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The Effect of Physical Activity on Macrovascular Disease in Type 1 Diabetes Mellitus

By

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The undersigned certify that they have read and recommended to the Faculty of Graduate Studies for acceptance, a thesis entitled "The Effect of Physical Activity on Macrovascular Disease in Type 1 Diabetes Mellitus" submitted by Sharisse E.L. Kyle in partial fulfillment of the requirements for the degree of Master of Science in Kinesiology.

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ABSTRACT

This study compared the risk of macrovascular disease outcome to binomially classified physical activity level in a population of type 1 diabetics. The subject population was a well defined cohort from the Epidemiology of Diabetes Complication study from Pittsburgh Pennsylvania who have been followed over time since 1986.

Disease rates, relative risk of macrovascular disease and 95% confidence intervals were calculated for all comparisons. Comparisons included short and long term effects of exercise, effects of consistency of exercise, and effect of gender and age on exercise amounts and disease.

Risk differences were noted in most comparisons with a protective effect against macrovascular disease with higher activity levels. Recent physical activity was protective than remote activity.

Gender and age differences in activity levels and risk outcomes were noted and warrant further study. Further follow up over time and analyzing physical activity as a continuous variable or in multiple levels would provide more insight into this topic.

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DEDICATION

This thesis is dedicated to my husband Andrew and my daughters Louise and Grace. Thanks so much for your patience and your support in all my endeavors.

> "The credit belongs to those people who are actually in the arena...who know the great enthusiasts, the great devotions to a worthy cause; who at best, know the triumph of high achievement; and who, at worst, fail while daring greatly, so that their place shall never be with those cold and timid souls who know neither victory nor defeat."
>
> *Theodore Roosevelt*

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Chapter 1: Introduction

1.1. Purpose:

The purpose of this study was to determine if there was a difference in the rate of macrovascular complications in type 1 diabetes mellitus (T1DM) related to physical activity. Physical activity was categorized and cardiovascular disease, including angina, myocardial infarction, cerebrovascular events, peripheral vascular disease (specifically, claudication and amputation related to vascular disease) or mortality related to any of the preceding events was measured.

1.2. Significance:

Type 1 diabetes mellitus affects young people resulting in a high rate of morbidity and mortality. Reports have suggested that only 40% will survive 40 years or more of diabetes; and, of those survivors, half will have diabetic complications. Physical activity is known to have a beneficial effect on health in the general population; specifically in reduction of cardiovascular morbidity and mortality. Type 1 diabetes mellitus is associated with an increased prevalence of acquired vascular disease, thus exercise has presumed benefits. However, few epidemiological studies have been done in this area, and long-term epidemiological studies are necessary to determine clinical outcomes. The limited studies that have been done looking at this issue have concluded that physical activity does not have a detrimental effect and may have a beneficial effect on clinical outcomes in type 1 DM. Conclusions in cross

sectional studies have been limited because of the difficulty in inferring a causal relationship between exercise and outcome; due to the possible effect of initial health status on exercise level (or; do active people stay healthier vs. healthy people being more active?). Biologic plausibility suggests that physical activity has a true effect on morbidity and mortality and longitudinal study design would elucidate this relationship more clearly.

This study will add epidemiological knowledge to an understudied and clinically important area.

The health burden of diabetic end organ disease continues to grow, and individuals with diabetes have increased prevalence rates of cardiovascular disease, eye and kidney disease and of neuropathies. The morbidity and mortality of these conditions remains significant. It is therefore important to modify risk factors and manage diabetes to reduce this burden. It is presumed that exercise is valuable in diabetes management, however supported by little study. This study will contribute to the evidence of effectiveness of exercise in macrovascular disease risk reduction in type 1 DM.

1.3. Specific aims:

1). To determine the relationship between physical activity, and morbidity or mortality related to macrovascular complications in subjects with type 1 DM. It is hypothesized that increased physical activity is associated with decreased levels of diabetic complications.

1.1). To study the effect of consistency of physical activity on macrovascular disease outcomes in this population

1.2). To study the short term and long term effects of physical activity on macrovascular disease outcomes in this population

1.3). To determine the effect of gender on the relationship of physical activity and diabetic complications.

Chapter 2: Background

Literature exists relating health benefits of exercise in the general population (17, 19,103,120,122) and in the prevention of diabetic complications (64, 69, 89). Individuals with T1 DM have an increased risk of organ disease with resultant morbidity and mortality (29), and exercise is currently recommended as an adjunct in diabetes management because of its presumed benefits (5). Few studies have shown conclusive evidence of the benefits of exercise in prevention of macrovascular complications in T1 DM.

2.1. Physical activity:

There is evidence to support the view that physical activity is beneficial in the general population to reduce the risk of cardiovascular disease and resultant morbidity and mortality (17,103,109,129). A published meta-analysis of 27 cohort studies evaluating the association of physical activity and cardiovascular disease (CVD) revealed a 90% elevated risk of CVD in sedentary versus active individuals and a relative risk of 1.6 (109). In the US, the proportion of CVD deaths related to a sedentary lifestyle has been estimated at *34.6* % and this excess is higher than for any other cardiac risk factor except elevated lipid levels. Physical activity in itself is beneficial, with observed reduction in vascular disease independent of other risk factor modification, but also reduction of risk factors for cardiovascular disease such as hypertension, lipids, obesity, platelet adhesiveness and fibrinolysis (58,109). Secondary benefits may include lifestyle changes to include a more health conscious diet and nonsmoking status (129). Psychological benefits have been shown to include improved mood, better self-esteem and less depressive symptoms (104,111); all of which are inversely related to cardiovascular disease (8,31).

The fact that physical activity is beneficial to health outcomes in the general population is well recognized; however, certain details of this benefit remain unknown. It is unknown whether recent or past physical activity

patterns are more important in health outcomes. Some studies have compared past versus recent physical activity patterns in health outcomes and have shown that recent physical activity appears to be of greater importance (103,113,131). It is also unknown whether a dose-response relationship exists between physical activity and health outcomes. A recent review of this literature by Blair, Cheng and Holder revealed an inverse dose-response gradient across physical activity categories for most health outcomes (16); however, it is not clear that this relationship exists for type 1 diabetes mellitus.

2.1.1. Definition of physical activity:

Physical activity is defined as any bodily movement produced by contraction of skeletal muscle that substantially increases energy expenditure (58). It is further described by frequency, intensity, duration, and type of activity. Physical activity may be defined in terms of METs or metabolic equivalents [defined as the ratio of the working metabolic rate of an activity divided by the resting metabolic rate (38)] or energy expenditure, as in kilocalories per activity or per day.

Energy expenditure is defined as the energy cost of physical activity behavior and is used to define physical activity in a meaningful way. The subjectivity of classifying physical activity as "occasional" or "moderate" is reduced by applying a value of energy expenditure. Thus valued, some cross population comparisons can be made and information regarding dose response of physical activity can be obtained (66).

Physical fitness is a more readily measured condition and is defined by specific attributes including cardiorespiratory endurance, muscle strength and muscle endurance (58). Previous research studies have attempted to define the relationship between physical activity and physical fitness because of the more objective nature of measuring physical fitness; however, a clear relationship has not been elucidated. Further discussion of this research is beyond the scope of this project.

2.1.2. Measurement of physical activity:

Appropriate measurement of physical activity is necessary to determine if a relationship between physical activity and health outcomes exists (58). There are many dimensions of physical activity, including caloric or energy expenditure, aerobic intensity, weight bearing, flexibility and strength (62) and it is important to focus on the aspects of physical activity most likely to be associated with the outcome of interest. In the present study, energy expenditure and its relationship with disease outcome was examined.

Ideally, specific information regarding frequency, duration, intensity and exact energy expenditure would be used to assess this relationship. This information is very difficult to gather, especially in large, long duration epidemiologic studies where questionnaires, recall diaries or physical activity records are often used. Because of the subjective nature of these methods and the contributing factors of recall and reporting bias, inaccurate assessment of physical activity can result. Other methods of measuring physical activity exist, including objective and subjective measurements. Objective measures

are thought to be more accurate, however are expensive and time consuming thus not practical to use in large scale or longitudinal studies (67). Objective measures of physical activity such as accelometry, calorimetry, pedometer use and heart rate monitors have been used to estimate energy expenditure of activities. A study by Ainsworth et al (2) attempted to categorize activities and their respective energy expenditures and, in the category of walking, energy expenditure varied from as little as 2.0 METs to as much as 12.0 METs depending on variables including intensity of activity, speed and terrain.

The fact remains that activity is difficult to categorize and exact energy expenditure difficult to ascertain; however, measuring physical activity based on self-assessments rather than precise physiologic measurements may allow more practical recommendations regarding exercise and health to the general public (126).

The Paffenbarger physical activity questionnaire was developed in 1978 primarily to identify leisure time physical activity associated with hypertensive cardiovascular disease in college alumni. It has been found to be valid and reliable for many populations over time (1,3,49). Questions in the survey include amount and pace of walking, amount of stair climbing, as well as sport participation. Sport participation is further defined by amount and intensity. From this information, energy expenditure is calculated as follows:

Kilocalories for walking = 8 kcal/city block walked.

Kilocalories for stair climbing = 4 kcal/flight of 10 stairs

Light intensity sports = 5 kcal/min

Medium intensity sports = *7.5* kcal/min Vigorous intensity sports = 10 kcal/min (56).

2.1.3. Physical activity and cardiovascular disease

Consistently in the literature, an association between physical activity and reduced risk of cardiovascular disease is found. In the United States, attributable risk of cardiovascular disease related to inactivity has been estimated at 34.6%; and is higher than for any other known cardiac risk factor other than serum cholesterol (80). Several landmark long term prospective epidemiologic studies have established a relationship between physical activity and lower rates of cardiovascular disease (12, 71, 114). Two more recent large epidemiologic studies have focused on the benefit of physical activity on cardiovascular disease in women, with similar results. Both the Iowa Health study (82) and the Nurses' Health study (65) showed graded inverse associations between physical activity and risk of coronary heart disease.

The question of amount of physical activity, as well as type and intensity of activity necessary for health benefit to be seen remains unanswered. Some studies have shown maximal benefit for health occurring between sedentary and moderately active individuals, with declining benefits with more vigorously active individuals. In both the British Regional Heart study (112) and the Multiple Risk factor intervention trial (74), the most significant reduction in coronary heart disease mortality was seen between the

sedentary and moderately active groups. More vigorous levels of activity did not confer any additional benefit.

Evidence exists supporting the notion that exercise needs to be current and continued to provide health benefits (103, 127). The Harvard Alumni study analyzed the relationship of both remote (ie. college) and recent physical activity on health outcomes with the conclusion that the recent activity only was correlated with health outcomes. The more recent British Regional Health study found that men who were active over time had the lowest risk of cardiovascular mortality. Subjects who were previously sedentary and became active had a lower risk than their sedentary counterparts and those who were previously active and became sedentary had just as high a risk as those who had always been sedentary.

2.2. Physiologic effects of physical activity on the cardiovascular system

Some of the positive effects of exercise on the cardiovascular system include acute effects of an exercise session such as reduction of systolic blood pressure, reduction of serum triglycerides, elevation of HDL cholesterol, and increased insulin sensitivity. Longer term effects include direct cardiac effects such as improved myocardial function, increased coronary artery size and vasodilatory capacity, improved vascular tone and decreased susceptibility to ventricular fibrillation. Exercise has been associated with decreased vascular inflammation and hemostasis, and with decreased levels of C-reactive protein and improved endothelial function. The British Regional Heart Study showed a significant inverse dose- response relationship with hemostasis factors such as

blood viscosity, platelet count and coagulation factors. This same study showed a strong predictive inverse relationship between physical activity and C-reactive protein (127). Other studies have also shown this relationship independent of other potential confounders (25, 36, 40, 86). Vascular endothelium mediates fibrinolytic and prothrombotic processes as well as controlling inflammatory responses. Physical activity has been shown to increase nitrous oxide and prostacyclin availability and improve endothelial dependant vasodilation (47,107) thus improving endothelial function and macrovascular health.

Physical activity over time can result in long term reductions in serum cholesterol, reductions in blood pressure, prevention of obesity, improved insulin sensitivity, and an inverse relationship with smoking behaviors (118); thus modifying these important cardiovascular risk factors.

However, physical activity seems to have an independent risk reduction effect, in addition to risk factor modification. A study by Manson et al found an association between physical activity and decreased incidence of macrovascular disease independent of BMI (81). Studies by Kraus et al and Fahlman et al showed beneficial effects of physical activity on lipoprotein profile independent of diet or weight changes (61, 32).

2.3. Physical activity and Insulin sensitivity

The underlying mechanism for physical activity as a risk modifier may be related to insulin sensitivity, as it is known that exercise improves insulin sensitivity (52, 94, 125, 109). Insulin resistance and hyperinsulinemia have been shown independently to be risk factors for macrovascular disease (48, 50, 92, 95) thus supporting a theoretical link between physical activity and reduced risk of macrovascular disease through insulin sensitivity. Insulin as a mediating factor in the physical activity-cardiovascular disease relationship has been postulated in at least one study (133). More research is needed in this exciting and understudied area.

The primary tissue responsible for accelerated glucose disposal following exercise is muscle. After an acute bout of exercise, enhanced glucose transport and augmented glycogen synthesis are largely responsible for the improvement in glucose tolerance. The beneficial effects of chronic physical training on glucose metabolism appear to be explained by multiple factors, including increased muscle mass, augmented muscle blood flow and capillary area, enhanced mitochondrial oxidative enzyme capacity, and activation of the glucose transport system (60, 63).

2.4. Type 1 diabetes mellitus:

Type 1 diabetes mellitus is an endocrine disorder of hyperglycemia and hypoinsulinemia leading to disordered metabolism, and an increased risk of multiple organ disease including nephropathy, neuropathy, retinopathy and cardiovascular disease. Diabetes prevalence is steadily increasing and is a

major cause of cardiovascular disease and mortality (29). Estimated annual incidence of type 1 DM in the US is 9.2 per 100,000 in adults. (130) Age standardized incidence of type 1 DM per 100,000 per year in Canada is estimated at 24 per 100,000. (54) Estimated prevalence of CVD in type 1 DM is between 4 & 21 %. (130) although some studies have shown prevalence rates of up to
45 %(88).

2.5. Cardiovascular disease and type 1 DM:

In the diabetic population, there is a higher incidence of cardiovascular disease than in the general population. (39, 125, 43, 88). A two to three fold increase incidence of CVD is seen in diabetic versus matched non-diabetic persons (83), and CVD, including coronary heart disease, cerebrovascular disease and peripheral vascular disease represent the largest threats to health and life for individuals with diabetes (55). The most significant difference in prevalence of cardiovascular disease is in the 35 to 64 age group, where prevalence is 16.2% among persons with diabetes versus 3% in those without diabetes (29). Of note, women with type 1 DM seem to lose the protective effect of gender and have risks as high as men with type 1 DM, in contrast with the general population where women have lower rates of cardiovascular disease than men. (93, 39, 125, 43, 88, 29). Men with diabetes have a higher rate of cardiovascular disease as well as a higher mortality risk related to cardiovascular disease as compared to non-diabetic men (77). The increased risk of CVD has been found to be related to duration of diabetes,

hyperlipidemia, and hypertension, as well as other known risk factors such as hyperglycemia and presence of other diabetic complications (83, 131). Prevention of cardiovascular disease in diabetes involves management of the same risk factor as in the general population; however, more stringent guidelines exist, particularly in lipid and blood pressure levels (22, 23).

2.6. Exercise and type 1 DM:

The increased metabolic demands during exercise present a challenge in type 1 diabetes mellitus because of the difficulty in maintaining euglycemia during activity. Risk of both hypoglycemia and hyperglycemia potentially with ketoacidosis exists and can be a significant deterrent to the willingness of the diabetic individual to participate in activity and the willingness of medical personnel to recommend physical activity. In addition, because of the increased risk of cardiovascular disease in diabetic individuals, proper screening must be undertaken to ensure the safety of exercise in this population. A further consideration in recommending exercise is the presence or absence of diabetic complications including microvascular disease. The effect of exercise on each of these conditions is understudied and poorly understood.

Sufficient evidence of benefit in this population exists to recommend regular physical activity despite its challenges. In recent position statements by the American Diabetes Association, exercise was recommended as a primary goal for individuals with type 1 DM because of potential benefit for cardiovascular fitness and psychological well being as well as for social

interaction and recreation. In the literature regarding type 1 DM and exercise, exercise is presumed to be of benefit by reducing modifiable risk factors for cardiovascular disease such as hypertension, lipid levels, and obesity. As well there is improved insulin sensitivity with regular exercise (94, 125, 109). Because of the possible link between insulin resistance and cardiovascular disease, this effect may be of particular benefit in diabetic individuals.

Physical activity has not been shown to consistently improve glycemic control in type 1 diabetes mellitus. A study by Lehmann et al (73) showed physical activity to have an effect on cardiovascular risk factors including lipids, blood pressure and abdominal fat independent of glycemia. A study by Wallberg-Henriksson (124) demonstrated that physical training in insulin-dependent diabetics results in increased peripheral insulin sensitivity, a rise in muscle mitochondrial enzyme activities, decreased total plasma cholesterol levels, and unchanged blood glucose control. Similarly, a study by Roberts et al (108) looked at the effect of exercise training on glycemic control in both poorly controlled and well controlled diabetic subjects and found that average levels of HbA1c were not affected by exercise. Zinman et al (134) studied acute and long term effects of exercise on glucose control in type 1 diabetic subjects, concluding that exercise resulted in an acute glucose-lowering effect but no long term changes in glycemic control were noted. However, some studies have shown short term improvements in glycemic control with physical activity, particularly in those individuals who are following a supervised exercise program (116). This change may be related more to issues of motivation, better education and support.

Few studies have specifically addressed physical activity in type 1 DM; therefore, whether physical activity improves clinical outcomes in type 1 DM remains unclear.

2.7. Exercise and diabetic complications:

Currently there is a lack of evidence showing benefits of exercise in reducing complications in type 1 DM, and some experts have expressed concerns of worsening of microvascular and macrovascular complications with exercise. *(64,130)*

Some studies have shown no significant benefit of activity but no long-term negative consequences on risk of microvascular disease, macrovascular disease or death. (64, 69, 89) Some studies have concluded that there is no harmful effect of exercise on prevention of macrovascular complications, but have used historical physical activity as a measure (ie high school or college sports participation) (94). Other authors have concluded that present physical activity is a more important measure of complication risk (103, 113,131).

In a study by Moy et al (89) both current and past levels of physical activity were analyzed and both found to be inversely related to diabetic complications.

Short-term exercise studies were unable to evaluate longitudinal clinical outcome measures, but have revealed positive effects of exercise including reduced need for insulin (89). Negative effects of exercise include risk of hypoglycemia during or after exercise.

Many studies have shown a relationship between avoidance of complications and glycemic control (94); in particular glycemic control has been shown to reduce microvascular complications. The importance of glycemic control in the reduction in diabetic microvascular complications is well known and accepted, particularly following the landmark Diabetes Control and Complications Trial (DCCT). The DCCT was a large scale randomized control study in which subjects were randomized to either a conventional therapy group consisting of one to two insulin injections daily, or to an intensive therapy group which consisted of insulin pump therapy or three or more insulin injections daily. The intensive therapy group showed a decreased risk of diabetes related retinopathy, neuropathy and nephropathy; however, no difference in rate of macrovascular complications (27).

The association of glycemic control with macrovascular complications is less clear (77). In fact many studies show little if any effect of HbA1C on cardiovascular complications in type 1 diabetes (78, 7, 59) The Epidemiology of Diabetes Interventions and Complications (EDIC) is a follow up study utilizing the DCCT cohort. Relationships were found between increased intimal thickness in the carotid artery and some traditional cardiovascular risk factors (age, smoking, elevated cholesterol); with no noted association with HbA1C or intensive insulin therapy (30).

In a study by Wei et al (129), exercise benefits were shown to persist across plasma glucose levels, emphasizing the importance of exercise irrespective of blood glucose levels. In this same study, after adjustment for age, parenteral history of cardiovascular disease, alcohol consumption, cigarette smoking, high cholesterol level, high blood pressure, and lipid profile there persisted an association between low fitness or inactivity and mortality. Thus, physical activity may contribute to weight loss, glycemic control, improved insulin sensitivity, blood pressure, and lipid profile; but also may have an independent effect on mortality rates. Physical activity was also shown to be independently beneficial in a study by Moy et al (89) after controlling for potential confounders of age, BMI, insulin dose, reported diabetes complications, cigarette smoking, and current alcohol drinking.

This implies a less critical role of glycemic control on macrovascular complications in diabetes. No specific correlation has been made between glycemic control and reduced incidence of macrovascular disease. This perhaps increases the interest in other factors, including physical activity, and how these factors impact macrovascular disease in diabetes.

2.8. Summary:

Exercise has many proven beneficial effects on health and specifically on reduction of cardiovascular disease. Type 1 diabetes mellitus has a known increased risk of macrovascular disease with a resultant high degree of morbidity and mortality. Studies relating prevention of cardiovascular complications to levels of physical activity have shown an inverse relationship in the general population; however, this evidence is lacking in the type 1 DM population. At present, the beneficial effect of exercise in type 1 diabetes is only presumed.

Chapter 3: Research Methods

3.1. Study Design:

This study was conducted using a subset of the Epidemiology of Diabetes Complications Study (EDC) from Pittsburgh Pennsylvania. The first data collection for this group began in 1986 based on a cohort of type 1 diabetic individuals diagnosed between 1950 and 1980 living within 100 miles of Pittsburgh. New cycles of data collection have continued every two years and data cycle 10 is currently underway.

3.2. Subjects:

Subject data has been collected in conjunction with the Epidemiology of Diabetes Complications Study (EDC) from Pittsburgh, Pennsylvania. The first data collection for this group began in 1986 based on a cohort of type 1 diabetics diagnosed between 1950 and 1980. New cycles of data collection have continued every two years and data cycle 10 is currently underway. The study population originally consisted of 658 subjects diagnosed with type 1 diabetes prior to the age of 17 (333 males and 325 females).

At baseline, mean age of subjects was 28 years, with a range from 8 to 48 years. Mean duration of diabetes was 20 years. No new subjects have been added to the cohort and deceased subjects have been left in the data set. By cycle 5, only 5 subjects had failed to provide follow up data. Cycle 6 of data

collection was the most recently completed data set available at the commencement of this project.

Demographics of the data set in cycle 6 include an n of 562 still living at the time of data collection for cycle 6, with 282 males and 280 females. Mean age of the subjects was 37.25 years, with a range of 18.3 to 57.31 years. Twenty-eight subjects were lost to follow up from baseline and 68 subjects were deceased since baseline evaluation. Deceased subjects were included in the analysis if their death was related to cardiovascular causes.

3.3. Data Collection – Procedure:

3.3.1. Reporting

The Epidemiology of Diabetes Complications Study commenced in 1985 and data was collected on the study population based on the Children's Hospital of Pittsburgh County registry. The population consisted of individuals diagnosed with type 1 diabetes between 1950 and 1980. Clinical exams commenced in 1986 with baseline data completed by 1988. Complete data collection for cycle 6 was complete in 1998. Data was collected in an identical fashion for each cycle including demographic data, health history, physical activity history, and full medical examination. Questionnaire tools utilized for data collection were identical for each cycle of information gathered and standardized examinations were carried out.

Specifically, questionnaires include general medical history, self-care practices, and health care utilization including preventative services, smoking, weight history, alcohol use and basic demographic data. Standardized instruments including the Rose angina and claudication questionnaire, the

Michigan Neuropathy Screening Instrument, the SF36 and Beck depression and anxiety scales were used. Measure of physical activity was done via Paffenbarger Harvard Alumni survey, whereby subjects log the type and duration of activities for the previous week. Logged activities are converted to kilocalories of energy expenditure per week (Appendix A).

3.4. Data Collection – Definition of macrovascular disease outcome

Macrovascular disease was defined as physician diagnosed stroke, myocardial infarction, angina, intermittent claudication and amputation related to lower extremity arterial disease (LEAD). Angina and intermittent claudication were assessed using the Rose questionnaire. In deceased patients, causes of death were obtained and utilized for classification as to disease status.

3.5. Data Entry

All data entry was done on site at the University of Pittsburg. Six standardized forms (Appendices A – F) were used by subjects and examiners to collect raw data. This data was then recorded and classified by a data manager at the University of Pittsburg. The recorded data was available, by cycle, in Microsoft Excel® documents.

3.6. Data extraction & reclassification

Data of interest was extracted from the recorded data in each cycle.

Data of interest for the present study included cycle of study (time factor), patient age at each cycle of interest, gender, physical activity history (including recent and past), as well as consistency of activity, activity level compared to age and incidence of cardiovascular event.

3.6.1. Cycle of study

From baseline data collection in 1986, subjects have been recalled and data collected on this cohort every 2 years. Each data collection point is termed a cycle. For this study data was analyzed up to and including cycle 6.

3.6.2. Gender

This variable was classified binomially as male or female.

3.6.3. Age

Age was binomially classified for each cycle into an older and younger age group; the older group classified as those subjects greater than or equal to 35 years of age and the younger group classified as those less than 35 years of age. Age is of interest because of the effect of increasing age on incidence of cardiovascular disease.

3.6.5. Measurement of Physical Activity

Physical activity was assessed via questionnaire as per previous EDC studies, using questions from the Harvard Alumni Survey. Physical activity was expressed as kilocalorie expenditure per week value. To simplify analysis, energy expenditure values for the study population were averaged over cycles 1 and 2; 3 and 4; and 5 and 6 to obtain a median kcal/week value. These median energy expenditure values were then binomially classified as 1). High – energy expenditure greater than or equal to the median value for the study population in the cycles of interest, or 2). Low – energy expenditure less than the median for the study population in the cycles of interest.

Accurately measuring physical activity in a reliable fashion, particularly in a large population, remains a formidable challenge. Subjective measurement remains the practical, cost efficient method of collecting this data. The Paffenbarger physical activity questionnaire was developed in 1978 and has been widely used since the time of its inception. It has been found to

be valid and reliable for many populations over time (69). Questions in the survey include amount and pace of walking, stair climbing and sport participation. The questionnaire used for this study focuses on the activity in the week preceding the completion of the questionnaire, and asks comparative questions with "normal" amounts of activity, both for the individual and compared to peers (Appendix A).

From the responses on the questionnaires, a kilocalorie per week value of energy expenditure was derived for each subjects' physical activity. For the 562 subjects, a median value of physical activity was calculated, and subjects were classified into "low" and "high" physical activity categories.

3.6.6. Consistency of Physical Activity over time

Using median energy expenditure values, a new category was made representing consistency of activity over time. Three categories were formed for descriptive analysis: consistently active, consistently inactive and inconsistent activity over time. Subjects whose physical activity levels remained in the high category in all cycles were categorized as consistently active, subjects whose physical activity levels remained in the low category in all cycles were categorized as consistently inactive and those subjects whose activity levels varied from cycle to cycle were categorized as inconsistently active. The inconsistently active group included those who were active and became inactive, as well as those who were inactive and became active.

For calculating risk, a binomial variable was created by grouping the inconsistent exercisers with the low physical activity group and comparing outcomes with the high physical activity group.

3.6.7. Physical Activity versus Age

Age was binomially classified into older (greater than or equal to 35 years) and younger (less than 35 years) age groups and comparison of physical activity levels for these two age groups was made. Changes over time were also analyzed for these two groups because of the overall declining physical activity levels with age in this cohort. Thus the definition of "active" versus "sedentary" varied across age groups. In fact, if an individual subject maintained an identical physical activity level over time, it is feasible that with this categorization that subjects may switch from being classified as inactive to being classified as active relative to others their age. A relationship may not be apparent between physical activity and macrovascular disease in the young adult, but may become clear as the population ages. In addition, physical activity levels may decline with age.

3.6.8. Macrovascular Disease

Outcome measures were the appearance of a macrovascular event at any time between the end of cycle 2 and the end of cycle 6. Subjects having macrovascular disease in cycle 1 or 2 were excluded from analysis. Definitions

and diagnosis of the event conditions were identical to the previous study definitions determined by the EDC. Specifically, cardiovascular disease was defined as the presence of myocardial infarction, angina, cerebrovascular events or stroke, peripheral vascular disease manifested by claudication or amputation due to vascular disease, abnormal ankle to arm systolic blood pressure ration or mortality related to any of the preceding events.

3.6.9. Summary

New variables were formed as follows.

1. high and low physical activity in each cycle. This was done by determining the median energy expenditure for the subjects in that cycle, then binomially classifying each subject into high or low, depending on whether their activity level was above or below the median respectively.

2. macrovascular disease. This variable was created by combining variables of cardiac disease and cerebrovascular disease, as well as determining cause of death in deceased subjects.

3. age. As age was a changing variable, subjects were aged for each cycle past baseline for analysis.

4. consistency of physical activity. Once subjects were classified into high or low physical activity groups as above; the consistency of activity over time was of interest.

3.7. Data Analysis Strategy

3.7.1. Final Data Set

In some cases, there was insufficient information on physical activity levels or on presence or absence of macrovascular disease and these subjects were therefore eliminated from the analysis. In the instance of death prior to the end of the study period, if cause of death was macrovascular disease, these subjects were included in the analysis.

3.7.2. Analysis Software

The subject data was imported into Microsoft Excel® (Microsoft Corporation, Redmond, WA) and Stata™ (Stat Corporation, College Station, TX) for analysis. Once imported the data was checked to ensure that the recorded values were plausible.

3.7.3. Descriptive Analysis

The study population was described in terms of gender, age, level of physical activity, level of activity over time, and appearance of macrovascular disease.

3.7.4. Univariate Risk Analysis

The relationship between physical activity and macrovascular outcome was summarized and displayed using tables. Relationships between physical

activity and macrovascular disease by gender, average physical activity by cycle and by age, overall incidence of macrovascular disease, overall incidence of macrovascular disease by age, relationship of activity in cycle 1/2 to macrovascular disease by cycle 4, relationship of activity in cycle 1/2 to macrovascular disease by cycle 6, relationship of activity in cycle 3/4 to macrovascular disease by cycle 6, relationship of activity in cycle 5/6 to macrovascular disease by cycle 6, relationship of activity in cycle 3/4 to macrovascular disease by cycle 6 in women, relationship of activity in cycle 5/6 to macrovascular disease by cycle 6 in women.

Relative risk tables were constructed for each of these analyses. These data were then grouped by gender, age and consistency of physical activity.

Relative risk analysis was performed on consistently active versus consistently inactive subjects over time. As well, a relative risk analysis was done on consistently active versus a combined category of consistently inactive and inconsistently active subjects over time. This analysis was done on the two age groups (age less than 35; age equal to or greater than 35) separately. Data was analyzed to determine if subjects who were consistently active throughout the cycles versus inconsistent exercisers or consistently inactive individuals had a lower incidence of macrovascular disease. Additionally, physical activity in cycle 1/2 was compared with macrovascular disease outcomes in cycle 3/4 as well as outcomes in cycle 5/6 to determine if physical activity has long term effects; and more importantly to determine cause and effect.

Chapter 4: Results

4.1. Study Population

4.1.1. Subjects

At baseline, mean age of the 658 subjects was 28 years, with a range from 8 to 48 years. Mean duration of diabetes was 20 years. No new subjects have been added to the cohort and deceased subjects have been included in the data set. Data on deceased subjects was used at the last available data collection point. Cycle 6 of data collection was the most recently completed data set available at the commencement of the study.

In total, 28 subjects were lost to follow up from baseline and 68 subjects were deceased since baseline evaluation. Deceased subjects were included in the analysis if their death was related to cardiovascular causes and there was sufficient other data for that subject for analysis (n=18), thus total n available for analysis was 580.

Demographics of the data set in cycle 6 include an n of 562, with 282 males and 280 females. Mean age of the subjects was 37.25 years, with a range of 18.3 to 57.31 years. Appendix B summarizes the demographics of this population.

4.2. Measurement of Physical Activity

Table 1. Range of physical activity in kcal/week by cycle.

	Lowest kcal expenditure per week	Highest kcal expenditure per week
Cycle 1/2	0	9675
Cycle 3/4	0	10294
Cycle 5/6	0	11440

Table 1 reflects the wide range of physical activity as subjectively reported in the study population.

Table 2. Median physical activity with standard deviations for all subjects by cycle and age.

	Age<35		Age ≥ 35	
	Median physical activity	**Standard deviation**	**Median physical activity**	**Standard deviation**
Cycle 1/2	2875 kcal/week	2535	1822 kcal/week	3062
Cycle 3/4	2071 kcal/week	2745	1320 kcal/week	1511
Cycle 5/6	1334 kcal/week	1783	1153 kcal/week	1559

Table 2 reveals median physical activity level per cycle group and by age; illustrating a declining median physical activity level over time and with increasing age.

4.3. Gender differences in Physical Activity

Percentage of males and females categorized into the low and high physical activity groups is illustrated in **Figure 1.**

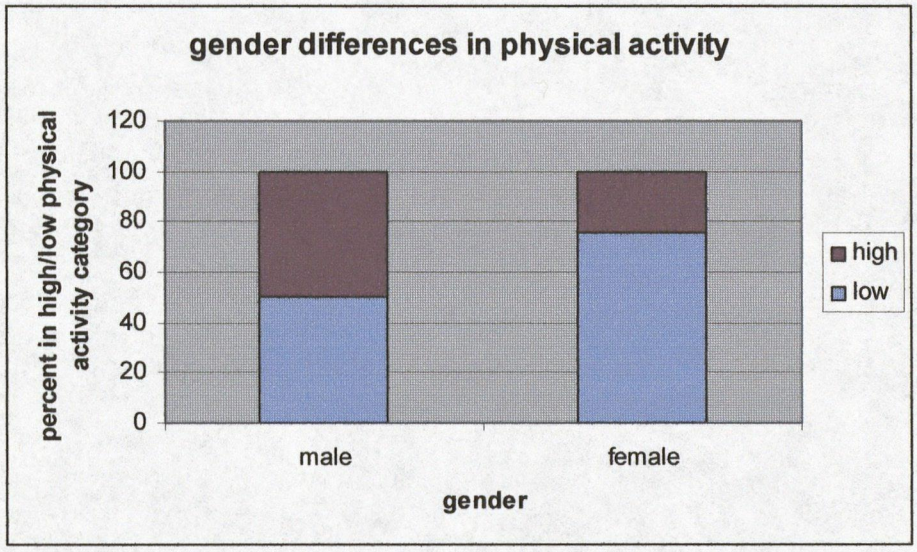

Figure 1. Gender differences in physical activity expressed as percentage of total.

Over the period of study, 76% of women fell into the low physical activity group versus 50% of men. This trend of women being less physically active than men held across all cycles.

Table 3. Gender differences in physical activity

	Gender	N	Median physical activity (kcal/wk)
Cycle 1/2	**Male**	282	2568
	Female	275	1758
Cycle 3/4	**Male**	229	1823
	Female	232	1304
Cycle 5/6	**Male**	202	1251
	Female	205	1173

Absolute values of gender differences in median physical activity by cycle are illustrated in **Table 3.**

4.4. Overall prevalence of Macrovascular disease

Table 4. Overall prevalence of macrovascular disease by the end of cycle 6 by sex.

	Total number of subjects	Number of subjects with macrovascular disease by end cycle 6	Prevalence of subjects with macrovascular disease by the end of cycle 6
Male subjects	293	66	0.22
Female subjects	287	86	0.30
All subjects	580	152	0.26

Risk ratio: 0.75
95% Confidence Interval: 0.57 – 0.99

In this study population, being female conferred a risk to the development of macrovascular disease. The prevalence of macrovascular disease in women was higher than that of men, and risk of disease in males was 0.75 times the risk of disease in females.

Table 5. Overall prevalence of macrovascular disease by the end of cycle 6 by age.

Age in cycle 6	Total number of subjects	Number of subjects with macrovascular disease by end cycle 6	Prevalence of subjects with macrovascular disease by the end of cycle 6
Age < 35 years	190	44	0.23
Age ≥ 35 years	390	108	0.28

Risk Ratio: 0.84

95% Confidence Interval: 0.62 – 1.13

Table 5 reflects the overall prevalence of macrovascular disease in subjects < 35 years of age in cycle 6, and in those 35 years of age or older.

4.5. Relationship between physical activity and prevalence of macrovascular disease

Table 6. Prevalence of macrovascular disease by cycle 6 in low and high physical activity groups for all cycles.

	Physical activity level	Total numbers	Number of prevalent cases (macrovascular disease)	Rate of macrovascular disease	Risk ratio	Confidence interval
Cycle 1/2	Low	370	100	0.27	1.04	0.78 - 1.39
	High	201	52	0.26		
Cycle 3/4	Low	358	104	0.29	1.26	0.94 - 1.69
	High	213	49	0.23		
Cycle 5/6	Low	388	113	0.29	1.44	1.04 – 2.00
	High	183	37	0.20		

This table shows the trend over time in the two activity groups of absolute numbers in high and low activity groups and prevalent cases of macrovascular disease. The rate and risk ratio show an increasing risk difference in disease outcome over time between the low and high activity groups. Confidence intervals also suggest this trend.

4.6. Physical Activity and Incidence of Macrovascular Disease

Table 7: Physical activity levels, rate of macrovascular disease and risk ratios for all cycles.

	Physical activity level	Total numbers	Number of incident cases (macrovascular disease)	Rate of macrovascular disease	Risk ratio	Confidence interval
Cycle 1/2	Low	375	69	0.18	3.14	1.74 – 5.61
	High	205	12	0.06		
Cycle 3/4	Low	365	88	0.24	3.7	2.16 – 6.34
	High	215	14	0.07		
Cycle 5/6	Low	397	89	0.22	2.93	1.72 – 5.00
	High	183	14	0.08		

This table shows the trend over time in the two activity groups of absolute numbers in high and low activity groups and incident cases of macrovascular disease. The rate and risk ratio show a clear risk difference in disease outcome between the low and high activity groups. Confidence intervals illustrate that the risk difference may be lower or significantly higher than the risk ratio calculated.

4.7. Relationship of physical activity and macrovascular disease for specific groups

4.7.1. Female gender

Table 8. Incidence of macrovascular disease by cycle 6 in low and high activity groups in cycles 3 and 4 for female gender only.

	Total subject number	Incidence of macrovascular disease	Rate of macrovascular disease
Low activity (<1304 kcal/week)	147	52	0.35
High activity (>1304 kcal/week)	88	20	0.23

Risk ratio: 1.56

95%Confidence Interval: 0.99 – 2.42

In women, although there was a lower rate of macrovascular disease in the high activity group, the confidence interval suggested that there was not a significant difference.

Table 9. Incidence of macrovascular disease by cycle 6 in low and high activity groups in cycles 5 and 6 for female gender only.

	Total subject number	Incidence of macrovascular disease	Rate of macrovascular disease
Low activity(<1173 kcal/week)	124	40	0.32
High activity (>1173 kcal/week)	81	17	0.21

Risk ratio: 1.54

95%Confidence Interval: 0.94 – 2.52

In women, the rate of macrovascular disease was higher by cycle 6 in the low activity group as categorized in cycle 5 and 6, however this analysis did not reach statistical significance.

4.7.2. Outcome of macrovascular disease by cycle 4

Table 10. Relationship between physical activity in cycles 1 and 2 and macrovascular disease outcome by cycle 4.

	Total subject number	Incidence of macrovascular disease by cycle 4	Rate of macrovascular disease
Low physical activity in cycles 1 and 2	352	40	0.01
High physical activity in cycles 1 and 2	205	11	0.05

Risk ratio: 2.12

95%Confidence Interval: 1.11 – 4.04

A significant difference was noted in the incidence of macrovascular disease between the two activity groups; with higher physical activity in cycle 1/2 statistically correlated with a protective effect against the development of macrovascular disease by cycle 4.

4.7.3. Consistent versus inconsistent physical activity over time and macrovascular disease outcome by age

Table 11. Incidence of macrovascular disease by cycle 6 in low, high and inconsistent physical activity groups for subjects less than age 35.

	Total subject number under age 35 by end of cycle 6.	Incidence of macrovascular disease	Rate of macrovascular disease
Consistently high physical activity over time	69	12	0.17
Consistently low physical activity over time	61	21	0.34
Inconsistent physical activity over time	60	11	0.18

For high and low physical activity and outcome of macrovascular disease:

Risk ratio: 0.51

95%Confidence interval: 0.27 – 0.94

For high versus low and inconsistent, and outcome of macrovascular disease:

Risk ratio: 0.66

95%Confidence interval: 0.36 – 1.19

In this analysis, the relationship of consistent physical activity to the development of macrovascular disease was elucidated. In subjects less than 35 years of age in cycle 6, there was a statistically significant difference between the consistently high physical activity group and consistently low physical activity group in the development of macrovascular disease. Rate of

macrovascular disease in the consistently high physical activity group was 17% and rate of macrovascular disease in the consistently low physical activity group was 34% .

Combining low activity groups with inconsistent exercisers over time made this relationship insignificant. Rate of macrovascular disease in the inconsistent activity group was more similar to the rate of macrovascular disease in the high activity group at 18%.

Table 12. Incidence of macrovascular disease by cycle 6 in low, high and inconsistent physical activity groups for subjects age 35 and older.

	Total subject number age 35 and older at end of study	Incidence of macrovascular disease	Rate of macrovascular disease
Consistently high physical activity over time	114	26	0.23
Consistently low physical activity over time	163	46	0.28
Inconsistent physical activity over time	113	36	0.32

For high and low physical activity and outcome of macrovascular disease:

Risk ratio: 0.81

95%Confidence interval: 0.53 – 1.23

For high versus low and inconsistent, and outcome of macrovascular disease:

Risk ratio: 0.77

95%Confidence Interval: 0.52 – 1.13

In subjects 35 years of age or older in cycle 6, there was no statistically significant difference between the consistently high physical activity group and consistently low physical activity group in the development of macrovascular disease. Rate of macrovascular disease in the consistently high physical

activity group was 23% and rate of macrovascular disease in the consistently low physical activity group was 28%.

Combining low activity groups with inconsistent exercisers over time in comparison with the high activity group also did not reach statistical significance. Rate of macrovascular disease in the inconsistent activity group was 32%.

4.7.4. Incidence of Macrovascular disease compared with physical activity level in the young.

In this section, subjects less than 35 years were analyzed independently, with a median split of activity based on this age group only.

Table 13. Incidence of macrovascular disease in all cycles compared to high and low activity levels, with risk ratios and confidence intervals.

	Physical activity level	Total subjects	Number of incident cases (macrovascular disease)	Rate of macrovascular disease	Risk ratio	Confidence interval
Cycle 1	Low	372	34	0.09	1.21	0.49 – 2.97
	High	66	5	0.08		
Cycle 2	Low	323	21	0.07	0.98	0.35 – 2.74
	High	60	4	0.07		
Cycle 3	Low	285	24	0.08	2.23	0.54 – 9.16
	High	53	2	0.04		
Cycle 4	Low	249	29	0.12	2.62	0.65 – 10.6
	High	45	2	0.04		
Cycle 5	Low	206	25	0.12	1.64	0.41 – 6.53
	High	27	2	0.07		
Cycle 6	Low	155	22	0.14	1.42	0.36 – 5.59
	High	20	2	0.1		

Table 13 reveals a minimal increase in risk of disease in the low activity group other than in cycle 2. Rate of disease was most significantly different in cycles 3 and 4. Confidence intervals were such that risk of disease in the low activity groups could be less than the ratio suggests, or significantly more.

4.7.5. Incidence of Macrovascular disease compared with physical activity level in the old.

In this section, subjects 35 years and older were analyzed independently, with a median split of activity based on this age group only.

Table 14. Incidence of macrovascular disease in all cycles compared to high and low activity levels, with risk ratios and confidence intervals.

	Physical activity level	Total subjects	Number of incident cases (macrovascular disease)	Rate of macrovascular disease	Risk ratio	Confidence interval
Cycle 1	Low	116	8	0.07	0.76	0.10 – 5.52
	High	11	1	0.09		
Cycle 2	Low	142	7	0.05	0	0
	High	12	0	0.0		
Cycle 3	Low	164	14	0.09	0.85	0.12 – 5.86
	High	10	1	0.1		
Cycle 4	Low	198	23	0.12	0.69	0.23 – 2.09
	High	18	3	0.17		
Cycle 5	Low	222	20	0.9	0.78	0.25 – 2.45
	High	26	3	0.12		
Cycle 6	Low	252	28	0.11	1.78	0.44 – 7.11
	High	32	2	0.06		

Table 14 reveals a minimal increase in risk of disease in the low activity group in cycle 6 only. Confidence intervals suggest that true risk may be significantly

different than the calculated value. Numbers of incident cases were small thus power to determine true value is low.

4.7.6. Incidence of Macrovascular disease compared with physical activity level in female subjects.

In this section, female subjects were analyzed independently, with a median split of activity based on this age group only.

Table 15. Incidence of macrovascular disease in all cycles compared to high and low activity levels, with risk ratios and confidence intervals.

	Physical activity level	Total subjects	Number of incident cases (macrovascular disease)	Rate of macrovascular disease	Risk ratio	Confidence interval
Cycle 1	Low	247	16	0.06	1.00	0.24 – 4.16
	High	31	2	0.06		
Cycle 2	Low	237	24	0.10	2.84	0.4 – 20.16
	High	28	1	0.04		
Cycle 3	Low	227	29	0.13	1.19	0.39 – 3.66
	High	28	3	0.11		
Cycle 4	Low	227	36	0.16	1.08	0.42 – 2.82
	High	28	4	0.14		
Cycle 5	Low	215	29	0.13	1.69	0.43 – 6.65
	High	25	2	0.08		
Cycle 6	Low	208	28	0.13	3.1	0.44 – 21.7
	High	23	1	0.04		

Table 15 reveals a minimal increase in risk of disease in the low activity group in cycles 3 and 4, and a higher risk differential in cycles 2, 5 and 6. Confidence intervals were such that risk of disease in the low activity groups could be less than the ratio suggests, or significantly more.

4.7.7. Incidence of Macrovascular disease compared with physical activity level in male subjects.

In this section, male subjects were analyzed independently, with a median split of activity based on this age group only.

Table 16. Incidence of macrovascular disease in all cycles compared to high and low activity levels, with risk ratios and confidence intervals.

	Physical activity level	Total subjects	Number of incident cases (macrovascular disease)	Rate of macrovascular disease	Risk ratio	Confidence interval
Cycle 1	Low	241	16	0.7	0.76	0.27 – 2.18
	High	42	4	0.1		
Cycle 2	Low	231	5	0.02	0.48	0.1 – 2.38
	High	44	2	0.05		
Cycle 3	Low	228	8	0.04	1.23	0.16 – 9.52
	High	35	1	0.03		
Cycle 4	Low	218	15	0.07	1.2	0.29 – 5.04
	High	35	2	0.06		
Cycle 5	Low	214	16	0.07	2.09	0.29 – 15.19
	High	28	1	0.04		
Cycle 6	Low	206	19	0.09	0.86	0.27 – 2.72
	High	28	3	0.11		

Table 16 reveals an increase in risk of disease in the low activity group in cycles 3, 4 and 5; with the most significant risk difference being in cycle 5. Confidence intervals were such that risk of disease in the low activity groups could be less than the ratio suggests, or significantly more.

Chapter 5: Discussion

5.1. Summary of Findings

The study population was large and followed over a long period of time with little loss to follow up. From the baseline study n of 658, 580 subjects had data sufficient for analysis by cycle 6.

A wide range of physical activity was seen in all cycles, and activity levels declines over time and with increasing age. Women were less active than men in all cycles.

All groups studied had a higher incidence of macrovascular disease than is seen in non-diabetic populations, older subjects had a higher incidence of disease than younger subjects, and women had a higher incidence of macrovascular disease than men.

Higher physical activity was more significantly associated with lower incidence of macrovascular disease if it was recent. Remote activity history had a less strong association with disease or lack thereof.

In women, there was a lower rate of macrovascular disease in the higher activity groups; however the association was less strong than in the mixed gender group.

In subjects under age 35 who had consistently high physical activity over time, there was a significantly lower rate of macrovascular disease versus subjects who had consistently low physical activity over time. Inconsistent exercisers over time had only a slightly lower rate of disease compared to the

consistently high activity group. When the inconsistent group was combined with the low activity group for comparison to the high exercise group, the statistical difference between these groups was insignificant. In subjects age 35 or older, although the lowest rate of macrovascular disease was in the consistently high activity group, this relationship was not as strong.

5.2. Measurement of Physical Activity

Physical activity data in this study revealed average physical activity measures consistent with moderate activity levels as recommended by the Centers for Disease Control and Prevention (CDC) and the American College of Sports Medicine (ACSM). 1000kcal/week energy expenditure is generally accepted as a moderate level of physical activity (20) and is consistent with the above guidelines. Highest average physical activity level was in cycle 1/2 in subjects under 35 years of age (2875 kcal/wk) and lowest was in cycle 5/6 in older subjects (1153 kcal/week). Considering that moderate physical activity is activity performed at a relative intensity of 40% to 60% of VO2max (or absolute intensity of 4-6 METs); a rough estimate of kcal/week expenditure can be made as follows. METs can be converted to kcal/min by multiplying METs x 3.5 x body weight in kilograms x 4.9 kcal/L of O2 divided by 1000 mls. Assuming a calculation for a 50 kg woman and a 70 kg man, 30 minutes of moderate activity 7 days per week would yield a kcal/week expenditure of 900 kcal/week for an average weight woman, and 1261 kcal/week for an average weight man. A variety of different values have been used in the

literature for quantifying physical activity; however, most literature is consistent regarding the level of activity used to designate "sedentary" versus "active". Lee et al in studies from 1995 to 2000(TT) used values of <1000 kcal/wk to signify inactivity, values from 1000 – 2500 kcal/wk to signify moderate activity and >2500 kcal/wk to signify high activity. Oliveria (90) also used 1000kcal/wk as a cutoff point for sedentary subjects and Haapanen (44) used 800kcal/wk the sedentary group cutoff.

Large ranges and standard deviations of activity levels were seen in all cycles (Table 1, 2). This means that there exists significant variation in actual activity within the designated high and low activity groups. Nonetheless, mean activity level in each cycle was greater than 1000 kcal/week; therefore adequate to make the distinction between sedentary and active, given current opinion and definition based on ACSM guidelines.

Speculation still arises as to whether the assumptions made in this study in categorizing physical activity are accurate. Despite the fact that numerous studies add evidence to the relationship between physical activity and lower disease and mortality rates, a dose- response relationship has not been established between physical activity and health outcomes. This may be because there are also population and individual differences in the risk response to a given level of physical activity (21). The "healthy dose" of physical activity may be determined individually by genetic factors, gender and pre-existing disease states.

Categorizing physical activity in quartiles or quintiles better defines relationships between physical activity and health outcomes and several landmark studies have explored the relationship between health and activity at

several different levels. Steven Blair has published much research of this nature examining both physical activity levels and physical fitness levels and their relationship to health outcomes (13, 14, 15, 16, 17, 18). In most studies of this nature, the largest health benefit is seen between the lowest activity group and the second lowest activity group with declining benefits seen with increasing activity (16, 81, 97).

Two other general observations regarding physical activity in this study include the consistently lower levels of physical activity in women, and the decline, for both sexes, in physical activity over time.

Women were less active than men in all cycles of study and this difference was statistically significant (Table 3). This trend of gender difference in physical activity has been shown in other studies (9, 84, 106, 37, 76). It may be of particular importance as physical activity may be a more important disease modifying behavior in women versus men as evidenced by recent studies (78, 91, 110, 4). One study by Lloyd et al using Cox proportional hazards model, determined that risk factors for men and women with diabetes were different with physical inactivity being a more important risk factor in women (78). A recent prospective 16 year follow up study by Haapanen-Niemi et al looking at all-cause and cardiovascular disease mortality found that, compared with the most active subjects the men and women with no weekly vigorous activity had relative risks of 1.61 (95% confidence interval, CI, 0.98-2.64) and 4.68 (95% CI, 1.41-15.57), respectively, for CVD mortality (45). It is plausible that men and women may have different physical

activity "thresholds" for health benefits. Most studies have not quantified a dose-response for exercise benefit in either men or women, and not in the diabetic population.

The decline in physical activity over time may reflect the trend seen in the general population for decreasing physical activity with aging (34,37); as average physical activity levels were consistently lower for the older age groups versus younger age groups in each cycle. Table 2 depicts the mean physical activity for subjects stratified by age and shows a difference in each cycle, with the older group being less active; but also a decline over time in activity in both age groups. In 1996, the U.S. Surgeon General's report on physical activity and health reported statistics on activity involvement for individuals showing a trend of declining physical activity with increasing age. For individuals under the age of 21, 50% were involved in vigorous sports on a regular basis; 25% were involved in light to moderate sports regularly and 14% reported no activity. For adults 21 and older, 15% reported regular involvement in vigorous sport, 22% were involved in regular light to moderate sports and 25% reported no activity (121). Reasons for this decline in activity include many real and perceived barriers such as time constraints, physical health, opportunity for sport involvement, environmental factors and others (72,76). Full discussion of these barriers is beyond the scope of this project.

5.3. Overall Incidence of Macrovascular Disease

Data from this study supports the notion that the prevalence of macrovascular disease is higher in the diabetic population than in non-diabetics. Overall prevalence of macrovascular disease was 26%, with 22% of males affected and 30% of females affected (Table 4). CDC statistics on the prevalence of macrovascular disease in the United States indicate a 37% prevalence rate in persons aged 35 and older with diabetes versus 14% in the same age group without diabetes. CDC statistics for women with diabetes indicate a macrovascular disease prevalence rate of 19% versus 26% in diabetic men (29, 24).

Women in this study in particular had a disproportionately high rate of macrovascular disease. Incidence of macrovascular disease in female subjects was actually higher than their male diabetic counterparts. The reason for this is not clear; however in the general population, the identification of cardiac disease in women as a major public health problem is being recognized. Women have poorer prognoses than men with diagnosed cardiac disease, case fatality rates are higher for women with macrovascular disease versus men and declines in cardiovascular mortality seen in males are not mirrored in females (9). In addition, deaths from heart disease in women with diabetes have increased 23 percent over the past 30 years compared to a 27 percent decrease in women without diabetes. Some recent statistics on cardiovascular incidence

in diabetic women indicate a rate of 32% in white women with a higher rate (34%) in black women (6). Statistics on race in this population were not included in the analysis, but may have influenced the rate of macrovascular disease seen in this study.

5.4. Macrovascular Disease and Age

The data revealed a trend of higher incidence of macrovascular disease in the older (age thirty five or older) age group (Table 5). 28% of the older age group had developed macrovascular disease in the study time period. This figure is consistent with CDC statistics on the incidence of disease in diabetic subjects in this age group. There is less information on the younger population; however, the incidence of macrovascular disease in this study population was not significantly less than their older counterparts at 23%. This indicates a higher than expected risk for this age group (6).

Independent analysis of age groups (Tables 13 and 14) did not reveal a significant difference in rate of macrovascular disease; however, numbers of subjects per cycle were small and likely did not yield enough power to establish a relationship. In the younger age group, a minimal increase in disease rates was noted in the low activity group other than in cycle 2. The most significant rate difference was in cycle 3 and 4. In the older group an increase in risk of disease was noted in the low activity group in cycle 6 only. Confidence intervals were wide however, therefore it is unclear whether true differences exist.

Because median physical activity by age and by cycle was used in these risk calculations, and because number of incident cases was low; it is difficult to determine whether the risk of disease might be better defined by more continuous analysis of physical activity levels or by multiple levels of analysis such as quintiles.

5.5. Physical Activity and Incidence of Macrovascular Disease

This study provides evidence of an association between recent physical activity and decreased levels of macrovascular disease. Remote and inconsistent physical activity were less related to reduced incidence of macrovascular disease. This was true for both genders and for younger and older subjects.

The relationship between recent physical activity and decreased levels of macrovascular disease was true for early cycle and late cycle analyses. Higher physical activity in cycles 1 and 2 was significantly correlated with decreased levels of macrovascular disease by cycle 4 (Table 10); and higher levels of physical activity in cycles 5 and 6 were significantly correlated with decreased levels of macrovascular disease by cycle 6 (Table 6).

Analysis showed that physical activity levels in cycles 1 and 2 did not have a significant effect on incidence of macrovascular disease by the end of cycle 6 (Table 6). Similarly physical activity levels in cycles 3 and 4 did not have a significant effect on incidence of macrovascular disease by the end of cycle 6 (Table 6). This supports the notion that physical activity is beneficial in reducing cardiovascular risk and, importantly, provides further evidence to the

view that recent physical activity is more important than remote activity in determining health benefits (103, 113, 131). Many important studies on the epidemiology of physical activity and health outcomes have suggested that recent physical activity is an important determinant of reduced incidence of disease and mortality (53, 115). The Harvard Alumni studies (Paffenbarger et al) examined health habits and health outcomes of a large cohort of college alumni. Repeated studies showed that former varsity athletes who discontinued their sports activities had higher rates of disease and death than their teammates who continued energetic exercise. More importantly, subjects who became active later had the same low risk of disease and death as classmates who had been vigorously active all along (105, 102, 101, 99).

British Regional Heart Study examined change in physical activity over 14 years in male subjects; concluding that commencement of physical activity in previously sedentary individuals was associated with a 34% reduction in cardiovascular mortality compared to those who remained sedentary. Those who remained or became inactive had a higher risk of cardiovascular death (127). The relationship of physical activity to cardiovascular disease in this study supports an actual cause and effect for physical activity rather than state of health dictating ability to exercise. Because individuals with preexisting macrovascular disease were eliminated from this study, a better correlation can be made between physical activity and macrovascular disease. Questions have arisen in the past with regard to the association between health and activity; the important question being – does activity result in better health or are those individuals who are healthier able to do more activity? Subjects in this study were free of macrovascular disease at baseline, thus the conclusion that activity impacts health has more validity in this situation.

5.6. Women, physical activity and macrovascular disease

When stratified by sex and the relationship between physical activity and macrovascular disease outcome was explored for females only; those with higher physical activity levels in cycle 3 and 4 had a significant reduction in incidence of macrovascular disease by the end of cycle 6; with a similar relationship seen for physical activity levels in cycle 5 and 6 (Table 8, 9). For women with low activity levels in cycles 3 and 4, rate of macrovascular disease by cycle 6 was 0.35 and for women with high activity levels, rate was 0.23. Similarly, rate of disease for women with low activity in cycles 5 and 6 was 0.32 and rate of disease for women with high activity in these cycles was 0.21.

Based on previous studies linking physical activity to a reduction in cardiovascular risk in women (65, 78, 82) a consistent relationship would be expected for those women with higher physical activity levels. The Nurses' Health Study, a large cohort study of American nurses, has provided information on physical activity and cardiovascular disease in this cohort, concluding that there exists a strong inverse relationship between physical activity and cardiovascular disease (65). The Iowa Health study (82) concluded similar results.

Independent analysis of women with a median physical activity for the female subjects only (Tables 15) revealed a minimal increase in risk of disease in the low activity groups in cycle 3 and 4, and a higher risk differential in

cycles 2, 5 and 6. Confidence intervals were wide suggesting that the true risk value could be less than the risk ratio calculation suggests, or significantly more. However, subject numbers were low so this may affect the statistical relationships. Furthermore, using a median activity value based on overall activity of the females only for determining high and low activity groups may falsify the cutoff point. In fact, the level of activity for health may be higher than this arbitrary median. As with analysis of age groups, the risk of disease might be better defined by more continuous analysis of physical activity levels or by multiple levels of analysis such as quintiles.

5.7. Men, physical activity and macrovascular disease

Men were independently analyzed comparing the rate of macrovascular disease with physical activity levels in all cycles; using a median split of activity for men alone. Data obtained from this analysis is summarized in Table 16. An increase in risk of disease was noted in the low activity groups in cycles 3, 4 and 5; with the most significant risk difference being in cycle 5. Again, subject numbers were low affecting the statistical power and confidence intervals were wide suggesting that the true risk value could be less than the risk ratio calculation suggests, or significantly more. Median cutoff points between high and low activity groups may not accurately reflect the true relationship between activity and health outcome. As with analysis of age groups and female gender, the risk of disease might be better defined by more

continuous analysis of physical activity levels or by multiple levels of analysis such as quintiles.

5.8. Consistency of activity over time and macrovascular disease

Followed over time, subjects with consistently high physical activity showed more protection against macrovascular disease compared to subjects with consistently low activity (Table 11, 12). This relationship reached statistical significance in the subjects under age 35; with a trend revealed in older subjects. It is unclear why this relationship is not as strong in the older age group in this study. It is possible that other disease risk factors become more important in this age group, or, again, there may be an element of classification bias. As with the analysis on female subjects, it is plausible that there is a threshold activity level that has not been reached in classifying subjects as "high" activity subjects. It is also possible that if an activity threshold exists, it may not be generalizable. It is possible that this threshold is different across gender, age groups, racial groups and disease states. Further study is necessary to explore this relationship.

In the analysis done over time, adding inconsistent exercisers to the low activity group resulted in the loss of statistical significance (Table 11, 12). This may be because some of the subjects in the inconsistent activity group had been recently active; which analysis has shown to confer some disease protection. Recent physical activity appears to be associated with reduction in incidence of macrovascular disease. The key element in the relationship of

consistency of exercise and decreased macrovascular disease may in fact be the effect of recent activity on health outcomes.

5.9. Limitations

Limitations of a prospective cohort study include misclassification biases in exposure data and outcome data, the inability to retrospectively include data collection that was initially overlooked and loss to follow up.

Loss to follow up was not a significant factor in this study as there was only a 4% loss (28 of 652) over 12 years.

Limitations specific to this study include possible misclassification of exposure due to subjective assessment of physical activity data, which may result in recall and reporting bias; and physical activity categorization into only two categories (high, low) based on median energy expenditure values.

Physical activity data was gathered subjectively via Paffenbarger physical activity questionnaire. Although the Paffenbarger questionnaire has been appropriately validated and widely used, data gathered by questionnaire is subject to self report bias. For a large scale or longitudinal study of significant size, however it is a practical and efficient way of gathering information on a large number of subjects. Further study could include validation of subjective information with objective measures such as pedometer calculation of activity.

In addition to the difficulty with the description of physical activity, its quantification and categorization are equally difficult. Previous studies have assessed physical activity using self reported leisure time activity; categorized by such descriptors as "sedentary, slight, moderate, and heavy". METs, kcal/week, kJ/week, episodes of exercise per week, occupational activity and others have been used as study categories. Still other studies have used objective fitness measures for categorization.

Furthermore, physical activity assessment is fraught with difficulty as actual energy expenditure is difficult to elucidate from subjective reporting of physical activity. Specifics of intensity, duration and frequency are difficult to describe. Some studies have suggested that assessment of physical fitness is a more important measure than physical activity (16). Assessment of physical fitness or more specific description of energy expenditure is a highly time consuming and labor intensive process not feasible in large scale longitudinal studies such as this one.

This study identified only two levels of physical activity, high and low, based on median physical activity of the cohort. As such, the definition of high and low levels of physical activity was variable; dependant on the activity level of the cohort group. It may be in fact that there is a "set" exercise threshold that needs to be identified to determine health benefits and this threshold may not be generalizable between populations. In addition, with only 2 identified levels of physical activity, determining exercise threshold or levels at which health benefits are seen is more difficult. Many studies, such as the landmark studies from the Cooper Institute by Blair et al, have identified a progressively increasing health benefit with increasing quintiles of physical

activity (97). Further study including quintiles of activity may better elucidate exercise relationships and exercise thresholds for various study groups.

Misclassification of disease cases and controls may have occurred with subjective history taking and medical examination, although this seems unlikely due to the rigorous and well documented methods of medical exam (Appendix C). However, some subjects were classified as having "possible" disease and although not classified as cases, may have been. Also, there were subjects with "unknown" status at certain data points who may have had disease and not been classified as such.

A further limitation to this study is the exclusion in the analysis of other factors known to be predictive of macrovascular disease risk. Factors such as lipid levels, BMI, smoking status, and others were not included in this analysis. Race may be a factor both in involvement in physical activity and physiologic dose response to exercise. A necessary presumption for the conclusions of this study is that these other factors would be evenly distributed in the study population. This, however, may not be the case. Further analysis should include multifactorial analysis of these risk factors. Despite this limitation, previous studies have shown independent health benefits of physical activity in individuals with multiple cardiovascular risk factors and preexisting cardiovascular disease (85).

Further study is needed to explore questions regarding dose response to exercise, the interplay of other cardiovascular risk factors with exercise, and specific recommendations for gender and possibly racial differences in exercise response.

5.10. Summary

In summary, this study provided evidence of a higher incidence of macrovascular disease in diabetic subjects, a particular incidence of macrovascular disease in female subjects and a noted association between recent physical activity and reduced incidence of macrovascular disease.

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APPENDIX A. Physical Activity Questionnaire

EPIDEMIOLOGY OF DIABETES COMPLICATIONS
PHYSICAL ACTIVITY
FORM E

1. How many flights of stairs do you climb up each day?
   (Let one flight = 10 steps)

   _____flights per day

2. How many city blocks or their equivalent do you walk each day?
   (Let 12 blocks = 1 mile)

   _____ blocks per day

3. List any sports or recreation you have participated in during the past week. Please include only the time you were physically active (i. e., actual playing time, jogging time, swimming time, etc.).

Sport or recreation	Number of times per week	Average time per episode - hours	Average time per episode - minutes

4. List any sports or recreation you have actively participated in during the past year. Please remember seasonal sports or events.

Sport or recreation	Number of weeks per year	Time per week when active - hours	Time per week when active - minutes

5. List any sports teams you were on in high school or college.

Sport or recreation	Age when participated	Number of times in weeks	Average time per episode - hours	Average time per episode - minutes

6. Would you say that during the past week you were less active than usual, more active, or about as active as usual?

   Less active than usual _____
   More active than usual _____
   About as active as usual _____

7. At least once a week do you engage in any regular activity such as brisk walking, jogging, bicycling, etc., long enough to work up a sweat?

   YES ____ NO _____ If yes, how many times per week?
   _____

8. Please indicated if you have had any difficulties when you do the following activities:

   a. walking for a quarter mile (3-4 blocks) YES ____ NO _____

   b. walking up 10 steps without resting YES ____ NO _____

   c. standing or being on your feet for about 2 hours YES ____ NO _____

   d. lifting or carrying something as heavy as 25 pounds, such as two full bags of groceries YES ____ NO _____

9. The next few questions will ask about your household activities.

   a. Approximately how many hours per week do you spend doing household chores such as: scrubbing floors, vacuuming, cooking, sweeping, washing dishes, washing clothes, making beds, mowing the lawn, washing the car, etc.?
      _____ hours

b. When you do these household chores do you usually work so hard you need to take a break to catch your breath or cool off?

YES____ NO____ Sometimes____

10. The next few questions will ask about your job-related activities.

a. While on the job, how many hours or minutes per day do you spend actually lifting or carrying heavy objects?

___ hours ____ minutes ____ not applicable

b. Is this activity strenuous enough to force you to take breaks to catch your breath or cool off?

YES____ NO____ not applicable____

c. While on the job, how many hours or minutes per work day do you spend walking (do not include the time you spend lifting or carrying heavy objects)?

____ hours ____ minutes _____ not applicable

d. While on the job, how many hours or minutes per work day do you spend standing?

____ hours ____ minutes _____ not applicable

11. Compared with other people who are your age and the same sex, would you say that you are:

Much more active _____
Somewhat more active _____
About the same _____
Somewhat less active _____

12. The next two questions will ask about participation in physical activities at various ages during your lifetime.

    a. How often did you regularly participate in sports and leisure time activity (EXCLUDING WALKING)? (Please check in the appropriate box).

DURING AGE:	0 to 1 hour/week	2 to 3 hour/week	4 to 7 hour/week	Over 7 hour/week
14 – 17 yrs. (high school)				
18 – 21 yrs. (college)				
20-29 yrs.				
30-39 yrs.				
40-49 yrs.				
50+				

    b. How many miles did you normally walk each day outside the house or place of employment? (Please check the appropriate box).

DURING AGE:	Under 1 mile	1-2 miles	3-5 miles	Greater than 5 miles
14 – 17 yrs. (high school)				
18 – 21 yrs. (college)				
20-29 yrs.				
30-39 yrs.				
40-49 yrs.				
50+				

    REMEMBER: 12 blocks or 20 minutes of brisk walking is equivalent to approximately 1 mile.

APPENDIX B. Demographic data

Cycle	Baseline	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
Total N - males	293						282
Total N - females	365						280
N for analysis – males (alive)		287	275	263	253	242	234
N for analysis – females (alive)		278	265	255	255	240	231
Age range	8 - 48						18.3 – 57.3
Age mean	28						37.3
Duration of diabetes - range	7.69 – 37.4						
Duration of diabetes - median	18.5						
Incidence of macrovascular disease for males		20	7	9	17	17	22
Incidence of macrovascular disease for females		28	25	32	40	31	29
N <35 available for analysis		438	383	338	294	233	175
N 35 & older available for analysis		127	154	174	216	248	284
Incidence of macrovascular disease in young (<35)		39	25	26	31	27	24
Incidence of macrovascular disease in old (35 & older)		9	7	15	26	23	30
Number of deaths from all causes	NA	NA	13	15	12	12	16
Deaths from macrovascular disease	NA	NA	6	7	4	2	9

APPENDIX C. History and Physical Examination data collection

The following information on history and physical examination data collection is excerpted from the Epidemiology of Diabetes Complications complete set of data collection forms.

CL

Epidemiology of Diabetes Complications Check List - Baseline Exam FORM B-6

1. Urine Samples:

	Dare Collected	Time Started	Time Stopped	Time Period (hrs)
1) 24 hr.				
2) Overnight				
3) Pre-Clmic Spot				
(If no pre-clinic specimen, give time last voided)				
4) Post-Clinic (4 hour specimen)				

Social Security #_

Revised 11/25/96

Tnnf3l XVd 61:80 SOOS/C?/8(

PATIENT 'ID

2. Questionnaires:

	Completed	Reviewed	Date Sent/ Coding	Date Returned	Date Sent/ Entry	Date Returned
1) Genera] Medical History						
2) Psychosocial						
3) Nutrition						
4) Physical Activity						

Codes for "Completed":

1 = Pre C

-Self
- Phone
- Self
- Interviewer
-Self
- Phone

2 = Pre C '3 =
At C
4 - AtC
5 = Post C
6 = Post C 8 =
Refused

PATIENT ID

BLOOD DRAWS

1. Time: AM

Phlebotomis initials

Comments:

2. Samples Drawn:

		YES	NO	COMMEN
Whole Blood - Heparin - Fox	20ml			
Whole Blood - Saline/EDTA -	0.5ml			
Whole Blood - EDTA - CBC	3.0ml			
Whole Blood - Plasma				
Lipoproteins) (frozen)	20 ul			
Apoproteins (Cincinnati)	J. ml			
Glucose	1ml			
AGE LDL	1ml			
Total AGE	1ml			
Glucose (storage) ,	1 ml			
Plasma (storage)	3 ml			
Whole Blood - Citrated Fibrinogen	2ml			
Citrated Plasma	3 ml			
Whole Blood - Serum				
Creatinine	2ml			
Albumin	1 ml			
Lipids	2ml			
Storage	4ml			
	45.52 mls			

CL-^

PATIENT ID_ BLOOD SAMPLES DISPATHCH LOG

(C/A)

	Date Sent	Date Results Received	Results
20 ml Heparinized Whole Blood Fox Chase - Phos. Sugars			
0.5 ml Saline Whole Blood G-HB (Diabetes Lab)			
2.0 ml Serum Lipids (Bates)			
2.0 nil S. Storage/Sugar (Sugar) (Freezer)			
2.0 ml S. B12/Creatirdne (CLIC)			
1.0 ml Serum/Albumin (Ellis)			
2.0 ml Citrate Plasma/Fibrino?en (CLIC))			
3.0 ml EDTA Plasma/CBC (CLIC)			
2.0 ml AGE.-LDL/ Total AGE			
20 ul EDTA Plasma/ Dr. Robbms (Freezer)			
1.0 ml EDTA/Tras/etc. Plasma/Apoproteins (Freezer) (Cincinnati)			

SUBSEQUENT SERA DISPATCH CC/A)

(e.g. ICA/L-isulin antibodies/Somatomedins)

Test	Plasma or Serum	Volume Taken	Destination	Date Sent	Date Results Received

-4-

PATIENT ID

URINE

	Dare	Vol- (mis)	If Pro- blem Est. Vol. Lost	Dipstic									Micral 0=Nonn
				s G	P h	P	G	K	B R	U R	B	N	
24 hr													
Overnight													
•"Pre-clinic (Spot)													
Post-clinic													

Pre-chiuc results entered on preUminary results sheet.

	5ml Storage	5 ml - to Ellis (Date)	5 ml - CLIC (Date)
24 hr			
Overnight			
Pre-clinic (Spot)			
Post-clinic			

Epidemiology of Diabetes Complications Check List - Pre-Exam FORM A

ATTACH PARTICIPANT LABEL HERE

1. Letter sent to M.D.: YES NO N/A DATE:

If no, explain:

ATTACH M.D. LABEL HERE

2. M.D. returned form: YES If NO DATE:

yes, describe M.D. comments:_ If no,

date M.D. contacted; _By whom:,

Comment: __

3. Date participant invitation letter sent:_

4. Date nurse contacted:

5. Is participant eligible for study? YES __ NO If no,

explain:_____

6. Agreed: YES __ NO __ OTHER

If no, explain:.

If other, explain:

»riniai

XYj 81:80 SOOZ/CZ/80

7. Is participant aged 15 or less? *YES* __ NO __ If yes,

name and address of homeroom teacher:

8. Does the participant prefer a phone interview? YES __ NO If yes, when: _____

9. Appointment scheduled: YES __ NO

If no, explain: _____

Date appointment made: _____ *By whom:*_

Date of appointment; _____

Appointment entered into diary: YES __ NO Survey

dispatch entered into diary: YES __ NO Telephone

reminder entered into diary: YES __ NO

10. Participant asked not to take aspirin until seen: YES __ NO
11. Dispatch questionnaires/urine containers: Date: _____
Sent: YES __ OTHER __ If other, explain:

_____

(1) Cover Letter YES __ NO
(2) Description of Study YES __ NO (3) Map

YES __ NO

(4) 3 Urine Containers & 3 Plastic Bags YES __ NO
(5) Urine collection instructions YES __ NO
(6) General Medical History Form YES __ NO
(7) Psychosocial Questionnaire YES __ NO
(8) Physical Activity Survey YES __ NO
(9) HLA-DR Complete YES __ NO

12. For phone interviews; Name S phone number given to Charlotte Seltser YES __ NO Date:

_____.

13. Telephone reminder: Date:.

Appointment confirmed: • YES — OTHER If other, explain:_____

7. Is participant aged 15 or less? *YES* __ NO __ If yes,

name and address of homeroom teacher:

8. Does the participant prefer a phone interview? YES __ NO If yes, when:

_____

9. Appointment scheduled: YES __ NO If no, explain:

_____

Date appointment made:_____By whom:_

Date of appointment;_____

Appointment entered into diary: YES __ NO Survey

dispatch entered into diary: YES __ NO Telephone

reminder entered into diary: YES __ NO

10. Participant asked not to take aspirin until seen: YES __ NO
11. Dispatch questionnaires/urine containers: Date: _____
Sent: YES __ OTHER __ If other, explain:

_____

(1) Cover Letter YES __ NO
(2) Description of Study YES __ NO (3) Map

YES __ NO

(4) 3 Urine Containers & 3 Plastic Bags YES __ NO
(5) Urine collection instructions YES __ NO
(6) General Medical History Form YES __ NO
(7) Psychosocial Questionnaire YES __ NO
(8) Physical Activity Survey YES __ NO

(9) HLA
-DR Complete YES __ NO

12. For phone interviews; Name S phone number
given to Charlotte Seltser YES __ NO Date:

_____.

Date:.

Appointment confirmed: • YES — OTHER If other, explain:_____13. Telephone reminder:

Epidemiology of Diabetes Complications
Check List - Baseline Exam FORM B

ATTACH PARTICIPANT LABEL HERE

1. Time of Arrival; _A.M. Fasted (hrs):
Check name, address and birthdate on above label: YES___ NO_ List any changes:.

social Security #_

2. Urine Samples:

	Date Collected	Time Started	Time Stopped	Time Period (hrs)
1) 24 hrs				
2) overnight				

3) Pre-clinic spot				
(if no specimen, give time last voided)				
4) Post-clinic (4 hr specimen)				

3. Questionnaires:

	Completed	Reviewed	Date Sent/ Coding	Date Returned	Date Sent/ Entry	Date Returned
1) General Medical History						
2) Psychosocial						
3) Nutrition						
4) Physical Activity						
5) Myth (date sent:____)						

Codes for "Completed":

1=Pre C-Self, 2=Pre C-Phone, 3=At C-Self, 4=At C-Interv, 5=Post C-Self, 6=Post C-Phone, 8=Refused

1. Consent Signed: YES __ NO
2. Temperature Exam Rooms (for BP): _____p

BLOOD DRAWS

3. Time: ____A.M-

Phlebotomist: _____(initials)

Conimen.ts:

Samples Drawn:

	YES	NO	COMMENT
Whole Blood - Heparin - DR - 10 mis	__	__	_____
Whole Blood - Saiine/EDTA - GHb - 0.5 mis	__	__	_____

Whole Blood - EDTA - CBC - *f-mis* (Platelets) -
-*Somatornedin - *f.* mis
-*Apoproteins •" *Li* 4 mis Whole

Blood-Citrated - Platelet ***r-,\ Tn)a.*** mis *Fibrinogen - 4.5 nils

Whole Blood - Serum - See below - 20 mis (2x10)
50.5 mis blood *Spun Serum/Plasma: _____ Time completed:

4. Insulin given': _____A.M.
5. Collect spot urine (see page 1)
6. Complete Medical History (if necessary)
7. Complete Exam Form (questions 1-6)
8. Administer Eye Drops
9. Breakfast given: _____ A.M.

BLOOD SAMPLES DXSPATCH LOG (C/A)

	Date Sent	Date Results Received	Entered on Results Letter	
10 ml Heparinized Whole Blood (-->Immunology)			---	---
0.5 ml Saline Whole Blood GHB (-->Diabetes Lab)				
4 ml Serum Lipids (~->Bates)				
3 ml S. Storage/Sugar (->Sugar) (-->Freezer)			---	---
4 ml S.B,,/Folate/Creatinine (->CLIC)			---	---
1 ml Serum/Albumin (—>Ellis)			---	---
Citrate 2 ml Plasma/Fibrinogen (-->CLIC)			---	---
2 ml EDTA Plasma/CBC (-->CLIC)			---	---
EDTA 1 ml Plasma/Somatomedin (—>Freezer)			---	---
EDTA 1 ml Plasma/Somatomedin (-->Freezer)			---	---
EDTA/Tras/etc. 2 ml Plasma/Apoproteins (—>Freezer) (->Cincinnati)			---	---

Note: (ND = not drawn)
SUBSEQUENT SERA DISPATCH (C/A) (e.g. ICA/Insulin antibodies/Somatomedins)

CLINIC TEST RESULTS (C/A)

Blood:

Serum sugar mg/dl

Glucometer result

Est.R.B.C.

Platelet Count/uL

Platelet Count/uL

Platelet Count/uL

Est. EDTA

Est. Baseline (Citrate)

Est. Post 15 mins (Citrate)

Actual Cell Count _____

Actual/estimated x Estimated Platelet count

Actual EDTA ul/L _____

Pre Citrate _____

Post Citrate _____

URINE

	Date	Vol. (mls)	Est. Vol	Dipstic SG Ph P G K BR UR B N									Alb. Scree
24 hr													
Overnight													
Pre-clinic (Spot)	—	---											
Post-clinic													

24 hr						
Overnight			—			—
Pre-clinic (Spot)	—	—	—	—		
Post-clinic			—			(Use if no pre-

RESULTS LETTERS

Preliminary results letter given to participant: YES __ NO If no, explain:

OTHER TESTS RECORDED ON RESULTS LETTERS

1. Pulse
2. Blood pressure (S/DS; 3rd reading)
3. Intraocular pressure
4. Glucose/glucometer
5. Ankle/arm index

c Fundus photography

7. SITTING BLOOD PRESSURE EXAMINER ID:
Have participant seated comfortably with right arm exposed. Apply cuff

Peak Inflation Level Right Left Pulse obliteration pressure _

\+ _3_ _0

\+ Maximum Zero ___ Peak inflation

level _ _

Wait 4-1/2 minutes

Pulse rate: _____(beats/min)

Pulse is: Regular ___ Irregular ___ Not Obtainable ___ Cuff size:

Pediatric _ Normal Adult _ Large Adult _ Thigh _ Not Taken _

B.P. Machine #___'_.

First blood pressure level:

Systolic Diastolic 4th Phase Diastolic 5th Phase

Random **zero** ___ ___ ___

-Zero level - __ - __ - __ RZS1 ___ RZD41 ___

RZD51 ___•

Second blood pressure level:

Random zero ___ ___ _·__

-Zero level - __ - •_ - __
RZS2 ___ RZD42 ___ RZD52 ___

Third blood pressure level:

Random zero ___ ___ · ___
-Zero level - __ - __ ~ __

R2S3 ___ RZD43 ___ R2D53 ___

10. ELECTROCARDIOGRAM EXAMINER ID:

a. ECG recorded.?
If no, specify reason _ b. Any

technical problems?

If yes, describe _____

.11. PHYSICIANS EXAM EXAMINER ID:____ •

a) Height will be measured by the physician using the clinic stadio-meter, the patient being asked to take a deep breath, with the Frankfort plane being held horizontal.

Height == __ __ __ . __ cm

b) Weight will be measured by a balance beam in underclothing by the physician during the clinical examination- It will be measured to the nearest 0.2 Kg below.

Weight = __ __ __ . __ kg.

c) Waist girth will be measured using a cloth tape around the abdomen horizontally at midpoint between highest point of the iliac crsst and lowest part of the costal margin in the.mid axillary line.

__ __ __ . __ cm __ __ __ . .__ cm

d) Hip girth will be similarly measured at the widest point, usually at level of greater femoral trochanter.

__ __ __ . __ cm, __ __ __ • __ cm

e) Hand girth will be measured at the level of the mid-interphalangeal joints, wi-th the bottom end of tape applied to upper margin of proximal 5th phalange, and tape circumscribed around digits 2-5 inclusive. Repeat twice for both hands, individually, and together in praying position.

Hand girths: Left __ __ . ____ __ • __

Right _. __ . __ __ __ . __

Both __ .. __ __ __ • __

IVd 02:90 SOOZ/CZ/80

14. CARDIOVASCULAR EXAM

EXAMINER ID;

a. Does the participant have typical angina? YES __ NO

(Do Not Review Rose Questionnaire)

b. Does the participant have non cardiac chest pain/discomfort? YES __ NO

c. 1) Does the participant have "atypical angina"? YES __ NO

2) If YES, do you think this "atypical angina" is on the basis of disturbed coronary blood flow? YES __ NO

NOTE; Only answer a & b YES if you come to a clear diagnosis. Answer ^ YES for any other chest discomfort/pain.

d- Does the patient's history suggest a prior M.I.?
YES __ NO __ Suspect, but not sure __

e. Does the participant have heart failure?

YES __ NO __ Don't know __

f. Is the C-V.P, normal? .. YES __ NO

If abnormal, estimate level _____cmH2O

g. Is there ankle edema? YES __ NO

(Sacral if confined to sitting)?

If YES, is it pitting?- YES __ **NO** . Rate 1-4 _____

h. Is the location of the apex normal? YES NO

1) Specify the location
(intercostal space/vertical line)

2) Is the size of the impulse increased? YES __ NO
3) Is the impulse: Normal YES __ NO

Sustained YES __ NO

Hyperdynamic YES __ NO

i. Is there a third heart sound? YES __ NO

j. is there a fourth heart sound? YES __ NO

k. Is there a murmur? YES NO

Location	Murmur 1	Murmur 2
Constant		
Inconstant		
Transmitted		
Localized		
Systolic		
Presystolic		
Diastolic		
Soft (gr 1-2)		
Mod (gr 3-4)		
Loud (gr 5-6)		
After exercise: Increased		
Absent		
Unchanged		
decreased		

Location diagram:

Are there basal crepitations (rales) present? YES __ NO __

If YES, are they bilateral? YES __ NO __

Are they basilar only? YES __ NO __

Please rate the pulses according to protocol:

PULSE QUALITY

Carotid Pulse - palpate medial to sternocleidomastoid muscle at the mid-neck. Palpate only one side at a time as pressure on both carotids may cause fainting in some individuals.

Carotid Bruits - Ask the participant to take a deep breath in, out, in, out and then hold his/her breath. Ask the participant to take a deep breath in, out, in, out and then hold his/her breath. While the patient is holding his/her breath at end expiration. Carefully listen for a bruit. Auscultation should begin at the supraclavicular region and proceed cephalad along the anterior borders of the sternocleido mastoid muscle to the angle of the jaw. Next, auscultate over the chest region to rule out referral of heart +/or aortic murmurs to the carotid area. A referred bruit would be loudest at the base of the neck and into the right subclavian region.

Dorsalis Pedis - palpate only on dorsum (top) of foot between the first, and second tendons. Ask the subject's permission, .then mark an "X" with a red indelible marker over the pulse. Explain that this is for ankle blood pressure testing later in the examination.

Posterior Tibial - palpate only posterior to-the medial malleolus (inside ankle bone). Mark with a red pen as **above.**

Femoral Pulse/Bruit – palpate in both groins, midway between Art ilian spine and pubic rami. Ausculate in similar manner.

Pulse grading:

1 = Normal - distinct upstroke and downstroke.

2 = Diminished - Upstroke is attenuated and delayed. Pulse is present, but difficult to find (don't apply too much pressure with fingers).

. 3 = Absent - After careful examination, unable to locate pulse.

*Bruits grading:

l=Absent
2=Audible
3=Severe

	Right	Left
Carotid Pulse		
Carotid Bruits*		
Dorsalis Pedis		
Posterial Tibial		
Femoral Pulse		
Femoral Bruits*		
Thyroid Bruits*		

ıine lower extremities according to protocol and. complete below. Respond to as many

rmalities as are present at each level as follows:

None of the listed abnormalities are present-Ulcer, - This is a loss of skin revealing

ɔous tissue.

. Occurs In the distal portion of the digits, or on amputation sites. In severe ischemia may occur

ıroximal locations on foot and leg. Base of ulcer is yellow to gray, with -little evidence of

ɔn tissue. May be surrounded by dead (brown to black) tissue. Sensory exam is normal- Ulcer

.

ɔic. Occurs at pressure points, e.g., metatarsal heads, heel contact with tight-fitting shoes.

ɜers are often deep. There is always an abnormal sensory exam and the ulcers are painless.

ıtasis. Occurs between lower calf and top of foot - maximally at the ankle. They are superficial,

ɜed, and are surrounded by dark brown pigmentation and scarring. Sensory exam is normal.

not particularly painful.

ı. Answer if an ulcer is not easy to classify.

ɜ - This is dead, necrotic tissue which is brown to black in color with no evidence of healing. It

.ay not be infected.

on - Surgical removal of the part.

- Localized redness, tenderness, and swelling. Pus may be expressed (not necessary for

).

omic locations are defined as follows: .

ve the Knee - A physical finding occurring above the knee.

ow the Knee - Includes the knee and the calf to the most superior portion of the ankle

s).

cle - Includes the malleolus to the top of the foot.

ot - Includes the heel, dorsum of the foot and metatarsal heads.

es - 1 is the great toe, 5 the little toe.

CTIONS: A. Check appropriate box(es) at each level for each leg, if normal check NL.

B. For ulcers code: 1=normal, no ulcer; 2=ischemic; 3=neurotropic; 4=venous stasis; 5=present, type uncertain

Right	NL	Ulcer	Gangrene	Amp	Infection
Abv Knee					
Blw Knee					
Ankle					
Foot					
Great toe					
2nd toe					
3rd toe					
4th toe					
5th toe					

Left	NL	Ulcer	Gangrene	Amp	Infection
Abv Knee					
Blw Knee					
Ankle					
Foot					
Great toe					
2nd toe					
3rd toe					
4th toe					
5th toe					

17. ECG REVIEW

a. Any abnormalities?

If yes, specify _

b. Any pathological "Q" waves?

If yes, leads _____

C. ECG approved for treadmill?

d. Patient informed of any abnormalities?

,If yes, specify _____

e. M.D. informed of any abnormalities?

If yes, specify _____

f. Patient approved for treadmill?
(Check question 6)

g. PHYSICIAN SIGNATURE:

. TREADMILL/BLOOD PRESSURE (DOPPLER) EXAM EXAMINER ID;

BLOOD PRESSURE:	Auscu-	;d, supine,	right arm	- NO	•lie 5
3MS	ltate	Systolic	Diastolic	SMOKING c	
	R irm 1			4 Diastolic	
	l L irm 1		———	———	
	;				

Cuff size	Pediatric	Adult	Lg.Adult	Thigh
Arm				
Ankle				

USING DOPPLER:

Cycle 1 Cycle 2. Final

Ann Pressure (Right unless Left Systolic Right by 10 or more mm Hg)
(Circle Right or Left)

Same side Ankle D.P.

Same side Ankle T.P.

Mean Ankle B. *E.*

Opp side Ankle D.P.

Opp side Ankle T.P.

C. F.

Mean Ankle

1st Cycle:
Ratio 1: Mean Ankle (B) / Ann 1 (A)

Ratio 2: Mean Ankle (C) / Arm 2 (D)

2nd Cycle:
Ratio 1: Mean Ankle (E) / Arm 2 (D)

Ratio 2: Mean 'Ankle (F) / Arm 2 (G)

	Lowest Ratio <	*RIGHT*	*LEFT*
DO THIGH PRESSURES IF:	0.8		
DO EXERCISE IF:	>0.8		
DO REACTIVE HYPEREMIA IF:	*a) > 0.8 and b) excluded from exercise*		
DO NOT DO EXERCISE OR REACTIVE HYPEREMIA IF:	< 0.8		

IF ANKLE PRESSURE IS > 100 mmHG OVER ARM, DO NOT DO THIGH PRESSURES, EXERCISE, OR REACTIVE HYPEREMIA.

Treadmill Settings

1.5 MPH, 8% grade, 30 seconds; 2 MPH, 8% grade, 4 minutes, 3 0 seconds

Total Duration of test __ minutes ___ seconds Test stopped because subject described:

1 No Symptoms 2 Claudication 3 Angina 4 Shortness of Breath

5 Fatigue 6 Other _____ 8 Not exercised
Please Specify

DOPPLER PRESSURES

Actual Times	Time Post Exercise	Arm	Right Ankle	Right Ankle/ Ann Ratio	Left Ankle	Left Ankle/ Arm Ratio
.____	*1 minute*					
.____	*3 minutes*					
	5 minutes					

888 = Not exercised

REACTIVE HYPEREMIA_SYSTOLIC PRESSURES

Procedure

Thigh cuff inflated 20 mmHg above, systolic pressure of ___ mmHg for 2 minutes-

Time Post Release	Arm'	Ankle Immediate	_	*Arm*	*Ankle*
2 minutes					

888 = Not done

Name of person completing form:
Relationship to diabetic:

EPIDEMIOLOGY OF DIABETES COMPLICATIONS GENERAL MEDICAL HISTORY FORM D-6

GENERAL MEDICAL HISTORY

1. Please list all the times you have been hospitalized in the last 3 years. Check if not hospitalized____

REASON FOR HOSPITALIZATION	HOSPITAL 'INCLUDE CITY & STATE	DATE (Month/Year)

2. Who is the physician currently treating your diabetes? Name:

Address:

(Building) . . (Street)

(City) . *(State)* *(Zip)*

Phone: (. •)_____

How many times per year do you see this physician in connection with diabetes?_ When did you last see this physician?_____

Is there a particular clinic, doctor's office or other place that you usually go to when you are sick or want advice about your health? YES NO___

a. If yes, what kind of place do you go to?
___private doctor's office ___school clinic
___community health center ___company clinic
___HMO complex . ___hospital emergency room
___hospital clinic ___other:_____

b. Is this the same place or person you see for your diabetes care?
YES___ NO___

c. About how long does it take for you to travel to this place? ___minutes ___hours

d. About how long do you have to wail before you are seen by a doctor or other medical person? ___minutes ___hours

In the last year, did you have any diabetes-related health problems **that you would have liked to**
have seen a doctor or other medical person about, **but you** did **not?**
YES NO___

a. If yes, which of the following reasons explain why you did **not** see a doctor for this condition? (mark all that apply)
___Thought it would cost too much Did not have anyone to care for the children
___Did not have time to see a doctor __Felt the doctor could not do very much ___Office hours were not convenient ___Other:_____
___Did not have a way to get to the doctor

Have you ever been seen by an ophthalmologist (a medical doctor who cares for. and treats eye disease? • YES NO___ DON'T KNOW___

If yes, what is the name and address of this physician?
Name:_____
Address:_____
Phone number: f}_____

How many times during the last two years have you seen an ophthalmologist? ____ times
When was your last visit?_____

Has a physician ever told you that you have:	YES	NO	Age Condition diagnosed
Rheumatoid arthritis	___	___	_____
Gout	___	___	_____
Stroke or cerebrovascular accident	___	___	_____
Heart attack or myocardial infarction	___	___	_____
Angina pectoris	___	___	_____
Any other heart trouble (specify _____')	___	___	_____
High cholesterol	___	___	_____
High triglycerides	___	___	_____
High blood pressure	___	___	_____

. 2

Poor circulation in your legs
Peripheral vascular disease
Ulcers or sores on legs/feet
Amputation (specify_____)

Peptic, stomach or duodenal ulcer
Ulcerative colitis
Spastic colon or mucous colitis
Crohn's disease
Neuropathy
Emphysema
Impotence
Gallstones
Liver Disease (specify type, if known, e.g.
hepatitis, etc._____)
Ankylosing Spondylitis (rheumatoid spondylitis,
spinal
arthritis)
Reiter's
Syndrome
Under-active thyroid (Hashimoto's
thyroiditis) Over-active thyroid
(Grave's Disease) Vit-B12
Deficiency (Pernicious Anemia)
Psoriasis
Chronic Active Hepatitis Celiac Disease
Multiple Sclerosis (MS) Myasthenia
Gravis Lupus Hay Fever Allergies
(specify:_____)
Adrenal gland problem
Anemia
Asthma
Cancer (specify_____)
Cataracts (specify eye: R__ L__ Both__) Glaucoma (specify eye:
R__ L__ Both__) Blindness (specify eye: R__ L__ Both__) ___
___ _
If yes, please specify what caused your blindness by checking each one
that applies:
Cataracts__Glaucoma___Vitreoushemorrhage(bleeding)__Other(specify__
_____)
Are you legally blind? ___ ___ _____
Laser treatment for eye problems ___ ___ _____
(specify eye: R__ L__ Both__) Eye surgery (specify
type:_____) ___ ___ . _____
Kidney disease (specify_____)___ ___ _____
Protein/Albumin in your urine ___ ___ _____
Are you on dialysis? ___ ___ _____
(If so, specify: hemodialysis___ peritoneal___) Have you had a kidney
transplant? ___ ___ _____
(If yes, specify date(s)_____)

're you ever had:

	Yes	No	Age diagnosed
a) Coronary by pass surgery?			
b) Coronary angioplasty?			
c) Coronary end arterectomy?			
d) Coronary angiogram (catheter) study?			
e) Carotid end arterectomy? "			

7a) Have you ever had pain or discomfort in the chest? (If yes, continue with question 7c)

b) Have you ever had any pressure or heaviness in the chest? (If no, continue with question 8)

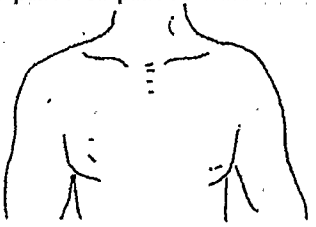
c) Do you get it when walking uphill or hurrying?

d) Do you get when walking at an ordinary pace or on the level?

e) When you get it in the chest, what do you do?
Stop ___ Slow down ___
Continue at same pace ___

f) Does it go away when you stand still? If yes, how soon?
Less than 1 min. ___ 10-30 minutes 1-10 minutes ___ 'More than 30 min-

g) Where do you get this pain or discomfort? (Mark the place or places with an "X" on the diagram.)



h) Have you ever had a severe pain across the front of the chest lasting for half an hour or more?

Have you ever had chest discomfort relieved by nitroglycerine within 2-3 minutes?

Do you ever get any discomfort (including heaviness or pain) in the jaw, neck, left arm or had during any exertion or under stressful conditions?

If yes, does it usually go away within 10 minutes if you slow down **or** stop the activity that brought it on?

•YES NO

10. Do you ever get any discomfort (including heaviness or pain) in the chest, jaw, neck or left arm/hand when you are not doing any activity; for example, just sitting down? ___ ___

If yes:

a) Is it worse when you are lying flat? (e.g. at night)
b) Is it worse if you bend over?
c) Is it worse in certain positions? (for example, working at a desk, driving, etc.)
d) Does taking a deep breath or moving help relieve it?
e) How long does it usually last? (check one)

Less than 1 min. ___
1 -10 minutes ___
10-30 minutes ___
30-60 minutes ___
More than 60 min. ___

f) Would you describe it as burning?

11. a) Do you get a pain in either leg on walking? (If no, continue with question 12.)
b) Does the pain ever begin when you are standing still or sitting?
c) Do you get this pain in the calf (or calves)?
d) Do you get it when walking uphill or hurrying?
e) Do you get it when walking at an ordinary pace on the level? _
f) Does the pain ever disappear while you are still walking?
g) What do you do if you get it when walking?

Stop ___ • Slow down ___ Continue at same pace ___

h) What happens when you stand still?

Usually continues more than 10 minutes Usually disappears in-10 minutes or less

12. a) Do your fingers, hands and wrists ache or are they numb at night after work?

b) Do you experience numbness or tingling in your hands during the night?

If yes, does the numbness and/or tingling only affect the first four fingers of your hand (not including the pinky)?

c) Have you noticed any unusual clumsiness, such as dropping things or having difficulty in buttoning a shirt?

d) Have you or anyone doing the same job as you had an operation on the wrist or hand?

e) Do you use a tool on your job?
If yes, do you have trouble gripping your tool?

f) Do you frequently bend or flex your wrist(s) on your job?

g) Have you ever been told by a doctor that you have arthritis in your hands?

13. Please take a few minutes to -answer the questions below about the feeling in your legs and feet.

Check yes or no based on how you usually feel	YES NO
a) Are your legs and/or feet numb?	___ ___
b) Do you ever have any burning pain in your legs and/or feet?	___ ___
c) Are your feet too sensitive to touch?	___ ___
d) Do you get muscle cramps in your legs and/or feet?	___ ___
e) Do you ever have any prickling feelings in your legs or feet?	___
f) Does it hurt when the bed covers touch your skin?	___ ___

g) When you get into the tub or shower, are you able to tell the hot water from the cold water?

h) Have you ever had an open sore on your foot?

i) Has your doctor ever told you that you have diabetic neuropathy?
j) Do you feel-weak all over most of-the time?
k) Are your symptoms worse at night?
1) Do your legs hurt when you walk?
m) Are you able to sense your feet when you walk?
n) Is the skin on your feet so dry that it cracks open?

o) Have you ever had an amputation?

14. Are you currently taking any medication, other than •insulin — including aspirin, blood pressure pills, diuretics, vitamins, etc.?
YES ___ NO___ If YES, please give the following details?

Dosage
How many times per day?
Reason for taking
Regularly or only when needed?

a) Since you were told you have diabetes, has there ever been a period in your life longer than three months when you regularly took at least one aspirin or a pill containing aspirin every day? YES___ NO___
If NO, skip to Question 16.

If YES, what was the reason you took the aspirin regularly? Headaches ___

Prevent eye changes ___

Arthritis
Other Pains ___
Other (Specify:_____)
Blood Thinner _____

FOLLOW-UP FORM - EDC STUDY

NAME _____:_____ Who completed the form? __ self
ADDRESS _____ __ spouse
_____ __ other
PHONE _____

Gender (Please circle): Male Female
Date of Birth: _____ Date of Diagnosis: _____
Month Day Year Month Day Year
Date form completed:___ ___ ___
Month Day Year

FOLLOW-UP QUESTIONS:

. I. Has a physician ever told you that you have/had:

	YES	NO	Age of 1st Diagnosis
Stroke or cerebrovascular accident	. ___	___ ...	____
Heart attack or myocardial infarction			
Angina (chest pain from the heart)			
Any other heart trouble (specify,_____)			
High cholesterol or triglycerides (If yes, are you on medication for this?)			
High blood pressure (ff yes, are you on B.P. medication?)			
Poor circulation in the legs?			
Peripheral vascular disease (poor circulation in legs) If yes, have you had:			
1) Surgery for this problem (bypass or arterectomy) and/or			
2) Amputation:			
If yes, which applies: Left leg Right leg Toes only . ___ ___.			
Below Knee ___ ___			
Above Knee ___ ___			
Neuropathy			

Cataracts If so, one or both
eyes: Left eye_ Right_

Glaucoma
If so, one or both eyes: Left eye Right eye__
Blindness
If so, one or both eyes: Left eye_ Right eye_

Laser treatment for diabetic eye problems
(Proliferative retinopathy or hemorrhage)

If so, one or both eyes: Left eye _ Right eye _

Retinopathy, i.e. diabetes has affected the retina (back of eyes)

Vitreous opacity/hemorrhage as a result of proliferative retinopathy

Do you have any kidney problems relating to diabetes?
(If no, skip to the next question)

If yes: Have you had a kidney transplant? If yes:'
Date _____

Are you on chronic hemodialysis?

Are you on chronic peritoneal dialysis?
(Includes chronic ambulatory dialysis)

Have you been told you creatinine is higher than normal?
Increased protein (albumin) **in** the urine

Cancer (If yes, specify:_____

Do you have numbness in your hands?

a) .Are your legs and feet numb? . .
b) Do you ever have any burning pain in your legs and feet?
c) Are your feet too sensitive to touch?
d) Do you get muscle cramps in .your legs and feet?
e) Do you ever have any prickling feelings in your legs or feet?
f) Does it hurt when the bed covers touch your skin?
g) When you get into the tub or shower, can you tell the hot water from the cold?
h) Have you ever had an open sore on your foot?
i) Has your doctor ever told you that you have diabetic neuropathy?
j) Do you feel weak all over most of the time?
k) Are your symptoms worse at night?
1) Do your legs hurt when you walk?
m) Are you able to sense your feet when you walk?
n) Is the skin on your feet so dry that it cracks open?
o) Have you ever had an amputation?

. Please list all the times you have been hospitalized in the last 3 years. Check if not hospitalized____

REASON FOR Hospitalization HOSPITAL (INCLUDE CITY & STATED

For FEMALES only:

a) Have you started having menstrual periods? YES_ NO

b) If yes, how old were you when your periods began? YEARS

c) Are your periods regular? YES_ NO__

d) Have you ever been pregnant? YES_ NO__

If yes, please list date and outcome (e.g., normal, termination, full term, malformation, etc.) Date Outcome

YES. NO.

16. a) Have you ever had pain or discomfort in the chest? (If yes, continue with question 13c)

b) Have you ever had any pressure or heaviness in the chest? (If No, STOP)

c) Do you get it when walking uphill or hurrying?

d) Do you get it when walking at an ordinary pace on the level?

e) When you get it in the chest, what do you do?

Stop
Slow down
Continue at same pace _

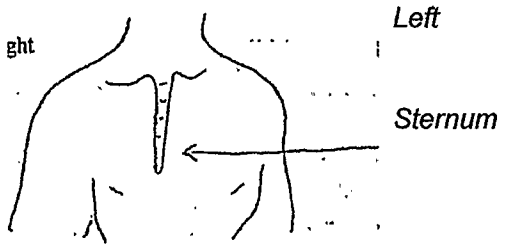
STOP if Yes

*STOP if NO, unless you never walk uphill.

f) Does it go away when you stand still? If yes, how soon?

	Yes	*No*
Less than 1 minute		
1-10 minutes		
10-30 minutes		
More than 30 minutes		

g) Where do you get this pain or discomfort? (Mark the place or places with an "X" on the diagram.)



h) Have you ever had a severe pain across the front of the chest lasting for half an hour or more? Yes_ No _

i) Have you ever had chest discomfort relieved by nitroglycerine within 2-3 minutes? Yes _ No _