of cardiovascular disease. It would be especially important to determine if homocysteine levels gradually decline with training and at what point homocysteine has a plateau affect. However, even though the present study only showed a slight decline in homocysteine levels with exercise, the trend was toward lowering homocysteine levels. Perhaps, with the combination of exercise and diet, homocysteine levels may be reduced to lessen the incidence of coronary heart disease.

## CHAPTER 5

### SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

#### Summary

Cardiovascular disease is the major cause of death in the United States. Elevated serum homocysteine is an accepted risk factor for coronary heart disease along with hypertension, uncontrolled diabetes, elevated cholesterol levels, cigarette smoking, lack of exercise, and obesity. Homocysteine was originally discovered in the 1933 and elevated levels were seen in children with mental retardation. However, research, which showed the relationship between elevated homocysteine levels and coronary heart disease, did not start until 1976 (Wilcken et al., 1976). Since then several studies have related elevated homocysteine levels with heart disease (Boushley et al., 1995, Malinow et al., 1994, Nygard et al., 1995, Stampfer et al., 1992, Kang et al., 1986, etc). Even though most medical diagnostic laboratories indicate homocysteine levels between 5 and 15  $\mu\text{mol/L}$  to be a normal range, studies (Segala et al., 2000) have demonstrated that homocysteine levels above 6.3  $\mu\text{mol/L}$  cause a progressive risk of a heart attack.

It has also been determined that elevated homocysteine is a heritable factor (Malinow et al., 1996, Genest et al., 1991, Reed et al., 1991, Berg et al., 1992). Age, gender, menopause, elevated cholesterol, diabetes, kidney disease, and Alzheimer's disease have also been linked to elevated homocysteine levels. However, little research has been completed showing the relationship between regular exercise and homocysteine

levels. Total cholesterol and particular low-density lipoproteins, which are both, important in coronary heart disease, have been shown to be beneficially effected by regular exercise. This relationship sparks an interest as to whether exercise may also beneficially effect homocysteine levels.

The purpose of the current study was to determine whether a 12-week exercise program lowered homocysteine levels in men and women. Homocysteine levels were determined prior to the beginning of the 12-week period and again at the end of the 12 weeks. Homocysteine levels were then assessed for changes. A dependent t test revealed a statistically significant decrease in homocysteine levels after the 12-week exercise program.

In order to lower the risk for heart disease it is important to eat a healthy diet in order to lower cholesterol levels and homocysteine levels and also supplement the diet with Vitamin B12, B6, and folic acid if needed. The results of the present study indicate that regular exercise also assists in lowering elevated homocysteine levels.

### Conclusion

Twelve weeks of regular, progressive exercise for 45 minutes five days a week, produced a statistically significant reduction in serum homocysteine levels in 10 male and female subjects.

### Recommendations for Further Research

1. It is recommended that a larger number of subjects be studied. Ten subjects were examined in the current study and more subjects may change the results of the



study and would allow a better opportunity to make inferences about the general population.

2. It is recommended that subject's diets be more carefully assessed and controlled. Subjects were asked not to change their diets during the experimental period and it was assumed that all subjects were compliant with the request. However, a daily diet record, and a record of supplement use would present evidence that it was not dietary change that effected the homocysteine levels.
3. It is recommended that prior to subject selection that a questionnaire be completed by all subjects to determine any use of medication, supplements, and vitamins, and to indicate the amount and kind of exercise they have participated in.
4. It is recommended that a longer exercise period be studied. Twelve weeks produces changes in physical fitness but blood variables may need prolonged activity to produce significant and meaningful changes.
5. It is recommended that different types of exercise programs be used. The present study used an overall general fitness regimen. It would be desirable to determine if changes occurred with a more intense aerobic training and/or with strictly anaerobic training such as strength training.

## **APPENDIX A**

### **EXERCISE CLASS DESCRIPTION**

### Exercise Class Description

The University of Nevada, Las Vegas Adult Exercise Research Program is designed to improve the quality of lifestyle by providing a program of physical exercise prescribed on the basis of sound physiological and biomedical principles.

The program of exercise starts at a low level of intensity and progresses in intensity each week. Time is needed to adapt to the stress of regular exercise.

The class meets as a group five days a week, Monday through Friday, beginning in September and continuing through August. The program has been meeting for the past 27 years and 25 individuals have been in the program for 20 years or more. With new people starting each September there is now over a total of 100 people. New members that start September are trained initially as a separate group from the other ongoing members. Both groups (beginning and old) meet at the same time, in the same facility, and share the same instructors, but are exercised separately. In February, the beginning group has progressed sufficiently to join the "on-going" class. The combined group then completes the year as one class. The following September the cycle starts again.

### **The Testing Program.**

The program includes laboratory evaluations of physical fitness, body composition, blood pressure, heart rate, a complete blood profile, and an electrocardiogram. A locker, exercise mat, surgical tubing, chinning bar and the daily exercise leadership are also provided. Medical clearance from the participant's personal physician is required prior to starting the program to determine whether or not there is any pathological reason why one should not participate in this exercise study. After receiving medical clearance and signing an informed consent form and a spouse agreement form, participants will be tested in the UNLV Exercise Physiology Laboratory, and a blood profile will be taken at a local medical facility.

Although the blood profile is an executive panel, it has an emphasis on the lipid items: i.e. HDL Cholesterol, LDL

Cholesterol, Total Cholesterol, total/HDL ratio, triglycerides, apolipoprotein A-1, B and their ratio (an excellent biochemical marker of coronary heart disease). Additional blood components such as glucose, uric acid, electrolytes, blood enzymes and a complete CBC are included. Physical fitness measurements include cycle ergometer test, maximum oxygen uptake, body type (somatotype) photograph, flexibility, strength, body composition (underwater weighing, bioimpedance, and skinfolds) and the heart's response to exercise.

All these tests are administered in September and in May during the first year, and then each May thereafter. From our data, the changes that occur from September to May dramatically show the beneficial effect of regular exercise on coronary risk factors and physical efficiency. The effect over time shows that regular exercise prevents the decline in fitness attributed to age.

### **The Exercise Program**

The supervised exercise consists of four components: 1) warm-up and stretching, 2) strength and muscular endurance, 3) cardiorespiratory or aerobic, and 4) cool-down.

The *warm-up period* includes 5-7 minutes of flexibility exercises consisting of bending, stretching and twisting. These exercise are designed to stretch the muscles while allowing the joints to go through their full range of movement. At the beginning of the year more time is spent in this phase than later. Emphasis is put on exercises for low back pain.

Exercises for *muscular strength and endurance* include calisthenics such as push-up, sit-ups, chest raising, chins etc. These exercises are designed to exercise each major muscle group using the body's weight as resistance.

For the *aerobic or cardiorespiratory portion* of the class; the women bench step and jog, and the men bench step and swim. Swimming is not a prerequisite of the class since the university pool is divided into a 25-yard deep pool and a 25-yard shallow pool. The beginning class does water walking.

The final part of the program is the *cool-down period* during which time the body returns to its resting pre-exercise level. These exercises are similar to the warm-up exercises, and are more important in the women's class as the heat generated by the exercise and jogging needs to be dissipated, whereas the swimming tends to cool the body down in the pool.

## **The Research**

The exercise research program studies three main emphasis: 1) the longitudinal effect of daily, regular exercise on the factors that play a role in the development of heart disease. 2) the effect of short term exercise on selected physiological variables; 3) the effect of regular exercise on the aging process.

It is not a program for individuals who have a history of heart disease, major risk factors or are symptomatic. It is not a cardiac rehabilitation program. Attendance is taken each day and is an important component of the study. 70% attendance (4 time a week) is requested although few busy professional people can attain that attendance. But regular attendance is encouraged since regular, progressive exercise is safe, whereas sporadic, irregular exercise can be potentially dangerous. The experimental and progressive period is from September to May. During the summer the program meets four days a week and does not progress in intensity.

In addition to the above research, class members are also able to participate in other research studies that the laboratory conducts. This is strictly voluntary. In the past these studies have included the effect of exercise on body composition, weight loss, thermoregulation, diet and blood pressure, certain blood variable, etc.

## **The Benefits**

Research evidence (both ours and others) has shown that participation in regular, vigorous exercise is extremely beneficial. In 1996 the Surgeon General of the United States released the Surgeon General's Report on Physical Activity and Health clearly summarizes these benefits. Physiological and psychological changes, which have been shown with routine exercise, include:

- Decrease in resting and exercise heart rate
- Decrease in arterial blood pressure
- Increase in cardiac efficiency
- Improved body composition (more muscle and less fat)

- Reduction in total serum cholesterol and an increase in HDL cholesterol (the good cholesterol)
- Prevention of strength loss with age
- Reducing, preventing or slowing down the physiological effects of aging
- Improved self-image
- Improved sense of well-being
- Reducing stress levels

Changes such as these, reduce the risk of coronary heart disease (the leading cause of death in men and women); provide greater sources of energy for work and leisure; and create a positive outlook toward life.

From Golding, Lawrence. (1992). Adult Exercise Research Program-Handbook. Unpublished participants handbook. University of Nevada, Las Vegas.

## **APPENDIX B**

### **FITNESS TEST BATTERY FORM**

**UNIVERSITY OF NEVADA, LAS VEGAS**  
**Adult Exercise Programs-Score Sheet**

**Be sure to fill in all spaces**

Subject's Name: \_\_\_\_\_ I.D. Number: \_\_\_\_\_

Name of Tester: \_\_\_\_\_ Date: \_\_\_\_/\_\_\_\_/\_\_\_\_  
 month day year

Age (yrs. day of test): \_\_\_\_ Birthdate: \_\_\_\_\_ Attendance (%): \_\_\_\_

1. Resting Heart Rate (bpm): \_\_\_\_\_ 2. Resting B.P. (mmhg): \_\_\_\_/\_\_\_\_

3. Weight (lbs): \_\_\_\_ 4. Height (ins): \_\_\_\_\_ 5. EKG: **YES/NO**

6. Skinfolds (mm): (Done by: \_\_\_\_ ) Caliper used circle: Lange / Harpenden  
Check off .

Chest: \_\_\_\_\_ mm Triceps: \_\_\_\_\_ mm

Abdomen: \_\_\_\_\_ mm Back: \_\_\_\_\_ mm

Hip: \_\_\_\_\_ mm Thigh: \_\_\_\_\_ mm

Side: \_\_\_\_\_ mm Waist Girth: \_\_\_\_\_ cm

- |     |       |
|-----|-------|
| 1.  | _____ |
| 2.  | _____ |
| 3.  | _____ |
| 4.  | _____ |
| 5.  | _____ |
| 6.  | _____ |
| 7.  | _____ |
| 8.  | _____ |
| 9.  | _____ |
| 10. | _____ |
| 11. | _____ |
| 12. | _____ |
| 13. | _____ |
| 14. | _____ |

7. Step Test (post-exercise 1 min. HR): \_\_\_\_\_ beats

8. Flexibility 2 trials-(ins.-circle best): \_\_\_\_\_ ins \_\_\_\_\_ ins

9. Grip Strength (circle R or L): \_\_\_\_\_ R L \_\_\_\_\_ kg

10. Bench (reps): \_\_\_\_\_ Curls (reps): \_\_\_\_\_ Crunches (1 min): \_\_\_\_\_

11. Bike Test: Seat height: \_\_\_\_\_  
 \_\_\_\_\_ 1st Wk.Ld: \_\_\_\_\_ kgm HR: 2<sup>nd</sup>Min. \_\_\_\_\_ 3<sup>rd</sup>min. \_\_\_\_\_ 4<sup>th</sup> min \_\_\_\_\_  
 \_\_\_\_\_ 2nd Wk.Ld: \_\_\_\_\_ kgm HR: 2<sup>nd</sup>Min. \_\_\_\_\_ 3<sup>rd</sup>min. \_\_\_\_\_ 4<sup>th</sup>min. \_\_\_\_\_  
 \_\_\_\_\_ 3rd Wk.Ld: \_\_\_\_\_ kgm HR: 2<sup>nd</sup>Min. \_\_\_\_\_ 3<sup>rd</sup>min. \_\_\_\_\_ 4<sup>th</sup> min \_\_\_\_\_  
 \_\_\_\_\_ 4th Wk.Ld: \_\_\_\_\_ kgm HR: 2<sup>nd</sup>Min. \_\_\_\_\_ 3<sup>rd</sup>min. \_\_\_\_\_ 4<sup>th</sup> min \_\_\_\_\_

**NOTE: Check boxes for workloads & heart rate to be used.**

12. Photo (circle): Yes / No 13. Blood Appointment: Yes / No  
 (no shoes or socks) (Give blood order form if not received)

**14.CHECK NOW - ARE ALL SPACES FILLED IN?**

**PUT IN COMPUTER? YES/NO**

**Printed out: YES/NO**

**COMPLETE? YES/NO**

**Mailed: YES/NO**

From Golding, Lawrence. (1992). Adult Exercise Research Program-Handbook.  
 Unpublished Participants handbook. University of Nevada, Las Vegas.



## APPENDIX C

### CONSENT FORM

### **Informed Consent**

I, Tracey Zuehlsdorff am a graduate student in the Exercise Physiology department at the University of Nevada, Las Vegas. As a graduate student I am working on my thesis and conducting a research project to determine the effects of a 12-week training program on homocysteine levels in men and women. I invite you to participate and act as a subject in this research project. The study is 12 weeks in length and prior to the training program, blood tests will be done to determine homocysteine levels. Those with homocysteine levels above 10  $\mu\text{mol/L}$  will undergo a 12-week aerobic type exercise program at least three times a week. At the end of the 12 weeks, homocysteine levels will be evaluated again.

There are many benefits to participating. First, your involvement will help discover the effects that exercise have on homocystiene levels, a new risk factor for heart disease. As well, there are many personal benefits to exercise such as weight loss, reducing cholesterol, controlling hypertension, and fighting other risk factors for heart disease. There is no cost to you as a subject and all information concerning you is confidential and will be in file locked in a cabinet in Dr. Larry Golding's office.

If you have any questions concerning the project please contact myself, Tracey Zuehlsdorff at 437 – 8745 or Dr. Larry Golding (SIRC 100) at 895 – 3766. For any questions about the rights of research subjects, contact the Office for the Protection of Research Subjects at 895 – 2794.

Participation in this study is voluntary and one may withdraw at any time during the study; however, your full participation is greatly appreciated.

---

I wish to participate

---

Date

## APPENDIX D

### RAW DATA

### Raw Data

Subject	hcy wk 1	hcy wk 12	difference
1	10.3	10.1	0.2
2	12.6	11	1.6
3	12.6	11	1.6
4	11.1	10	1.1
5	12.7	12.6	0.1
6	14.9	13.7	1.2
7	15.1	12.7	2.4
8	10.5	9.1	1.4
9	11.6	10.3	1.3
10	13.3	11.3	2
Mean	12.47	11.18	1.29
SD	1.660689	1.430462	0.714065
Std error	0.525156	0.452352	0.225807

### t-Test: Paired Two Sample for Means

	<i>Variable 1</i>	<i>Variable 2</i>
Mean	12.47	11.18
Observations	10	10
Hypothesized Mean Di	0	
df	9	
t Stat	5.712838	
P(T<=t) one-tail	0.000145	
t Critical one-tail	1.833114	

## APPENDIX E

### CHANGES IN FITNESS LEVELS

### Changes in Body Composition

Subject	Wt (lbs)		% Fat		Ht(in)	
	Wk 1	Wk 12	Wk 1	Wk 12	Wk 1	Wk 12
<b>Males</b>						
1	177	175	26	25	70	70
2	225	210	36	30	74	74
3	177	175	26	26	70	70
4	170	170	23	22	69	69
5	180	175	26	25	70	70
6	185	180	29	25	73	73
Mean	186	181	28	25	71	71
<b>Females</b>						
7	125	120	28	23	53	53
8	120	120	32	26	52	52
9	118	120	29	25	51	51
10	175	170	38	31	53	53
Mean	134	132	32	26	52	52
<b>Total avg</b>	<b>165</b>	<b>161</b>	<b>29</b>	<b>26</b>	<b>63</b>	<b>63</b>

### Changes in Strength

Subject	Bench*		Curls*		SitUps*		Grip*	
	Wk 1	Wk 12	Wk 1	Wk 12	Wk 1	Wk 12	Wk 1	Wk 12
<b>Males</b>								
1	12	16	13	15	30	38	30	42
2	10	15	9	16	25	33	28	40
3	10	15	11	12	33	40	36	42
4	14	16	10	16	36	15	30	41
5	9	15	11	15	30	36	29	38
6	9	16	11	11	25	32	28	40
Mean	11	15	11	14	30	32	30	40
<b>Females</b>								
7	10	15	10	13	30	38	32	41
8	12	17	9	15	32	41	32	45
9	13	14	10	15	28	32	30	40
10	3	6	6	10	16	26	25	36
Mean	9	13	9	13	26	34	30	40.0
<b>Total avg</b>	<b>10</b>	<b>14</b>	<b>10</b>	<b>14</b>	<b>28</b>	<b>33</b>	<b>30</b>	<b>40</b>

\*Note: Bench, Curls, and Sit Ups are measured in repetitions and Grip Strength is measured in Kg.

### Cardiovascular Fitness Changes

Subjects	RHR		BP-S/D		PWC(kg)		VO2(ml/kg)		Step Test	
	Wk 1	Wk 12	Wk 1	Wk 12	Wk 1	Wk 12	Wk 1	Wk 12	Wk 1	Wk 12
<b>Maies</b>										
1	81	72	130/90	125/85	1000	1400	33	36	129	109
2	83	71	120/95	120/85	900	1200	26	32	136	110
3	88	73	135/85	130/80	1100	1250	34	35	123	112
4	77	69	130/80	130/80	900	1150	30	33	116	108
5	76	68	145/90	130/90	850	1200	26	32	125	110
6	81	72	155/95	145/85	950	1350	30	36	132	116
<b>Mean</b>	<b>81</b>	<b>71</b>	<b>136/89</b>	<b>132/84</b>	<b>950</b>	<b>1258</b>	<b>30</b>	<b>34</b>	<b>127</b>	<b>111</b>
<b>Females</b>										
7	84	70	130/85	125/80	980	1250	29	32	136	110
8	83	71	135/90	130/85	800	1100	26	31	140	121
9	81	72	140/80	130/75	950	1250	25	28	136	119
10	86	81	145/90	140/80	800	1100	21	30	152	135
<b>Mean</b>	<b>83</b>	<b>73</b>	<b>137/86</b>	<b>131/80</b>	<b>882</b>	<b>1175</b>	<b>25</b>	<b>30</b>	<b>141</b>	<b>121</b>
<b>Total avg</b>	<b>82</b>	<b>71</b>	<b>136/88</b>	<b>130/82</b>	<b>928</b>	<b>1228</b>	<b>28</b>	<b>32</b>	<b>132</b>	<b>115</b>

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## VITA

Graduate College  
University of Nevada, Las Vegas

Tracey Michelle Zuehlisdorff

### Home Address:

7827 Meandering Path Ave  
Las Vegas, Nevada 89131

### Degrees:

Bachelor of Science, Kinesiology, 1999  
University of Nevada, Las Vegas

Thesis Title: The Effects of a 12 Week Exercise Program on Homocysteine Levels in Men and Women

### Thesis Examination Committee:

Chairperson, Dr. Lawrence Golding, Ph.D.  
Committee Member, Dr. Jack Young, Ph.D.  
Committee Member, Dr. Richard Tandy, Ph.D.  
Committee Member Dr. Keith Schwer, Ph.D.