EPIDEMIOLOGIC EVIDENCE FOR PHYSICAL ACTIVITY AS A PREVENTATIVE FACTOR FOR METABOLIC SYNDROME AND FRAILTY: THE HEALTH ABC STUDY

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ABSTRACT

MATTHEW J. PETERSON: Epidemiologic Evidence for Physical Activity as a Preventative Factor for Metabolic Syndrome and Frailty: the Health ABC Study
(Under the direction of Carol Giuliani and Miriam C. Morey)

The presence of metabolic syndrome (MS) or frailty aligns an older adult with increased risk for health decline. Physical activity is an important part of health maintenance in older adults, but optimal doses of physical activity are unclear with these two health conditions. This study examined the longitudinal associations between different doses and types of physical activity and incidence of MS and frailty. Participants from the Health, Aging and Body Composition Study were followed for six years to ascertain long-term MS and frailty status. Physical activity doses at baseline included weekly time (low, recommended, high), intensity (sedentary, light, moderate, vigorous) and type (sedentary, lifestyle active, exercise active). In MS as the outcome, in men, dose-response curves generally were linear, with increasingly lower doses of time, intensity and activity type resulting in a higher incidence of MS. In women, intermediate doses of time and intensity were associated with the lowest incidence of MS, indicating a U-shaped dose-response curve. Results also indicated that the time and intensity physical activity doses were not associated with frailty; however, being exercise active was associated with reduced risk for frailty. In those who had progressed to frailty within six years, we found that the sedentary and lifestyle active participants were at increased risk for severe frailty compared to the exercise active in a dose-response manner. The optimal dose of physical activity for reducing the risk of MS in older men is spending,

on average, more than thirty minutes per day in vigorous activities. The optimal dose of physical activity for reducing the risk of MS in older women is meeting the current recommendations for time spent in weekly physical activity in activities of light intensity such as light housework, shopping, or volunteering. Expending 1000 kcals/week in physical activities that are done with the intent of exercising, such as walking for exercise, strength training or aerobic dance, can reduce the risk of frailty onset and severity in older adults.

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Chapter I. BACKGROUND

The US is in the midst of an unprecedented aging boom. By the middle of this century the eighty-five and older age group is expected to rise four-fold (U.S. Census Bureau Population Division National Projections Program 2004). However, the expansion of older age group brackets also brings the issues of their healthcare needs. Medical advancements have allowed the possibility of surviving longer, but this is associated with higher rates of chronic illnesses, disability, and substantial healthcare burdens (Guralnik and Simonsick 1993). Two health conditions particularly prevalent in older adults that have received increasing attention in the medical and research communities over the last two decades are frailty and metabolic syndrome. Because of their associations with poor health outcomes, preventing and treating frailty and metabolic syndrome remain priorities for gerontology researchers (Hogan, MacKnight et al. 2003; Scuteri, Morrell et al. 2005).

Physical activity has been proposed and tested as an intervention in older adults to positively impact their health and quality of life (Singh 2002). Physical activity also has shown to be a strong preventative factor for many age-related health conditions (American College of Sports Medicine 1998). The mechanisms underlying the physical activity-disease prevention relationship are very clear in some cases. For instance, lifetime joggers have a lower probability of heart disease compared to age-matched lifetime sedentary groups (Pollock, Mengelkoch et al. 1997). The cause-effect link between chronic aerobic exercise and reduced risk for heart disease is clear in the literature.

The physical activity-disease prevention link is less clear in multi-dimensional health conditions, such as frailty and metabolic syndrome, both of which consist of clusters of conditions that can have multiple and differing pathogeneses. The lack of a cause-effect link is especially true in older adults with frailty and metabolic syndrome, thus studies to determine appropriate modalities and doses of physical activity are important for determining how to treat and positively affect frailty and metabolic syndrome in older adults.

Aging and the Metabolic Syndrome

The metabolic syndrome is a constellation of risk factors for diabetes, coronary heart disease, and coronary heart disease related deaths (Ford, Kohl et al. 2005; Scuteri, Morrell et al. 2005). The prevalence of metabolic syndrome increases substantially with aging, from approximately 20% in the middle-aged to approximately 40% in the elderly in some studies (Ford, Giles et al. 2002; Goodpastor, Krishnaswami et al. 2005). According to the Adult Treatment Panel III consensus statement, three or more of the following factors indicate the presence of metabolic syndrome: increased waist circumference (>102 cm. in men and >88 cm. in women), high triglycerides ($\geq$ 1.7 mmol/l), low HDL cholesterol (<1.04 mmol/l in men and <1.29 mmol/l in women), high blood pressure ($\geq$130/85 mmHg or pharmacological treatment of hypertension), and fasting glucose ($\geq$6.1 mmol/l). The aggregate effect of these risk factors are greater than any one factor alone (Ford, Kohl et al. 2005), and the startling increased risk of insulin resistance with the presence of metabolic syndrome has been identified as a major public health concern (Panagiotakos, Pitsavos et al. 2004).

Epidemiologic studies have shown consistent associations between low levels of physical activity and increased risk for metabolic syndrome (Farrell, Cheng et al. 2004; Katzmarzyk, Church et al. 2004; Ford, Kohl et al. 2005; Katzmarzyk, Church et al. 2005).

However, to date there are no published reports on the associations between physical activity levels and metabolic syndrome in older adults. This is important because with lower levels of activity and higher prevalence of metabolic syndrome and chronic illnesses in older adults, these associations and their interactions are important to understand for the design of effectively tailored health interventions.

Aging and Frailty

Frailty in older adults is a concerning state for the individual, his/her family and healthcare providers. Frail older adults are more likely than the non-frail to experience rapid functional decline and disability (Gill, Williams et al. 1995). Ferrucci defines frailty as, "a pathologic condition that results in a constellation of signs and symptoms and is characterized by high susceptibility, impending decline in physical function and high risk of death" (Fried, Ferrucci et al. 2004). By definition frailty is a pre-disability state, and can be considered a primary pathway to disability. Approximately 4-7% of the U.S. population over sixty-five years old is frail (Fried, Tangen et al. 2001). Compared to the non-frail, frail individuals are more likely to fall, have worsening mobility and ADL disability, require hospitalization or institutionalization, and die over three and seven year follow-up periods (Fried, Tangen et al. 2001). An equally troubling statistic is the estimated prevalence of pre-frail older adults (those transitioning to frailty), with estimates ranging from 28% to almost 50% of adults over age sixty-five. The risks for adverse health outcomes for the pre-frail and frail groups are very similar, and in some instances pre-frail risks are slightly higher, such as risk for future mobility limitations (Fried, Tangen et al. 2001).

The impact of physical activity on frailty is not well known. Several studies have explored the effectiveness of a physical activity intervention on frailty risk factors, such as

mobility limitations, strength and endurance (Keysor and Jette 2001), or studies have examined functional outcomes in a cohort identified at baseline as frail (Gill, Baker et al. 2002). To appropriately design physical activity intervention studies it is first necessary to look in the epidemiologic evidence to determine which, if any, targeted interventions have the greatest probability of affecting frailty status.

Physical Activity Types and Doses

Determining the optimal dose of physical activity that has the greatest impact on subsequent health is a difficult endeavor. In 2000, the Canadian and US governments co-sponsored a symposium entitled, "Dose-response issues concerning physical activity and health: an evidence-based symposium." This symposium provided an opportunity to review and synthesize the evidence regarding optimal doses of physical activity to generate health benefits. Only one paper presented evidence on the dose-response associations between physical activity and health outcomes (quality of life and independent living) specifically in older adults (>65 y.o.) (Spirduso and Cronin 2001). These authors concluded that, "Whether a PA group defined "dose-response" exists, or whether an activity level threshold is operative, is unclear." The lack of evidence can be partly attributed to lack of studies exploring specific doses of physical activity *a priori.* In fact, the authors state that most dose-responses are observed in post-hoc analyses of clinical trials, where the participants are grouped using attendance or physiological monitoring (i.e. exercise heart rates). Optimally, trials using older adults as participants would be designed to test the effect of differing doses of physical activity on health outcomes. Use of large population-based data sources to

examine potentially effective dose-response associations could assist in designing these trials.

Since the landmark 1996 Surgeon General's Report on Physical Activity and Health, there has been much debate surrounding the issue of whether health professionals should recommend increased physical activity or exercise for health benefits. Physical activity is defined as any bodily movement produced by skeletal muscles that results in increased energy expenditure. Exercise is defined as planned, structured, and repetitive bodily movement for the purpose of improving or maintaining one or more components of fitness. By definition exercise is a form of physical activity; however, not all types of physical activity can be classified as exercise. For instance, housework and gardening, while fitting the definition of physical activity, can be repetitive in nature, but not likely performed to improve fitness levels---thus difficult to classify as exercise. Research has shown physical activity and fitness (a product of regular exercise) to have differing dose-response associations with health outcomes such as major chronic diseases (CHD, CVD, cancer, stroke) and mortality. In fact, when physical activity and cardiorespiratory fitness were included in the same hazards model, physical activity was not associated with mortality, while the highest fitness levels group showed a 70% reduction in risk of death compared to the lowest fit group (Blair, Cheng et al. 2001). The motivation, purpose, and context of physical activity and exercise are often times quite divergent, thus it seems plausible that their pathways of health benefit also differ. It may be advantageous to consider physical activity and exercise as differing entities. This will assist in determining their differing impact on the health outcomes of older adults with and without metabolic syndrome and frailty, and determining if such differences do exist.

Public Health Implications

The potential public health implications of this work are extensive. First, the costs of physical inactivity are well documented. It is estimated that one in three cases of heart disease, a substantial health risk in those with metabolic syndrome, is attributable to physical inactivity (NA Garrett AJPM, 2004). Further, the medical expenditures of those with diabetes, also a major risk of metabolic syndrome, is almost 2.5 times that of a non-diabetic (ADA, Diabetes Care, 2003). The potential to decrease the risk of heart disease and diabetes with focused physical activity interventions aimed at preventing or attenuating metabolic syndrome is a potential public health benefit of this research. The public health results for this work in affecting frailty are also substantial. For instance, sarcopenia, a direct cause of one frailty factor (poor strength), cost an increase in healthcare expenditures of approximately $900 per person in 2000 (I Janssen, JAGS, 2004). And it is estimated that, in hospitalized elders, for each 0.1 meter/second/year increase in gait speed (a second frailty factor) an associated reduction of $1100 in yearly health care costs is observed. The prevention of strength and mobility loss can directly impact frailty status and the subsequent public health impact of disability; therefore, determining those doses and types of physical activity that are most closely associated with the prevention of frailty is of great importance.

Statement of the Problem

Frailty and metabolic syndrome are two conditions that affect a growing number of older adults. Unlike other well-studied aging-related health conditions, physical activity interventions aimed at frailty and metabolic syndrome have been designed and conducted without sufficient epidemiologic evidence for targeted interventions. Specifically, questions such as the strength of the associations between regular physical activity and frailty and metabolic syndrome, physical activity exposure and subsequent severity of disease status, dose-response associations, and differing effects in sub-populations (minorities, healthcare disparate, military veterans, oldest-old) are largely unexplored with these conditions. Using data from the Health, Aging and Body Composition Study, the analyses in this dissertation will explore the prospective relationships between physical activity and the outcomes of frailty and metabolic syndrome. This proposed body of work will assist in beginning to understand which specific behavioral interventions have the greatest potential to combat the deleterious effects of metabolic syndrome and frailty in older adults.

Objectives and Hypotheses

Objective 1:

To determine if there are longitudinal associations between physical activity and metabolic syndrome in older adults.

*Hypothesis 1 (Focused on **Intensity** of Physical Activity)*: Older adults who engage in ***vigorous (6+ Mets)*** physical activity on a regular weekly basis have a lower incidence of metabolic syndrome as compared to those who engage regularly in physical activities of ***moderate (3-6 Mets)*** or ***light (<3 Mets)*** intensity, or to those who are ***sedentary***.

*Hypothesis 2 (Focused on **Time** Spent in Physical Activity)*: Older adults who engage in greater than the recommended amount of weekly time ***(200+ minutes/week)*** in physical activity have a lower incidence of metabolic syndrome as compared to those who engage in the recommended amount ***(150-200 minutes/week)***, or less than the recommended weekly amount of time ***(<150 minutes/week)***.

*Hypothesis 3 (Focused on **Type** of Physical Activity)*: Older adults who expend weekly energy primarily from ***exercise activities*** have a lower incidence of metabolic syndrome as compared to those whose expenditure is primarily ***lifestyle activities***, or to those who are ***sedentary***.

Objective 2:

To examine how different doses and types of physical activity affect the development and severity of frailty status in older adults.

*Hypothesis 1 (Focused on **Intensity** of Physical Activity)*: Older adults who engage in ***vigorous (6+ Mets)*** physical activity on a regular weekly basis have a lower incidence of frailty as compared to those who engage regularly in physical activities of ***moderate (3-6 Mets)*** or ***light (<3 Mets)*** intensity, or to those who are ***sedentary***

*Hypothesis 2 (Focused on **Time** Spent in Physical Activity)*: Older adults who engage in greater than the recommended amount of weekly time ***(200+ minutes/week)*** in physical activity have a lower incidence of frailty as compared to those who engage in the recommended amount ***(150-200 minutes/week)***, or less than the recommended weekly amount of time ***(<150 minutes/week)***

*Hypothesis 3 (Focused on **Type** of Physical Activity)*: Older adults who expend weekly energy primarily from ***exercise activities*** have a lower incidence of frailty as compared to those whose expenditure is primarily ***lifestyle activities***, or to those who are ***sedentary***.

LIST OF ABBREVIATIONS

Blood pressure (BP)

Centimeters (cm)

High density lipoprotein (HDL)

Kilocalories per week (kcals/week)

Metabolic equivalents (Mets)

Meters per second (m/sec)

Milligrams per deciliter (Mg/dl)

Millimeters of mercury (Mm/Hg)

Ninety-fifth percentile confidence interval (95%CI)

Odds ratio (OR)

Definition of Terms

Metabolic Syndrome- defined as having three or more of the following metabolic risk factors: (The Expert Panel on Detection 2001)

1) Waist circumference of 102 cm. for men and 88 cm. for women,

2) serum triglyceride 150 mg/dl,

3) HDL < 40 mg/dl for men and 50 mg/dl for women,

4) BP > 130/85 mm/Hg or taking anti-hypertensive medications,

5) serum glucose > 110 mg/dl or taking oral/injectible diabetes medications.

Frailty- a pathologic condition that results in a constellation of signs and symptoms and is characterized by high susceptibility, impending decline in physical function and high risk of death.

Frailty Model- adapted from Gill et al (Gill, Baker et al. 2002), and includes the following criteria:

1) Inability to rise from a chair five times with arms folded
2) A usual pace gait speed less than 0.60 m/sec.

Not Frail- defined as fitting neither of the frailty criteria.

Moderate frailty- defined as fitting one of the two frailty criteria.

Severe frailty- defined as fitting both criteria.

Physical Activity Groups- based on current recommendations for weekly energy expenditure via physical activity (U.S. Department of Health and Human Services 1996) (American College of Sports Medicine 1998).

Intensity Group- these intensity doses were based American College of Sports Medicine guidelines for determination of activity intensities based on Met level cut-offs (Ainsworth, Haskell et al. 2000) and on recommended accumulated weekly energy expenditure for health benefits (minimum of 1000 kcals/week) (U.S. Department of Health and Human Services 1996).

Vigorous Intensity Dose- individuals accumulating a minimum of 1000 kcals/week in physical activities of an intensity of 6 Mets or greater.

Moderate Intensity Dose- individuals accumulating a minimum of 1000 kcals/week in physical activities of an intensity of 3-6 Mets, and less than 1000 kcals/week in vigorous intensity activities.

Light Intensity Dose- individuals accumulating a minimum of 1000 kcals/week in physical activities of an intensity of less than 3 Mets, and less than 1000 kcals/week in vigorous and moderate intensity activities.

Sedentary Dose- individuals accumulating less than 1000 kcals/week in any physical activities.

Time Group- these doses were based on current recommendations for weekly accumulated time spent in physical activity (U.S. Department of Health and Human Services 1996) (Pate,

Pratt et al. 1995). Due to availability of data, these groups were constructed using only the sum of minutes per week spent walking of any intensity

High Time Dose- individuals accumulating a minimum of 200 minutes/week in physical activities of any intensity.

Recommended Time Dose- individuals accumulating between 150-200 minutes/week in physical activities of any intensity.

Low Time Dose- individuals accumulating less than 150 minutes/week in physical activities of any intensity.

Activity Types- These activity type groups are based on previous construct developed by Brach et al. (Brach, Simonsick et al. 2004) using current physical activity recommendations (U.S. Department of Health and Human Services 1996) (Pate, Pratt et al. 1995) for weekly energy expenditure (minimum of 1000 kcals/week) and on distribution of weekly energy expenditure in total physical activity in the Health ABC cohort (25^{th} percentile = 2,719 kcals/week).

Exercise Active - individuals accumulating greater than 1000 kcals/week in exercise activities.

Lifestyle Active - individuals accumulating at least 2719 kcals/week in physical activity and less than 1000 kcals/week in exercise activity.

Sedentary - individuals accumulating less than 1000 kcals/week in exercise activity and less than 2719 kcals/week in physical activity.

Chapter II. MANUSCRIPT ONE: Physical Activity Doses and Incident Metabolic Syndrome in Older Adults: The Health ABC Study

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Abstract

Having metabolic syndrome (MS) places an individual at substantial risk for diabetes, cardiovascular disease, and cardiovascular disease-related death, and the prevalence of MS in older adults is approximately 40%. The optimal doses of physical activity to reduce risk for MS are not currently known. PURPOSE: To examine how different doses and types of physical activity affect the six year incidence of MS in older adults. METHODS: 1266 participants from the Health ABC Study were followed for six years. MS status was determined by having three of five factors that include high waist circumference, high blood pressure, low HDL cholesterol, high triglycerides, and high blood glucose levels. Hierarchical physical activity doses at baseline were divided into three categories, 1) **time** (low, recommended, high), 2) **intensity** (sedentary, light, moderate, vigorous) and, 3) **activity type** (sedentary, lifestyle active, exercise active). Gender specific logistic regression models were used to develop odds ratios and 95% confidence intervals for incident MS. RESULTS: 20% of men and women developed MS over six years. In men, dose-response curves generally were linear, with increasingly lower doses of **time**, **intensity** and **activity type** resulting in a higher incidence of MS, with the low time dose being significantly different from the high time dose (OR=1.67; 95%CI 1.01-1.74). In women, intermediate doses of **time** (incidence of MS in recommended dose-14% vs. high dose-24%) and **intensity** (incidence of MS in light dose-18% vs. vigorous dose-31%) were associated with the lowest incidence of metabolic syndrome, indicating a U-shaped dose-response curve. Within the **activity types**, being exercise active potentially placed a woman at greater risk for metabolic syndrome compared to being sedentary (sedentary vs. exercise active OR=0.55; 95%CI 0.28-

1.10). CONCLUSIONS: The optimal doses of physical activity in preventing MS are different in men and women. In men doses of physical activity beyond the current recommendations are of added benefit. In women, meeting the recommended weekly time (150-200 minutes/week) and engaging in light intensity activities are optimal in preventing MS, resulting in a U-shaped dose-response curve. This indicates that the highest doses of physical activity may place an older woman at increased risk for metabolic syndrome compared to intermediate dose. However, further studies are needed to add to these findings.

Introduction

Metabolic syndrome is a constellation of factors that, when present, substantially increase the risk for diabetes mellitus, cardiovascular disease, coronary heart disease and cardiovascular disease-related deaths (Ford, Giles et al. 2002). The prevalence of metabolic syndrome in the US adult population is estimated to be 25%, however, prevalence increases with aging such that up to 40% of adults aged sixty-five years and older have the condition (Scuteri, Morrell et al. 2005) (Park, Zhu et al. 2003). The third Adult Treatment Panel defines the presence of metabolic syndrome as having a combination of any three factors that include increased waist circumference (>102 cm. in men and >88 cm. in women), high triglycerides ($\geq$ 1.7 mmol/l), low HDL cholesterol (<1.04 mmol/l in men and <1.29 mmol/l in women), high blood pressure ($\geq$130/85 mmHg), and fasting glucose ($\geq$6.1 mmol/l) (The Expert Panel on Detection 2001).

Physical activity is a protective factor for numerous poor health conditions. However, the association between physical activity and metabolic syndrome is not clear in the literature, particularly when considering the optimal dose of physical activity for reversal, prevention, or delay of metabolic syndrome. This may in part be due to the differing dose response associations seen with physical activity and the individual metabolic syndrome factors. For instance, there is evidence for linear dose-response associations between physical activity and dyslipidemia, and obesity measured as total body fat (Kraus, Houmard et al. 2002) (Slentz, Duscha et al. 2004); however, the dose-response associations between physical activity and impaired glucose tolerance, and blood pressure indicates a potential threshold of benefit with moderate activity (Houmard, Tanner et al. 2004) (Ishikawa-Takata,

Ohta et al. 2003). There is a need for studies to determine the optimal doses of physical activity in preventing metabolic syndrome, where the above individual factors interact with one another.

Therefore, the objective of this study was to examine how different doses and types of physical activity affect the incidence of metabolic syndrome in older adults. Using data from the Health, Aging and Body Composition (Health ABC) Study, we tested the hypotheses that, 1) Older adults who engage in ***vigorous (6+ Mets)*** physical activity on a regular weekly basis have a lower incidence of metabolic syndrome as compared to those who engage regularly in physical activities of ***moderate (3-6 Mets)*** or ***light (<3 Mets)*** intensity, or to those who are ***sedentary***, 2) Older adults who engage in greater than the recommended amount of weekly time ***(200+ minutes/week)*** in physical activity have a lower incidence of metabolic syndrome as compared to those who engage in the recommended amount ***(150-200 minutes/week)***, or less than the recommended weekly amount of time ***(<150 minutes/week)***, and 3) Older adults who expend weekly energy primarily from ***exercise activities*** have a lower incidence of metabolic syndrome as compared to those whose expenditure is primarily ***lifestyle activities***, or to those who are ***sedentary***.

Methods

Health ABC Study

The Health ABC Study is a longitudinal, prospective study with the broad objectives of measuring higher functioning older adults to allow examination of health decline and improvement over several years, and to allow comparisons with other well-studied populations (i.e. EPESE, Women's Health and Aging Study). Specifically, the study aims include investigation of the interrelationships between health conditions, body composition,

social and behavioral factors, and functional change (Simonsick, Newman et al. 2001). Clinic-based examinations and self-report measures were collected over a seven year period.

Study Population

The Health ABC Study cohort consists of 3075 well-functioning black and white men and women aged 70 to 79. White participants were recruited from a random sample of Medicare beneficiaries in the zip codes surrounding Pittsburgh, Pennsylvania and Memphis, Tennessee. Black participants were recruited from all age-eligible residents of the areas in and surrounding Pittsburgh and Memphis. Potential participants were then screened for the following inclusion criteria, 1) No reported difficulty: walking ¼ mile, walking up ten steps, or performing basic activities of daily living, 2) no known life-threatening cancers, 3) no plans to leave the area for three years. The University of Pittsburgh and University of Memphis institutional review boards approved the study, and all participants provided written informed consent prior to participation.

For this analysis, participants were excluded due to having metabolic syndrome at baseline (N=1169) or to incomplete or unknown follow-up metabolic syndrome status (N=640), leaving 1266 participants for this study.

Study Measures

The outcome variable for this study was metabolic syndrome, which is defined as having three or more factors identified by the Third Adult Treatment Panel (ATP III) (The Expert Panel on Detection 2001). These criteria include a waist circumference of 102 cm. or greater for men and 88 cm. or greater for women; a serum triglyceride of 150 mg/dl or greater; serum HDL levels of 40 mg/dl or less for men and 50 mg/dl for women; resting blood pressure greater than 130/85; serum glucose greater than 110 mg/dl. Individuals on

blood pressure or diabetes medications were considered positive for that particular factor. The blood assays needed for the metabolic syndrome factors listed above were collected and analyzed at baseline and year six in the Health ABC Study.

The predictor variable of interest, physical activity levels, was collected from participants at baseline using a self-report instrument developed specifically for the Health ABC Study. The standardized questionnaire was developed using the model of several commonly used activity questionnaires, such as the Minnesota leisure-time physical activity questionnaire (Taylor, Jacobs et al. 1978). Kilocalories per week (kcals/week) expended in common exercise activities (i.e. walking for exercise, exercise classes, weightlifting) and lifestyle activities (i.e. gardening, housework, yard work) were collected. Specifically, participants were asked if they had engaged in physical and exercise activities at least ten times in the last twelve months. Those activities that were identified as positive over the last year were further examined regarding time for each activity over the last seven days. Based on self-reported weekly time and known metabolic costs for activities (Ainsworth, Haskell et al. 2000) a summary variable of kcals/week expended was calculated for each activity. The metabolic cost of activities is reported in metabolic equivalents (Mets). One Met is equivalent to resting energy expenditure, or 3.5 ml/kg/min.

For this study, physical activity doses and types were determined to allow for several associations to be tested based on current recommendations for weekly energy expenditure via physical activity (U.S. Department of Health and Human Services 1996) (American College of Sports Medicine 1998). The doses are hierarchical in nature, moving from the lowest dose to the highest dose, within each physical activity category. Specifically, ***time doses*** (low, recommended, high), ***intensity doses*** (sedentary, light, moderate, vigorous), and

activity types (sedentary, lifestyle active, exercise active) were tested. The format of the Health ABC questionnaire did not allow a physical activity weekly frequency dose-response to be tested for this study. The physical activity categories and specific doses are shown in Table 1.

Time doses were based on current recommendations for weekly accumulated time spent in physical activity (U.S. Department of Health and Human Services 1996) (Pate, Pratt et al. 1995). Due to availability of data, these doses were constructed using only the sum of minutes per week spent walking of any intensity and time spent in exercise. Intensity doses were based on American College of Sports Medicine guidelines for determination of activity intensities based on Met level cut-offs (Ainsworth, Haskell et al. 2000) and on recommended accumulated weekly energy expenditure for health benefits (minimum of 1000 kcals/week) (U.S. Department of Health and Human Services 1996). Activity type groups were based on the previous construct developed by Brach et al. (Brach, Simonsick et al. 2004) using current physical activity recommendations (U.S. Department of Health and Human Services 1996) (Pate, Pratt et al. 1995) for weekly energy expenditure (minimum of 1000 kcals/week) and on distribution of weekly energy expenditure in total physical activity in the Health ABC cohort (25^{th} percentile = 2,719 kcals/week).

Covariates that were collected at baseline and controlled for in the analyses include age, sex, race, percent body fat, education, marital status, count of chronic diseases (cerebrovascular disease, lower limb OA, pulmonary disease, circulation problems in extremities, and depression), smoking status and alcohol consumption. Heart disease was considered a separate covariate due to its strong association with metabolic syndrome. Race was dichotomized into black and white. Chronic diseases were ascertained by asking the

participant, “Has a doctor ever told you that you have…,” clinic data, and current medication use. Weight (kg) was measured by a standard balance beam scale, and height (m) was measured using a wall-mounted stadiometer. Waist circumference was measured by trained technicians using a tape measure at the level of the umbilicus directly on the skin. Smoking status was categorized as current smoker, former smoker, and never smoker. Weekly alcohol consumption was categorized as none, 1-7 drinks/week, and more than seven drinks/week. Education was categorized as less than high school, high school graduate, and any post-secondary education.

Statistical Analysis

Baseline characteristics of the cohort were examined using univariate procedures including proportions or mean $\pm$ SD, as appropriate. Binary associations between baseline predictors and incident metabolic syndrome at year six were tested using the Chi-square test. Three logistic regression models, one each for time, intensity, and activity types, were used to determine odds ratios and 95% confidence intervals with the highest dose as the reference in all models. Physical activity category x covariate interactions were tested in all three logistic models. Linear trends were tested using the chi-square test, with significance determined to be at the $P<0.05$ level. Keeping with the methods of Lee and Skerrett (Lee and Skerrett 2001), the total volume of physical activity (kcals/week) was entered as a covariate in all models to eliminate the potential confounding of this variable when testing dose-response associations. All analyses were conducted using SAS v8.2 software (SAS, Cary, NC).

Results

Table 2 displays baseline characteristics of the 1266 Health ABC participants with no baseline metabolic syndrome and complete six year follow-up data. Comparing between men and women indicates expected findings in anthropometrics, lifestyle characteristics, educational levels, and prevalent disease states. Men were taller, heavier, reported higher rates of smoking and alcohol consumption, and a higher proportion of post-secondary education than did women. Women reported higher rates of osteoarthritis and depression, which are also consistent with previous reports (Visser, Goodpastor et al. 2005).

When examining baseline prevalence of physical activity categories in men and women (Table 3), it is evident that in general men reported higher weekly doses of time spent in and intensity of physical activities than did women. However, a similar proportion of men and women (~40%) were meeting or exceeding recommended weekly time spent engaging in physical activity. A greater proportion of men (38% vs. 20%) reported being exercise active, i.e. regularly participating in activities such as walking for exercise, exercise classes, and weightlifting. Whereas women reported substantially higher rates of light intensity physical activities (52% vs. 30%) and in being lifestyle active (56% vs. 44%).

Six Year Incidence of Metabolic Syndrome

Six year incidence of metabolic syndrome, metabolic syndrome factors, and severity of metabolic syndrome is reported in Table 4. Women had a slightly higher rate of incidence of metabolic syndrome compared to men (22% vs. 18%). Comparison of these rates with previous studies is not possible, as to our knowledge this is the first study to report incident rates of metabolic syndrome in elder adults. Examination of incidence of metabolic syndrome factors indicates that development of a blood pressure factor (BP greater than

130/85 mmHg) was similar between genders. Rates of development of the other factors were higher in women, except for the glucose factor (fasting glucose >110mg/dl), where 12% of men and 9% of women developed this over six years. Table 3 also displays, among those men and women who did develop metabolic syndrome, the severity of the condition. The severity of metabolic syndrome was very similar between genders; with approximately a five to one ratio of those meeting the minimum criteria for metabolic syndrome (three factors) vs. all other groups combined.

Physical Activity and Incident Metabolic Syndrome in Men

Examination of physical activity x gender interactions (not shown) indicated that men and women had differing physical activity dose-metabolic syndrome response associations; therefore separate models were developed for men and women to estimate odds ratios and 95% confidence intervals for incident metabolic syndrome. Table 5 displays unadjusted and adjusted odds ratios and 95% confidence intervals for incident metabolic syndrome in men. Generally, adjustment of the models for confounders resulted in minimal changes in the magnitude of the odds ratios and their precision. Men reporting accumulating less than 150 minutes/week in physical activity (low dose) were 67% more likely (Adjusted OR=1.67; 95%CI 1.01-2.77) to develop metabolic syndrome than the high dose group (>200 minutes/week) in the covariate-adjusted model. No differences in risk were noted between the high dose and recommended dose of time in weekly physical activity in men. However, a significant dose-response trend was observed in the time category (P=0.03). The other finding of note in men was that those who reported being sedentary in the intensity category were twice as likely as those reporting regular vigorous doses to develop metabolic syndrome

(Adjusted OR=2.00; 95%CI 0.96-4.15). A marginal dose-response trend was found in the intensity category (P=0.07).

Physical Activity and Incident Metabolic Syndrome in Women

The incidence of metabolic syndrome in women's physical activity categories responded in a very different pattern than in the men. Unadjusted and adjusted odds ratios and 95% confidence intervals for incident metabolic syndrome in women are shown in Table 6. As with the models in the men, adjustment for confounders resulted in minimal changes in the magnitude of the odds ratios and their precision. The odds ratios in the women's models demonstrate that in every category of physical activity the lower doses conferred a protective, though not always significant, effect against incident metabolic syndrome compared to the highest, referent doses. Significant effects were found in the intensity category, which showed that compared to the vigorous dose, the light dose group was over 50% less likely to have metabolic syndrome at year six (Adjusted OR=0.48; 95%CI 0.28-0.81). In women, marginal dose-response associations were observed in the intensity (P=0.11) and activity types (P=0.08) categories. However, as indicated previously, the dose-response trends indicated a possible increasing protective effect against incident metabolic syndrome with lesser doses of physical activity. This was an unexpected finding given our research hypotheses.

To further examine the dose-response associations between men and women, Figure 1 provides curves for rates of incident metabolic syndrome within the physical activity categories. Generally the dose-response curves in all three physical activity categories in the men demonstrate reduced incidence of metabolic syndrome with an increasing dose. However, in women the time and intensity doses represent a U-shaped curve, where the

optimal dose may lie between the lowest and highest doses. Specifically the recommended time dose and the light intensity dose appear to be optimal doses in preventing incident metabolic syndrome in women, although the light intensity dose was the only dose found to be statistically different from the referent dose. An unexpected finding was that, in the women activity types (Figure 1c), the sedentary group had an incidence rate of metabolic syndrome that was 50% that of the exercise active group, a difference in risk that approached statistical significance (OR=0.55; 95%CI 0.28-1.10).

Discussion

In this six-year prospective study, we found that incidence of metabolic syndrome in men and women was approximately 20%, and that doses of time, intensity and activity types confer quite different effects on metabolic syndrome when comparing men and women. Dose response curves in men generally followed a form that we expected to see, with a decrease in incidence of metabolic syndrome with increasingly higher doses of physical activity. However in women the time and intensity doses displayed U-shaped dose-response curves, indicating that intermediate doses of time and intensity may be optimal in older women to prevent metabolic syndrome. Significant findings were that in men, the risk of incident metabolic syndrome in those reporting low levels of weekly time spent in physical activity was 67% greater than in those men reporting more than 200 minutes/week (high dose). In women, regular light intensity doses of physical activity confer a protective effect against metabolic syndrome compared to those reporting regular vigorous doses, and the magnitude of a 50% reduction in risk observed was quite large.

We were able to find only one study that examined the impact of physical activity on metabolic syndrome specifically in older adults. Stewart and colleagues conducted a 26-week

clinical trial with a three days per week exercise component that included strength training at 50% of 1-repetition maximum and forty five minutes of aerobic training at 60-90% of maximum heart rate(Stewart, Bacher et al. 2005). These exercise levels would be considered moderate to vigorous, and the accumulated time would meet weekly time recommendations (~180 minutes/week). However the impact of the intervention on the attenuation of metabolic syndrome was only borderline significant (P=0.06). Another study examined the associations between physical activity and selected metabolic syndrome factors in older adults. Petrella examined the long term effects (over ten years) of regular exercise compared with being sedentary in two groups who were self-selected (Petrella, Varallo et al. 2005). The training consisted of three days per week of aerobic activities (walking, jogging) for forty five minutes at 65-75% of maximum heart rate. These training zones are of moderate to vigorous intensity and exercisers demonstrated long-term improvements, compared to the sedentary controls, in all five metabolic syndrome factors. These studies indicate that in older adults, engaging in physical activity of moderate to vigorous intensity for 135-180 minutes per week may be adequate doses to prevent metabolic syndrome. Our findings in older men generally concur with these studies. However, in older women our findings do not support the above doses as optimal.

The pronounced gender difference in the risk of metabolic syndrome across physical activity doses was an unexpected finding and warrants discussion. Not only were the dose-response curves in women different from the men, but also the curves differed when looking *within* the women's physical activity categories. In women, time and intensity dose-responses resembled a U-shaped curve, whereas activity types tended to demonstrate a linear response, but in the direction of sedentary as being favorable. Rennie and colleagues (Rennie,

IJE, 2003) demonstrated that women had differing dose-response relationships from men when examining the profile of metabolic syndrome factors across a continuum of time spent in weekly vigorous activity. The group reporting the second lowest levels of any vigorous activity (<5 Met hours/week) had the best metabolic syndrome profile, demonstrating a similar U-shaped dose-response association to that observed in our study. These findings are also in line with previous studies that also demonstrated a U-shaped association between physical activity doses and cardiovascular disease risk. For example, Bijnen et al. reported a U-shaped dose response association between physical activity and risk for coronary heart disease in the Zutphen Elderly Study (Bijnen, Caspersen et al. 1998). Similarly, Shaper and colleagues demonstrated that middle-aged men who were vigorously active had a greater risk of heart attacks over an eight year follow-up period compared to moderate or moderately-vigorous exercisers (Shaper, Wannamethee et al. 1992). These studies indicate that the dose-response curve between physical activity and a cardiovascular-related outcome depends very much on the outcome itself, the population studied, and in the case of our results, the gender.

We later hypothesized that the high dose physical activity groups were perhaps at greater risk for metabolic syndrome via a higher baseline prevalence of one or two metabolic syndrome factors. Analyses (available upon request) indicated that this was not the case, with an equal distribution among physical activity doses of women with one or two baseline metabolic syndrome factors. We also examined post-hoc if women who reported high doses of physical activity had a higher proportion of individuals involved in strength training activities compared to men, as strength training activities would not be expected to impact cardiovascular-related outcomes at the level of endurance activities. Conversely, we found that compared to the women, men had double the ratio of kilocalories expended from

strength training to the overall kilocalories expended in high dose activities. Therefore, we can only speculate when discussing the vast gender differences in dose-response associations observed in this study.

The women's apparent increased risk of metabolic syndrome in all three of the physical activity categories' highest doses (high time dose, vigorous intensity dose, and exercise active) may be a result of musculoskeletal injury secondary to overuse, which could have lead to dramatic reductions in levels of physical activity in later years that we were not able to measure in this study. Gilchrist reported a dose-response association between increasing physical activity doses and increased risk of injury in women (Gilchrist, Jones et al. 2000). It is also plausible that unmeasured social or environmental changes could have occurred over the six years of follow-up. The women may have experienced the death of a spouse, moved to environments less conducive to physical activity, or had financial hardships that limited involvement in physical activity that required some level of monetary involvement. Of course all these scenarios are not necessarily independent of one another, and in fact are often inter-dependent (Savikko, Routasalo et al. 2005). Lastly, while no baseline health differences were noted between women in the highest dose groups with the respective lower dose groups (data available upon request), it is also plausible that health events within the six years of follow-up in the high dose groups could have precipitated a significant drop in levels of physical activity and a subsequent decline in health leading to metabolic syndrome.

Limitations to this study include the loss of 640 participants to follow-up. This represents one-third of the cohort who were free of metabolic syndrome at baseline and could have resulted in biased estimates of risk. Also, use of a self-report questionnaire to derive

levels of physical activity is subject to participant reporting and recall errors. Direct activity measures, such as accelerometers, could provide more accurate totals of weekly caloric expenditure (Bassett 2000). Finally, having only a baseline measure of physical activity levels is limiting, as follow-up status would provide an over time average of physical activity status.

Future studies similar to this one are needed to further understand the relationships that exist between differing doses of physical activity and metabolic syndrome. Although the evidence is compelling for a dramatic increased risk of diabetes, cardiovascular disease, and cardiovascular disease related deaths, metabolic syndrome is a condition that is largely understudied in determining optimal prevention strategies. This study suggests that optimal doses of physical activity are gender-dependent, such that doses of physical activity beyond the current recommendations are of added benefit to men, but not to women. Furthermore, high doses of physical activity may place an older woman at increased risk for metabolic syndrome.

Table 1. Physical activity categories and doses.

Time Category

Low Time Dose- individuals accumulating less than 150 minutes/week in physical activities of any intensity.

Recommended Time Dose- individuals accumulating between 150-200 minutes/week in physical activities of any intensity.

High Time Dose- individuals accumulating a minimum of 200 minutes/week in physical activities of any intensity.

Intensity Category

Sedentary Dose- individuals accumulating less than 1000 kcals/week in any physical activities.

Light Intensity Dose- individuals accumulating a minimum of 1000 kcals/week in physical activities of an intensity of less than 3 Mets, and less than 1000 kcals/week in vigorous and moderate intensity activities.

Moderate Intensity Dose- individuals accumulating a minimum of 1000 kcals/week in physical activities of an intensity of 3-6 Mets, and less than 1000 kcals/week in vigorous intensity activities.

Vigorous Intensity Dose- individuals accumulating a minimum of 1000 kcals/week in physical activities of an intensity of 6 Mets or greater.

Activity Types

Sedentary - individuals accumulating less than 1000 kcals/week in exercise activity and less than 2719 kcals/week in physical activity.

Lifestyle Active - individuals accumulating at least 2719 kcals/week in physical activity and less than 1000 kcals/week in exercise activity.

Exercise Active - individuals accumulating greater than 1000 kcals/week in exercise activities.

Table 2. Baseline characteristics of 1266 Health ABC participants with no metabolic syndrome and complete six-year follow-up data.

	Men (N = 629)	Women (N = 637)
Characteristics	Mean (SD)	Mean (SD)
Age, y	73.7 (2.8)	73.4 (2.9)
Height, m	1.73 (0.07)	1.60 (0.06)
Weight, kg	78.1 (11.8)	66.6 (13.4)
Waist circ., cm	97.5 (10.2)	94.4 (13.7)
	%	%
Race		
White	65.8	60.1
Smoking status		
Never	33.6	60.7
Former	56.5	30.7
Current	9.9	8.6
Alcohol (drinks/wk)		
None	37.7	54.7
1-7	49.6	41.8
7+	12.7	3.5
Education		
Less than HS	23.6	19.9
HS graduate	24.5	38.0
Post-secondary	52.0	42.1
Disease prevalence (%)		
Cerebrovascular disease	5.8	7.3
Heart disease	20.3	9.1
Hypertension	38.5	40.5
Lower limb osteoarthritis	5.8	11.9
Pulmonary disease	9.3	9.7
Diabetes	7.1	2.5
Circulatory problems	3.5	2.4
Depression	7.9	13.8

Table 3. Baseline prevalence of physical activity categories.

	Men N (%)	Women N (%)
Time		
Low Dose	354 (55.6)	379 (60.3)
Recommended Dose	49 (7.7)	49 (7.8)
High Dose	234 (36.7)	201 (32.0)
Intensity		
Sedentary Dose	97 (15.7)	72 (11.7)
Light Dose	183 (29.6)	316 (51.5)
Moderate Dose	199 (32.2)	111 (18.1)
Vigorous Dose	140 (22.6)	115 (18.7)
Activity Types		
Sedentary	120 (18.8)	147 (23.4)
Lifestyle active	277 (43.5)	354 (56.3)
Exercise active	240 (37.7)	128 (20.4)

Table 4. Metabolic syndrome (MS) status at year six in the Health ABC Study.

	Men N (%)	Women N (%)
Incidence of MS	115 (18.1)	136 (21.6)
Incidence of factors		
Blood pressure	117 (18.4)	120 (19.1)
Waist circ.	74 (11.6)	93 (14.8)
Glucose	78 (12.2)	58 (9.2)
HDL	45 (7.1)	58 (9.2)
Triglycerides	46 (7.2)	60 (9.5)
Number of factors among those with MS		
3	88 (76.5)	106 (78.0)
4	24 (20.9)	27 (19.9)
5	3 (2.6)	3 (2.2)

Table 5. Unadjusted and adjusted models of baseline physical activity and incident metabolic syndrome in men.

Variable	Unadjusted OR (95%CI)	Adjusted OR*(95% CI)
Time		
Low dose	1.92 (1.22-3.04)	1.67 (1.01-2.77)
Recommended dose	1.13 (0.47-2.75)	0.90 (0.35-2.31)
High dose	1.00	1.00
P for trend	*0.004*	*0.03*
Intensity		
Sedentary dose	1.76 (0.91-3.41)	2.00 (0.96-4.15)
Light dose	1.29 (0.71-2.34	1.39 (0.72-2.67)
Moderate dose	1.17 (0.65-2.11)	1.27 (0.68-2.39)
Vigorous dose	1.00	1.00
P for trend	*0.09*	*0.07*
Activity types		
Sedentary	1.49 (0.85-2.63)	1.46 (0.74-2.86)
Lifestyle active	1.37 (0.86-2.18)	1.33 (0.81-2.18)
Exercise active	1.00	1.00
P for trend	*0.13*	*0.19*

*Adjusted for total kcals, age, percent body fat, gender, race, education, marital status, smoking status, drinking status, heart disease, and count of other diagnoses.

Table 6. Unadjusted and adjusted models of baseline physical activity and incident metabolic syndrome in women.

Variable	Unadjusted OR (95%CI)	Adjusted OR* (95%CI)
Time		
Low dose	0.87 (0.58-1.30)	0.81 (0.51-1.27)
Recommended dose	0.53 (0.22-1.26)	0.63 (0.26-1.55)
High dose	1.00	1.00
P for trend	*0.57*	*0.25*
Intensity		
Sedentary dose	0.73 (0.38-1.42)	0.91 (0.44-1.88)
Light dose	0.47 (0.29-0.77)	0.48 (0.28-0.81)
Moderate dose	0.67 (0.37-1.21)	0.75 (0.40-1.39)
Vigorous dose	1.00	1.00
P for trend	*0.03*	*0.11*
Activity types		
Sedentary	0.53 (0.29-0.97)	0.55 (0.28-1.10)
Lifestyle active	0.90 (0.57-1.45)	0.84 (0.51-1.38)
Exercise active	1.00	1.00
P for trend	*0.04*	*0.08*

*Adjusted for total kcals, age, percent body fat, gender, race, education, marital status, smoking status, drinking status, heart disease, and count of other diagnoses.

Figure 1. Proportion (%) of men and women developing metabolic syndrome in each physical activity category, by gender.
◆ Statistically different from the highest dose group. Rec.=recommended; Sed.=sedentary; Mod.=moderate; Vig.=vigorous; L.A.=lifestyle active; E.A.=exercise active

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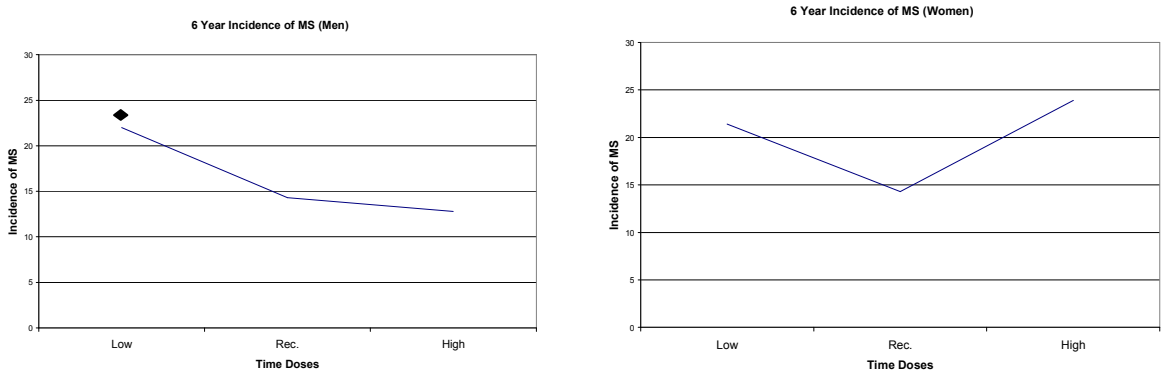

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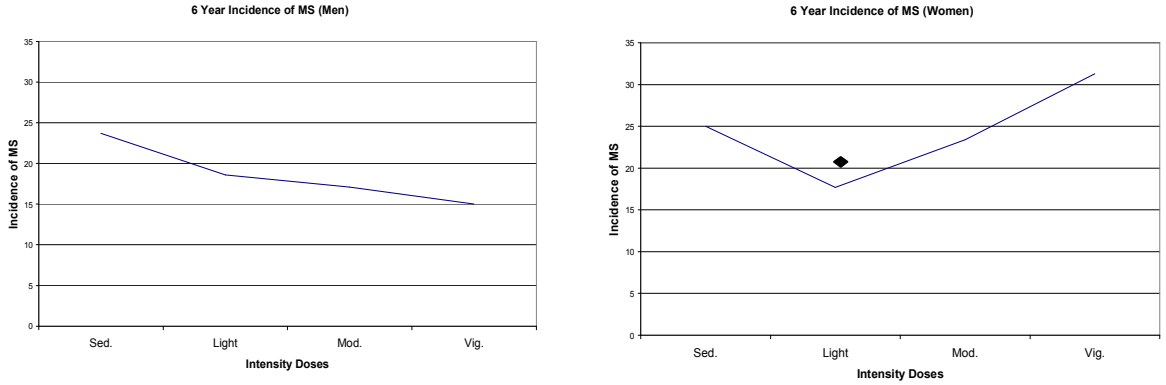

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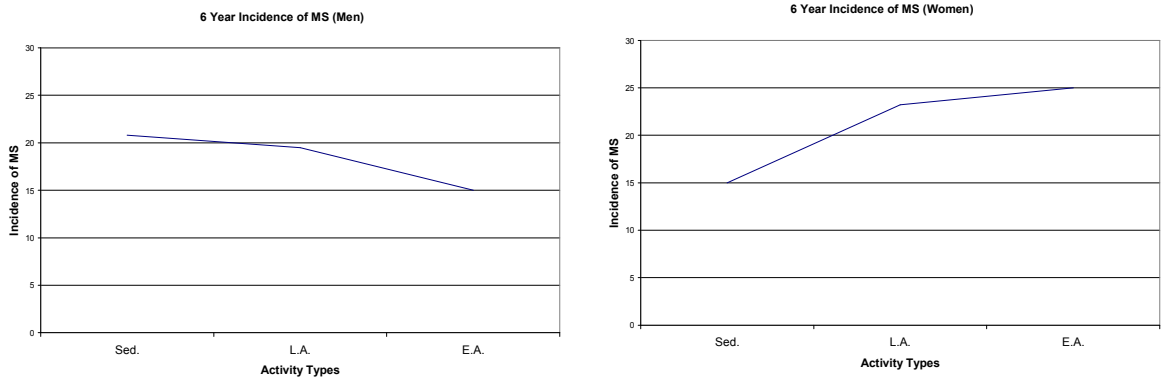

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Chapter III. MANUSCRIPT TWO: Epidemiologic Evidence for Physical Activity as an Attenuating Factor for Frailty: The Health ABC Study

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Abstract

The development of frailty in older adults places them at risk for adverse health and future disability. While physical activity recommendations for health benefits exist, the specific types and amounts of physical activity needed to prevent frailty are not known. PURPOSE: The purpose of this study was to examine how different doses and types of physical activity affect the onset and severity of frailty in older adults. METHODS: 3060 participants from the Health ABC Study were followed for six years to ascertain long-term frailty status. Frailty status was determined using a gait speed cut-off of <0.60 m/s and inability to rise from a chair five times, with moderate frailty having one of the two factors and severe frailty having both factors. Hierarchical physical activity doses at baseline were divided into three categories, 1) **time** (low, recommended, high), 2) **intensity** (sedentary, light, moderate, vigorous) and, 3) **activity type** (sedentary, lifestyle active, exercise active). Generalized estimating equations were used to develop risk estimates for onset of frailty. RESULTS: At baseline, a lower proportion of women than men were meeting the current recommendations for physical activity (19% vs. 30%). A majority of women (56%) reported regular light activities during the week (i.e. housework, care-giving). By year six, approximately 16% and 22% of the remaining men and women, respectively, had developed frailty. When examining the development of any frailty, covariate adjusted models indicated that **time** and **intensity** doses were not significantly different. Within the **activity types**, compared to the exercise active, the sedentary were at increased risk for frailty (OR=1.04; 95%CI 1.00-1.07). To determine predictors of transitioning from moderate to severe frailty in

those who had progressed to frailty (N=283), we found the **activity types** conferred differing risks, with the sedentary (OR=1.24; 95%CI 1.03-1.49) and lifestyle active (OR=1.19; 95%CI 1.05-1.35) at increased risk for severe frailty compared to the exercise active. We also observed a significant dose-response association within the **activity types** (P=0.02), suggesting a hierarchical relationship with severe frailty. CONCLUSIONS: Of all the physical activity doses and types examined in this study, regularly engaging in exercise activities (walking for exercise, weight training, aerobic dancing) appears to be most important in preventing and attenuating the severity of frailty. Additionally, the **intensity** of activities should be considered when designing interventions for frail, older adults.

Introduction

Older adult age groups are the fastest growing segments of the U.S. population. For instance, by the middle of this century those eighty-five and older are expected to increase by 400% (U.S. Census Bureau Population Division National Projections Program 2004). However, paralleling an aging population is an increase in chronic disease-related health concerns and a focus on maintaining independent living---or preventing disability (Guralnik and Simonsick 1993; Singh 2002).

There are several primary conceptual pathways to disability. These include, among others, the classic pathway described by Nagi, which describes a transition from pathology, to impairment, to functional limitation, to disability (Nagi 1965). A catastrophic pathway to disability describes sudden onset of disability caused by a trauma such as spinal chord injury or stroke. As described by Fried et al (Fried, Ferrucci et al. 2004), frailty can also be considered a primary pathway to disability. Frailty is defined as a pathologic condition that results in a constellation of signs and symptoms and is characterized by high susceptibility, impending decline in physical function and high risk of death (Ferrucci, Guralnik et al. 2004). By definition, frailty is a pre-disabled state, and the risk for future disability in the frail is approximately double that of the not frail (Fried, Tangen et al. 2001). Although many frailty models exist, the majority determines frailty status using some measure of strength and mobility (Hogan, MacKnight et al. 2003), factors strongly influenced by physical activity (Keysor and Jette 2001).

However, the association between physical activity and frailty is not well understood. Further, studies comparing specific doses and types of physical activity and long-term risks

for subsequent frailty do not currently exist. Studies to date have typically employed a single standardized intervention consisting of some combination of strength and endurance activities and tested its effectiveness on frailty compared to very low-level activities (i.e. stretching activities) or to no activity at all (Gill, Baker et al. 2002) (Brown, Sinacore et al. 2000) (Binder, Schechtman et al. 2002). Results of these studies have been modest at best. To appropriately design physical activity intervention studies that have the greatest probability of affecting frailty status, we must first determine the optimal combination of doses of frequency, intensity, duration and type of physical activity.

The objective of this study was to examine how different doses and types of physical activity affect the development and severity of frailty status in older adults. Using data from the Health, Aging and Body Composition (Health ABC) Study, we tested the hypotheses that, 1) Older adults who engage in ***vigorous (6+ Mets)*** physical activities on a regular weekly basis have a lower incidence of frailty as compared to those who engage regularly in physical activities of ***moderate (3-6 Mets)*** or ***light (<3 Mets)*** intensity, or to those who are ***sedentary***, 2) Older adults who engage in greater than the recommended amount of weekly time ***(200+ minutes/week)*** in physical activities have a lower incidence of frailty as compared to those who engage in the recommended amount ***(150-200 minutes/week)***, or less than the recommended weekly amount of time ***(<150 minutes/week)***, and 3) Older adults who expend weekly energy primarily from ***exercise activities*** have a lower incidence of frailty as compared to those whose expenditure is primarily ***lifestyle activities***, or to those who are ***sedentary***.

Methods

Health ABC Study

The Health ABC Study is a longitudinal, prospective study with the broad objectives of measuring higher functioning older adults to allow examination of health decline and improvement over several years, and to allow comparisons with other well-studied populations (i.e. EPESE, Women's Health and Aging Study). Specifically, the study aims include investigation of the interrelationships between health conditions, body composition, social and behavioral factors, and functional change (Simonsick, Newman et al. 2001). Clinic-based examinations and self-report measures were collected over a seven year period.

Study Population

The Health ABC Study cohort consists of 3075 well-functioning black and white men and women aged 70 to 79. White participants were recruited from a random sample of Medicare beneficiaries in the zip codes surrounding Pittsburgh, Pennsylvania and Memphis, Tennessee. Black participants were recruited from all age-eligible residents of the areas in and surrounding Pittsburgh and Memphis. Potential participants were then screened for the following inclusion criteria, 1) No reported difficulty: walking ¼ mile, walking up ten steps, or performing basic activities of daily living, 2) no known life-threatening cancers, 3) no plans to leave the area for three years. The University of Pittsburgh and University of Memphis institutional review boards approved the study, and all participants provided written informed consent prior to participation.

For this analysis, participants were excluded due to missing baseline functional testing data (N=15), leaving 3060 participants at baseline for these analyses. Participants with missing baseline health information (N=431) were imputed using standard methods (see Statistical Analysis)

Study Measures

The outcome variable for this study was frailty. Frailty status was ascertained at baseline, Year 4 and Year 6. The model of frailty for this study was the Gill frailty model, first developed and proposed in 1995 (Gill, Williams et al. 1995) and later refined in 2002 (Gill, Baker et al. 2002) for a clinical trial with a target population of frail elders. When developing and validating his frailty model, Gill found that those older adults, with a gait speed of less than 0.60 meters/second (m/s) and the inability to rise from a chair once with arms folded, were eight times more likely to develop incident ADL disability compared to performing above both cut-points. For this study, frailty was identified using functional performance cut-points similar to Gill's: a gait speed <0.60 m/s and the inability to rise from a chair five times with arms folded. We substituted inability to rise once from a chair with inability to perform five chair rises due to limited tracking of follow-up performance measures in this dataset. Ability to complete five chair rises was recorded and tracked for all follow-up tests, whereas ability to stand once was not consistently tracked. One advantage to using inability to perform five chair rises is the potential to identify those individuals with some functional strength reserve remaining that allows them to at least stand once from a chair---a prerequisite to moving on to the five chair stand test. Identifying these individuals could result in appropriately designed interventions to prevent further strength deterioration.

Gill utilized a two-tier frailty severity model, where being positive in any one frailty factor indicated *moderate frailty* and positive in both factors indicated *severe frailty*. This study also used the same ordered frailty severity system. Advantages to the Gill frailty model over other models are 1) the widely recognized performance measures (gait speed and chair stands) that are utilized as factors, 2) the low participant burden of the measures, 3) the low

cost of the measures, 4) the ease of personnel training to administer the tests. In addition, poor gait speed and chair stand performance predict several adverse health outcomes, including disability, institutionalization, and mortality (Guralnik, Simonsick et al. 1994) (Guralnik, Ferrucci et al. 2000).

The predictor variable of interest, physical activity, was collected from participants at baseline using a self-report instrument developed specifically for the Health ABC Study. The standardized questionnaire was developed using the model of several commonly used activity questionnaires, such as the Minnesota leisure-time physical activity questionnaire (Taylor, Jacobs et al. 1978). Kilocalories per week (kcals/week) expended in common exercise activities (i.e. walking for exercise, exercise classes, weightlifting) and lifestyle activities (i.e. gardening, housework, yard work) were collected. Specifically, participants were asked if they had engaged in physical and exercise activities at least ten times in the last twelve months. Those activities that were identified as positive over the last year were further examined regarding time for each activity over the last seven days. Based on self-reported weekly time and known metabolic costs for activities (Ainsworth, Haskell et al. 2000) a summary variable of kcals/week expended was calculated for each activity. The metabolic cost of activities is reported in metabolic equivalents (Mets). One Met is equivalent to resting energy expenditure, or 3.5 ml/kg/min.

For this study, physical activity doses and types were determined to allow for several associations to be tested based on current recommendations for weekly energy expenditure via physical activity (U.S. Department of Health and Human Services 1996) (American College of Sports Medicine 1998). The doses are hierarchical in nature, moving from the lowest dose to the highest dose, within each physical activity category. Specifically, *time*

doses (low, recommended, high), *intensity doses* (sedentary, light, moderate, vigorous), and *activity types* (sedentary, lifestyle active, exercise active) were tested. The format of the Health ABC questionnaire did not allow a physical activity weekly frequency dose-response to be tested for this study. Physical activity categories and doses are shown in Table 1. Time doses were based on current recommendations for weekly accumulated time spent in physical activity (U.S. Department of Health and Human Services 1996) (Pate, Pratt et al. 1995). Due to availability of data, these doses were constructed using only the sum of minutes per week spent walking of any intensity and time spent in exercise. Intensity doses were based on American College of Sports Medicine guidelines for determination of activity intensities based on Met level cut-offs (Ainsworth, Haskell et al. 2000) and on recommended accumulated weekly energy expenditure for health benefits (minimum of 1000 kcals/week) (U.S. Department of Health and Human Services 1996). Activity type groups were based on the previous construct developed by Brach et al. (Brach, Simonsick et al. 2004) using current physical activity recommendations (U.S. Department of Health and Human Services 1996) (Pate, Pratt et al. 1995) for weekly energy expenditure (minimum of 1000 kcals/week) and on distribution of weekly energy expenditure in total physical activity in the Health ABC cohort (25^{th} percentile = 2,719 kcals/week).

Covariates that were collected at baseline and that were controlled for in the analyses included age, sex, race, education, waist circumference, marital status, count of chronic diseases (cerebrovascular disease, heart disease, hypertension, lower limb OA, pulmonary disease, diabetes, circulation problems in extremities, and depression), smoking status and alcohol consumption. Race is dichotomized into black and white. Chronic diseases were ascertained by asking the participant, "Has a doctor ever told you that you have…," clinic

data, and current medication use. Weight (kg) was measured by a standard balance beam scale, and height (m) was measured using a wall-mounted stadiometer. Waist circumference was measured by trained technicians using a tape measure at the level of the umbilicus directly on the skin. Smoking status was categorized as current smoker, former smoker, and never smoker. Weekly alcohol consumption was categorized as none, 1-7 drinks/week, and more than seven drinks/week. Education was categorized as less than high school, high school graduate, and any post-secondary education.

Statistical Analysis

Baseline characteristics of the cohort were examined using univariate procedures including proportions or mean $\pm$ SD, as appropriate. Participants who were missing one or more baseline health information variables were imputed using standard methods. For variables with less than 1% of the entire cohort missing at baseline, the mean or mode, depending on distribution, was imputed for missing values. For those variables missing more than 1% in the cohort, multiple imputation methods with bootstrapping were used. Prevalence and incidence rates (cases/1000 person years) of frailty were calculated for all available waves of data collection (Years 1, 4 and 6). All individuals who were moderately or severely frail at baseline (N = 92) were then excluded from the primary analyses to allow for temporal associations to be examined. Binary associations between baseline predictors and incident frailty at year six were tested using the Chi-square test. The associations between baseline physical activity levels and incident frailty over six years were originally examined using proportional odds generalized estimating equation (GEE) regression modeling with an ordinal outcome (not frail, moderately frail, severely frail). A model was first fit to test for proportionality of the association between each physical activity category (intensity, time,

type) and incident frailty. Because the proportionality assumption was not met for any of the three physical activity categories, two separate GEE logistic regression models were then developed: the first model tested the association between physical activity and incident moderate or severe frailty. In other words, we wanted to determine if physical activity was associated with reduced risk for any type of frailty. The second model tested the association between physical activity and incident severe frailty; this tested if physical activity was associated with level of severity of frailty in those who do become frail over time. Physical activity group x covariate and group x time interactions were tested in both models. Linear trends were tested using the chi-square test, with significance determined to be at the $P<0.05$ level. Odds ratios and 95% confidence intervals for risk of incident frailty were calculated, with the most active group as the referent group in all models. Keeping with the methods of Lee and Skerrett (Lee and Skerrett 2001), the total volume of physical activity (kcals/week) was entered as a covariate in all models to eliminate the potential confounding of this variable when testing dose-response associations. All analyses were conducted using SAS v8.2 software (SAS, Cary, NC).

Results

Baseline Characteristics

The gender-specific baseline characteristics of the 3060 Health ABC participants are shown in Table 2. As expected men were taller and heavier then women, although waist circumference differed minimally between genders (mean difference = 2.7 cm). The proportion of white women was considerably less than the proportion of white men, which is consistent with previous Health ABC publications (Visser, Goodpastor et al. 2005).

Prevalence of smokers at baseline (~10%) was similar between men and women; however a higher proportion of men reported being former smokers (60% vs. 33%). Men tended to report more weekly alcohol consumption and have higher levels of education then did women. When examining prevalent diseases, men had higher rates of heart disease, diabetes, and circulatory problems than did women. And women reported higher rates of hypertension, osteoarthritis, and depression than men. These baseline characteristics are consistent with the literature (Hahn, Heath et al. 1998).

An analysis of those participants whose data were not available for analysis at year six (N=872) compared to those whose data were available for analyses at year six (N=2188) indicated that drop-outs were more likely to be older, male, have more health conditions, have higher rates of frailty, and be sedentary at baseline (All $P<0.05$) compared to those who remained for the duration of the study.

Table 3 provides the breakdown of physical activity groups at baseline. Consistent with previous reports (Hahn, Heath et al. 1998), women reported lower rates of physical activity by weekly time and type. However, the proportion of women classified as sedentary in the intensity group was less than men (12% vs. 16%, respectively). In fact, a majority of women (56%) reported accumulating at least 1000 kcals/week in activities of light intensity (<3 Mets). This activity level consists of light housework, shopping, doing volunteer or light paid work, and care-giving. Similar proportions of men and women (~7%) reported engaging in the recommended 150-200 minutes per week walking of any intensity, with a higher percentage of men exceeding the recommendations (34% vs. 25%). Men reported engaging in more physical activities of moderate and vigorous intensity and in exercise activities than did women at baseline. When summed, at baseline 30% of men and 19% of women reported

the recommended accumulation of at least 150 minutes per week in activities of a moderate intensity or greater.

Frailty Status Over Six Years

Prevalence and incidence of frailty status in the 2018 men and women with frailty information at all waves is shown in Table 4. At baseline approximately 2% of the men and 3% of the women were moderately or severely frail. In four years 5% and 10% of the men and women were frail, respectively. At year six prevalence rates of frailty grew to over 13% for men and 18% for women. There were 6111 person years of follow-up at year four and 9229 person years of follow-up at year six. Incidence rates at four and six years indicated that women had overall higher rates of incident moderate and severe frailty compared to men at both follow-up time points. The magnitude of the difference in rates of moderate frailty between men and women was greatest at four years, as incidence rates in men increased from 6.2/1000 person years to 10.1/1000 person years from year four to year six, whereas rates in women remained rather stable over the same time period.

Risk of Developing Any Frailty

Unadjusted and adjusted odds ratios and 95% confidence intervals (OR: 95%CI) for combined any incident frailty over six-years are seen in Table 5. No significant interactions were found, so the estimates displayed are from main effects models. Odds ratios within the time category indicate that, compared to the high time dose, those in the low dose (<150 minutes/week in any walking) were 25% more likely to become frail (OR=1.25; 95%CI 1.00-1.57). This increased risk dissipated completely when controlling for important covariates in the adjusted model. Intensity category unadjusted results interestingly showed that compared to the vigorous dose, the light intensity dose placed individuals at significantly greater risk of

incident frailty (OR=1.41; 95%CI 1.06-1.88). Being sedentary did not appear to confer an increased risk of frailty compared to the vigorous dose (OR=1.14; 95%CI 0.78-1.65). However, similar to the time category findings, the significant light vs. vigorous intensity dose finding was not maintained in the covariate-adjusted model. Finally, the activity type comparisons indicated that those who reported regular lifestyle activities (OR=1.38; 95%CI 1.07-1.88) or those who were sedentary (OR=1.92; 95%CI 1.39-2.64) were more likely to develop frailty over a period of six years compared to the exercise active. This significant increased risk was maintained in the sedentary when the adjusted model was fit, although the magnitude of risk was reduced to be only 4% greater than the exercise active (OR=1.04; 95%CI 1.00-1.07). All linear trends that were significant in the unadjusted models were dissipated in the adjusted models. The activity type linear trend (P=0.08), indicates that moving from being sedentary to being lifestyle active (i.e., gardening, heavy housework, walking the dog), and then to doing exercise activities (i.e., strength training, walking for exercise, exercise classes) may confer an equally stepped decrease in risk for any incident frailty.

Risk of Developing Severe Frailty

Of those that became and remained frail over six-years (N = 283), we sought to determine if higher doses of physical activity could prevent further deterioration to severe frailty status. Table 6 displays these findings, and indicates that physical activity doses may play an important role in preventing transitioning to severe frailty in those who are already frail. The amount of time spent in physical activities does not appear to attenuate the progression of frailty, as compared to the high time dose, low and recommended time dose odds ratios were 0.96 and 0.91, respectively, with 1.00 being well within both confidence

intervals. Within the intensity category, in the adjusted models there was some indication that, compared to the vigorous dose, the risk of transitioning to severe frailty in the light intensity dose (OR=1.13; 95%CI 0.96-1.34) and the sedentary dose (OR=1.23; 95%CI 0.98-1.53) was increased. There was a marginal intensity dose-risk response association in the intensity category (P=0.06).

Looking at the adjusted odds ratios within the activity types shows a significantly increased risk for severe frailty in the lifestyle active (OR=1.19; 95%CI 1.05-1.35) and the sedentary (OR=1.24; 95%CI 1.03-1.49), compared to the exercise active. A significant dose-response trend was observed between the activity types (P=0.02).

Discussion

This study examined how differing doses and types of physical activity are associated with the development and severity of frailty over several years in a high functioning group of older adults. We found that regularly engaging in exercise activities was associated with a reduced risk of any incident frailty and a reduced risk of transitioning to severe frailty in the already frail over a six year follow-up period. These associations were independent of important health and lifestyle characteristics that are commonly associated with physical activity and functional decline. We also demonstrated a significant dose-response association between moving from being sedentary to being a regular "exerciser" and transitioning to severe frailty. There was also some suggestion that engaging in increasingly vigorous physical activities may assist in preventing a transition to severe frailty in those who are already frail.

To our knowledge this is the first study to simultaneously examine the longitudinal relationships between several specific doses and types of physical activity and frailty.

Previous studies have examined the effectiveness of one or two physical activity programs in frail elders, with widely varied exposure to doses. Fiatarone found remarkable lower body strength improvements with a high-intensity strength training intervention performed three days per week in very old, frail adults (Fiatarone, O'Neill et al. 1994). Whereas Latham and colleagues were not able to demonstrate improvements in strength with a home-based strength-training program for quadriceps strength using ankle weights three days per week (Latham, Anderson et al. 2003). Gill reported a significant effect on the trajectory of a disability score, measured by the ability to perform daily tasks, in those provided with a low intensity conditioning program performed once daily (Gill, Baker et al. 2002). Similarly Brown found improvements in a summary disability score with a comparable low-level conditioning program provided only three days per week (Brown, Sinacore et al. 2000). These studies demonstrate a wide range of interventions on frail elders utilizing varying doses and types of physical activity, and as a result the effectiveness of the interventions was also varied.

The availability of our results could guide future studies in designing the optimal physical activity doses, and subsequently lead to interventions with a higher probability of effectiveness. For instance, when designing *frailty prevention* programs or when intervening on the *progression of frailty*, prescribing *exercise activities* appear to be optimal. This is consistent with the literature that suggests high intensity strength training exercises are of great importance for maintaining strength and mobility in older adults (Fiatarone, O'Neill et al. 1994) (Evans 1999). According our results, lifestyle activities such as housework, gardening, and leisurely walking are not sufficient in preventing or attenuating the progression of frailty. Our data also indicate that considering the intensity of the physical

activities, such as those with a Met level greater than six, may also be important in offsetting a transition to severe frailty. Our findings, in conjunction with very recent information indicating that frailty is a very dynamic process with good potential for response to intervention (Gill, Gahbauer et al. 2006), show promise for future studies.

Our findings regarding the potential protective effects of engaging in physical activity for the purpose of exercise vs. being lifestyle active or sedentary requires further discussion. This finding is in line with the work of Brach and colleagues (Brach, Simonsick et al. 2004), who used the same physical activity groups construct in the Health ABC cohort. They found that the exercise active group had better functional performance, such as gait speed, chair rises, and long distance walk times, than either the lifestyle active or the sedentary groups. Based on Brach's findings, the development of frailty over time, as measured by impaired mobility (gait speed) and strength (chair rises), should be more likely in the lifestyle and sedentary groups due to their lower physical performance at baseline. This longitudinal study lends some support to the idea that older adults who report being regularly exercise active maintain higher levels of subsequent functioning (strength and mobility) and are more likely to prevent a further decline to severe frailty. Our findings are also in concordance with those of Gill and colleagues (Gill, Baker et al. 2002), who found significant differences in the rate of functional decline between a moderately frail group who participated in a home conditioning program and a moderately frail control group. As stated above, the intervention was a once-daily, progressive conditioning program using therabands and competency-based exercises. The intensity at which these exercises were performed was not reported.

In her cross-sectional analyses of the Health ABC cohort, Brach speculated that the dose of higher intensity activities in the exercise active group could be the reason for their

better functioning (Brach, Simonsick et al. 2004). We found that individuals who regularly engaged in activities of intensities ranging from light (i.e., light household chores) to vigorous (i.e. weightlifting or aerobic dancing) had no differences in the risk of future frailty. However, when examining the risk of transitioning to severe frailty in the sub-group who had become frail in subsequent years, there was some indication that participation in activities of vigorous intensity (>6 Mets) may be optimal in deferring the transition to severe frailty. This indicates that perhaps the intensity of physical activity is not important in *preventing* frailty, but may be important in *preventing the progression* of frailty. We were constrained by a relatively small number of individuals who became and remained frail over time, so analyses within the frail group is likely underpowered in this study. Adequately powered studies should be undertaken to further test the physical activity intensity-frailty progression link.

An important strength to this study is that we controlled for the total volume of physical activity when modeling our estimates. Lee and Skerrett emphasized the importance of this control in their paper published as part of a physical activity dose-response symposium several years ago (Lee and Skerrett 2001). The rationale for controlling for total volume of physical activity is that dose-response associations are often confounded by the total volume of physical activity. For instance, higher intensity activities inherently result in higher levels of energy expenditure, thus producing a greater total volume of physical activity. Controlling for the volume allows for a true dose-response test of the parameter of interest, i.e. intensity, time, duration.

Limitations to this study include the use of a self-report questionnaire to derive levels of physical activity. Direct activity measures, such as accelerometers, could provide more accurate totals of weekly caloric expenditure (Bassett 2000). Also, having only a baseline

measure of physical activity levels is limiting, as follow-up status would provide an over time average of physical activity status, and likely a stronger physical activity effect. Finally, the missing follow-up data from the remaining cohort could lead to estimates not representative of the entire group. However, the use of GEE modeling allows for missing data, and those with data at only one time point are still used in determining estimates.

In conclusion, this study provides concurrent comparisons of differing weekly doses of time, intensity, and types of physical activity and their association with incident frailty in an initially high-functioning group of older adults. These data suggest that older adults who engage in activities for the purpose of exercise are at the lowest risk for developing any frailty or for transitioning to severe frailty if they are already frail. A dose-response association was also observed between the activity types (sedentary, lifestyle active, and exercise active). Additionally, engaging in physical activities of increasing intensity may also play a role in attenuating the transition to severe frailty in already frail older adults. Future studies are warranted to confirm or refute these findings.

Table 1. Physical activity categories and doses.

Time Category

Low Time Dose- individuals accumulating less than 150 minutes/week in physical activities of any intensity.

Recommended Time Dose- individuals accumulating between 150-200 minutes/week in physical activities of any intensity.

High Time Dose- individuals accumulating a minimum of 200 minutes/week in physical activities of any intensity.

Intensity Category

Sedentary Dose- individuals accumulating less than 1000 kcals/week in any physical activities.

Light Intensity Dose- individuals accumulating a minimum of 1000 kcals/week in physical activities of an intensity of less than 3 Mets, and less than 1000 kcals/week in vigorous and moderate intensity activities.

Moderate Intensity Dose- individuals accumulating a minimum of 1000 kcals/week in physical activities of an intensity of 3-6 Mets, and less than 1000 kcals/week in vigorous intensity activities.

Vigorous Intensity Dose- individuals accumulating a minimum of 1000 kcals/week in physical activities of an intensity of 6 Mets or greater.

Activity Types

Sedentary - individuals accumulating less than 1000 kcals/week in exercise activity and less than 2719 kcals/week in physical activity.

Lifestyle Active - individuals accumulating at least 2719 kcals/week in physical activity and less than 1000 kcals/week in exercise activity.

Exercise Active - individuals accumulating greater than 1000 kcals/week in exercise activities.

Table 2. Baseline characteristics of Health ABC participants (N = 3060).

	Men (N = 1483)	Women (N = 1577)
	48%	52%
Characteristics	Mean (SD)	Mean (SD)
Age, y	73.8 (2.9)	73.5 (2.9)
Height, m	1.73 (0.06)	1.60 (0.06)
Weight, kg	81.4 (13.3)	70.5 (14.7)
Waist circ. (cm)	100.9 (12.4)	98.2 (13.8)
	%	%
Race		
White	63.1	54.2
Smoking status		
Never	29.6	57.2
Former	59.7	32.9
Current	10.7	10.0
Alcohol (drinks/wk)		
None	43.0	57.8
1-7	45.5	38.6
7+	11.5	3.6
Education		
Less than HS	27.3	23.0
HS graduate	25.3	39.3
Post-secondary	47.3	37.8
Disease prevalence (%)		
Cerebrovascular disease	7.8	8.2
Heart disease	26.4	14.6
Hypertension	47.0	54.3
Lower limb osteoarthritis	7.2	13.6
Pulmonary disease	11.6	11.6
Diabetes	16.7	13.6
Circulatory problems	6.7	3.7
Depression	9.6	15.4

Table 3. Baseline prevalence of physical activity categories.

	Men N (%)	Women N (%)
Time		
Low Dose	873 (58.9)	1078 (68.4)
Recommended Dose	109 (7.4)	112 (7.1)
High Dose	501 (33.8)	387 (24.5)
Intensity		
Sedentary Dose	222 (15.5)	181 (11.8)
Light Dose	472 (33.0)	860 (56.2)
Moderate Dose	446 (31.6)	219 (14.3)
Vigorous Dose	292 (20.4)	271 (17.7)
Activity Types		
Sedentary	328 (22.1)	421 (26.7)
Lifestyle active	665 (44.8)	899 (57.0)
Exercise active	490 (33.0)	257 (16.3)

Table 4. Prevalence and incidence of frailty at Year 1, Year 4 and Year 6 in those with complete follow-up data (N=2018).

	Men (N=962)		Women (N=1056)	
	Moderately Frail	Severely Frail	Moderately Frail	Severely Frail
Prevalence, N (%)				
Year 1	18 (1.8)	1 (0.1)	32 (3.0)	3 (0.3)
Year 4	38 (4.0)	13 (1.4)	78 (7.4)	23 (2.2)
Year 6	109 (11.3)	20 (2.1)	153 (14.5)	41 (3.9)
Incidence*				
Year 4	6.2	2.1	12.8	3.8
Year 6	10.1	1.0	11.8	2.0

*Per 1000 person years

Table 5. Odds of incident moderate or severe frailty by physical activity category.

	Unadjusted OR (95%CI)	Adjusted OR* (95%CI)
Time		
Low	1.25 (1.00 – 1.57)	0.99 (0.97 – 1.02)
Recommended	0.96 (0.62 – 1.48)	0.98 (0.94 – 1.03)
High	1.00	1.00
P for trend	*0.04*	*0.40*
Intensity		
Sedentary	1.14 (0.78 – 1.65)	1.01 (0.97 – 1.05)
Light	1.41 (1.06 – 1.88)	1.01 (0.99 – 1.04)
Moderate	0.88 (0.63 – 1.22)	0.99 (0.96 – 1.02)
Vigorous	1.00	1.00
P for trend	*0.02*	*0.26*
Activity Types		
Sedentary	1.92 (1.39 – 2.64)	1.04 (1.00 – 1.07)
Lifestyle active	1.38 (1.07 – 1.78)	1.00 (0.97 – 1.02)
Exercise active	1.00	1.00
P for trend	*<0.0001*	*0.08*

*Adjusted for test wave, total kcals, age, gender, race, education, marital status, smoking status, drinking status, waist circumference and count of diagnoses.

Table 6. In the frail, odds of incident severe frailty by physical activity category.

	Unadjusted OR (95%CI)	Adjusted OR* (95%CI)
Time		
Low	0.88 (0.47 – 1.65)	0.96 (0.85 – 1.10)
Recommended	0.67 (0.23 – 1.94)	0.91 (0.75 – 1.11)
High	1.00	1.00
P for trend	*0.77*	*0.64*
Intensity		
Sedentary	2.83 (0.94 – 8.53)	1.23 (0.98 – 1.53)
Light	1.85 (0.77 – 4.45)	1.13 (0.96 – 1.34)
Moderate	1.23 (0.41 – 3.71)	1.05 (0.85 – 1.29)
Vigorous	1.00	1.00
P for trend	*0.06*	*0.06*
Activity Types		
Sedentary	2.67 (0.90 – 7.95)	1.24 (1.03 – 1.49)
Lifestyle active	2.37 (0.99 – 5.66)	1.19 (1.05 – 1.35)
Exercise active	1.00	1.00
P for trend	*0.09*	*0.02*

*Adjusted for test wave, total kcals, age, gender, race, education, marital status, smoking status, drinking status, waist circumference and count of diagnoses.

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Chapter IV. SYNTHESIS OF THIS RESEARCH

The work undertaken in this dissertation was done so to provide researchers and exercise professionals with information regarding the effect of differing doses and types of physical activity on two health conditions that are prevalent and deleterious to older adults. The two studies presented in this document can begin to assist in the designing of effective physical activity programs aimed at preventing or attenuating metabolic syndrome and frailty in older adults. Based on this research, specific summary conclusions include:

Physical Activity Levels in Older Adults

1) A higher percentage of men are meeting the recommendations for physical activity, although the percentage meeting the recommendations is still very low in both genders (30% in men and 19% in women).
2) A majority of older women (56%) are meeting the weekly recommendations for physical activity energy expenditure (<1000 kcals/week) by engaging in light intensity activities (i.e. light housework, shopping), but are not meeting the recommendations of engaging in moderate intensity activities.

Physical Activity and Metabolic Syndrome

1) The six-year incidence of metabolic syndrome in a high functioning group of men and women in their seventies is approximately 20%.
2) Older men and women differ considerably in their response to differing doses of physical activity when considering metabolic syndrome as an outcome.

3) The optimal doses of physical activity for reducing the risk of metabolic syndrome in older men are likely to be accomplished by spending on average more than thirty minutes per day (more than 200 minutes/week) in vigorous activities, such as heavy outdoor chores, climbing stairs, aerobic dance, or strength training. Additionally, physical activities done with the intent of being part of a structured exercise program may be optimal for older men.
4) The optimal doses of physical activity for reducing the risk of metabolic syndrome in older women are likely to be accomplished by meeting the current recommendations for time spent in weekly physical activity (150-200 minutes/week) in activities of light intensity such as light housework, shopping, or volunteering. Structured exercise activities do not appear to provide additional risk reduction for metabolic syndrome in older women.

Physical Activity and Frailty

1) Women are more likely than men to develop frailty over a period of six years (22% vs. 16%, respectively).
2) Men and women are similar in their responses to doses of physical activity and their effect on frailty.
3) Physical activity plays a bigger role in preventing the transition to severe frailty in those who are already frail than in actually preventing frailty altogether.
4) Accumulating a minimum of 1000 kcals per week energy expenditure by engaging in physical activities that are done with the intent of exercising, such as walking for exercise, strength training or aerobic dance, are the optimal activity types to reduce

the risk of frailty. Although the risk is reduced to a greater degree when attempting to prevent a transition to severe frailly in those who are already frail compared to the risk reduction when attempting to prevent any frailty.

5) Differing doses of time spent in physical activity and intensities of physical activity do not appear to be important considerations when attempting to prevent the onset or further transitioning of frailty to a more severe level.

Future Research Needs Based on These Findings

1) These findings are in a cohort of older men and women who were functioning at a high level at baseline. Future physical activity dose-response studies are needed in groups at higher risk of metabolic syndrome and frailty.
    a. With metabolic syndrome as an outcome, specific groups to study should include the obese, those with insulin resistance or diabetes, those with known cardiovascular disease to study secondary prevention, hypertensive groups, and those with dyslipidemia.
    b. Frailty outcome studies are needed in arthritics, Parkinson's patients and cancer patients.
    c. Lastly, metabolic syndrome and frailty outcome studies are needed in elder veterans who utilize Veteran's Health Administration services, who are known to be in poorer health than comparable aged men and women who receive health care outside the VA system.
2) Studies utilizing objective measures of physical activity are needed to assist in more accurately determining doses of physical activity in older adults.

3) Studies are warranted with consistent longitudinal tracking of physical activity levels to allow for a more accurate representation of changes in physical activity levels and the subsequent impact on metabolic syndrome and frailty.
4) Studies are needed to investigate the effect of physical activity **frequency** doses concurrently with time and intensity doses.

This research work is the first of a series of needed studies in older adults to quantify physical activity doses and their impact on high risk health states such as metabolic syndrome and frailty. This line of inquiry should continue forward to provide the health care community with the knowledge needed to best position our aging population to live their remaining years independently with a quality of life not compromised by health conditions.

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APPENDIX A. Metabolic Syndrome Review of Literature

Metabolic Syndrome

Metabolic syndrome (MS), synonymously referred to as Syndrome X or insulin-resistance syndrome, is a constellation of factors that increase one's risk for diabetes mellitus, cardiovascular disease (CVD), coronary heart disease (CHD) and CVD/CHD-related deaths. The prevalence of MS in the US adult population is estimated to be 25%, however, prevalence increases with aging such that up to 40% of adults aged sixty-five years and older have the condition (Scuteri, Morrell et al. 2005) (Park, Zhu et al. 2003). The third Adult Treatment Panel (The Expert Panel on Detection 2001), a group of medical experts commissioned by the National Institutes of Health, define the presence of MS as being positive in any three of the following factors: increased waist circumference (>102 cm. in men and >88 cm. in women), high triglycerides ($\geq$ 1.7 mmol/l), low HDL cholesterol (<1.04 mmol/l in men and <1.29 mmol/l in women), high blood pressure ($\geq$130/85 mmHg or pharmacological treatment of hypertension), and fasting glucose ($\geq$6.1 mmol/l).

As mentioned previously, MS is often referred to in the literature as Syndrome X or insulin-resistance syndrome. However, there is clear distinction between MS and these two other terms upon further exploration of their beginnings and current status in medical research. Their divergent lines of inquiry are highlighted in the publications of Dr. Gerald Reaven, the physician who coined the term Syndrome X in 1988 (Reaven 1988). Reaven's numerous reviews on the topic of Syndrome X specifically distinguish between Syndrome X and MS, particularly when diagnosing the condition. He believes the pathophysiologic

condition that truly requires attention is insulin resistance (Reaven 2005), while recognizing the consistent association between insulin resistance and dyslipidemia, obesity, and hypertension- all factors for MS. His rationale for the focus on insulin resistance as a predictor of diabetes and adverse health outcomes is justified; however, the clustering of MS factors as a clinical indicator of increased risk for CVD and CVD-related death is also of significance.

Lakka (Lakka, Laaksonen et al. 2002) found that middle-aged Finnish men (42-60 years at baseline) with MS were 2.9 and 2.6 times more likely to die of CHD, and of all causes, respectively, over a 11-year follow-up, compared to those without MS at baseline. This association persisted even after controlling for traditional CHD risk factors such as age, LDL cholesterol, smoking, family history of CHD, fibrogen levels, alcohol consumption, and socio-economic status. Similarly, Malik (Malik, Wong et al. 2004) showed a thirteen-year doubling of risk for CVD and CHD-related deaths in men and women (~50 years at baseline) in the NHANES II cohort. In this analysis, covariates included for adjustment were physical activity levels and gender.

Few studies have examined the longitudinal impact of MS in older adults. Of those, Lempiainen et al. (Lempiainen, Mykkanen et al. 1999) studied the seven-year incidence of CHD deaths in 1069 older Finnish men and women (~69 years at baseline). They found that high triglycerides, high systolic blood pressure, and low HDL levels were the factors that consistently predicted CHD deaths in older men and women. Interestingly, insulin resistance was not a consistent predictor of MS across genders, suggesting that perhaps the clustering of risk factors present in MS that are epitomized by insulin resistance in the middle-aged are not driven by insulin resistance in older adults. In a prospective study of slightly older adults

(~75 years at baseline), Scuteri et al. (Scuteri, Morrell et al. 2005) found that those with MS at baseline were 38% more likely to develop CVD than those without MS (27.5% vs. 17.8%, respectively). An interesting point with their analysis is the associations seen between MS and CVD were significant after adjusting for *individual* MS factors, indicating that the clustering of MS factors is a better predictor of CVD than any individual factor alone. This finding is contrary to the joint report of the American Diabetes Association and the European Association for the Study of Diabetes(Kahn, Buse et al. 2005), who contended that the clustering of MS risk factors adds no further prognostic value than independently focusing on the individual factors. These two papers were both published in 2005, so it is possible that the joint consensus authors did not have access to Scuteri's findings at the time of their writing. These studies demonstrate that 1) MS predicts CVD, CHD, and CVD-related deaths in older men and women, 2) Presence of clusters of MS add predictive value to adverse health that individual factors alone do not provide, and 3) the crux of MS in middle-aged adults, insulin resistance, is not necessarily the catalyst behind MS in older adults. In fact, Goodpastor et al. (Goodpastor, Krishnaswami et al. 2005) found that the distribution of adiposity, particularly higher inter-muscular visceral tissue, is independently associated with MS in older adults. This suggests that obesity and the distribution of fat mass later in life may be key in the development of MS in older adults. Studies are needed to further examine these associations in older adults.

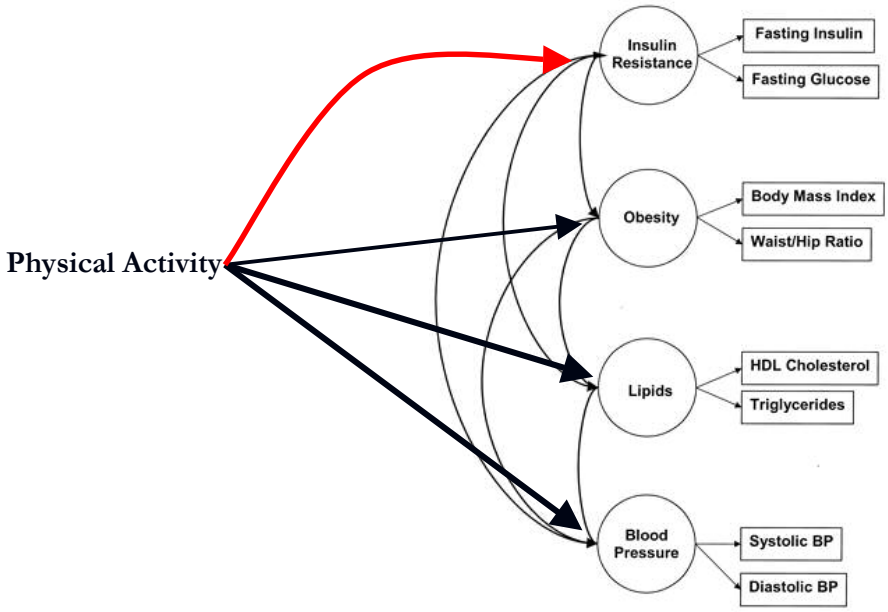
Some of the criticism of current criteria for MS revolves around the measurements of the specific factors. For instance, the cut-off for fasting glucose intolerance (>6.1 mmol/l) is reported to have very poor sensitivity (~10%) when compared to diagnosed diabetes, indicating that many individuals without insulin resistance could be inappropriately identified

as positive for that MS factor (Reaven 2005). Some clinicians and researchers support the use of an impaired glucose tolerance test (with a previous load of ingested glucose) to measure insulin sensitivity. (Tai, Goh et al. 2004). Also, the use of waist circumference as an indicator of obesity is arguable. There is marked variability within and between the person's taking the measurement, and Reaven, supporting the use of body mass index as a more practical measure of obesity, suggests that waist circumference is a burdensome measure for busy clinicians. Large epidemiologic studies show a very strong correlation ($r > 0.90$) between waist circumference and body mass index (Ford, Mokdad et al. 2003). However, from a prognostic viewpoint, the advantage to using waist circumference as an MS factor is the strong link between central adiposity and CHD/CVD (need ref). BMI is only an indicator of obesity, and cannot distinguish regional fat distribution.

Physical Activity and Metabolic Syndrome

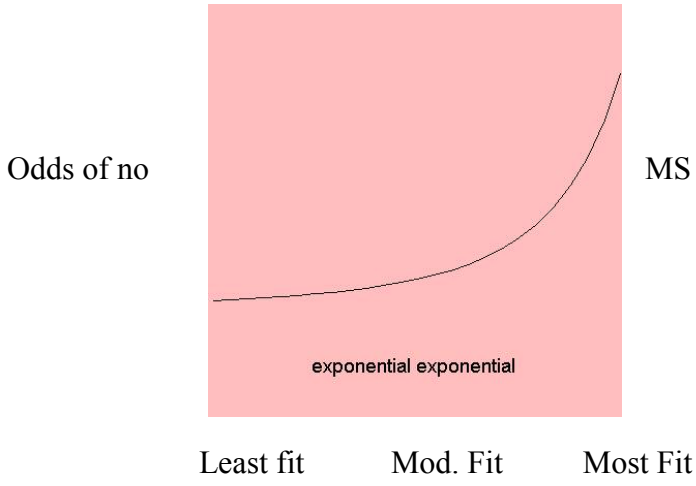
Physical activity (PA) as a preventative factor for CVD/CHD and related mortality is well established (Blair, Kampert et al. 1996) (Leon, Connett et al. 1987; Berlin and Colditz 1990). Increased levels of PA are also associated with reduced risk for type II diabetes (Simonsick, Lafferty et al. 1993; Wei, Gibbons et al. 1999), itself a risk factor for CVD (Reaven 1988). The association between PA and MS are not as clear, particularly when considering the optimal dose of PA for reversal, prevention, or delay of MS status. This is in part due to the differing dose response associations seen with PA and the individual MS factors. For instance, there is clear, linear dose-response associations between PA and dyslipidemia, and obesity (Kraus, Houmard et al. 2002) (Slentz, Duscha et al. 2004); however, the dose-response association between PA and impaired glucose tolerance (Houmard, Tanner et al. 2004) and blood pressure is reported to have a curvilinear form, with

a threshold for benefit at moderate doses (Ishikawa-Takata, Ohta et al. 2003). The known dose response associations between PA and individual MS factors are shown below.



The black arrows represent linear dose-response associations. In other words increasing volume and/or intensity of PA above and beyond current recommendations (150 minutes/week moderate intensity PA) (U.S. Department of Health and Human Services 1996)confers even greater response in lowered blood pressure, improved lipid profiles, and weight loss (MSSE dose-response supplement). However, Houmard (Houmard, Tanner et al. 2004) demonstrated that doses of PA above and beyond current recommendations did not result in greater sensitivity to insulin (red arrow), indicating moderate doses of PA are equally beneficial to higher doses. The differing dose-response associations between MS factors and PA present a unique challenge when studying the factors in a clustered fashion. How do these factors interact when observing their combined response to differing doses of PA? To date this question remains unanswered. General PA and MS associations have been reported in the literature. The epidemiologic data will be presented first, followed by interventions.

Several studies examining the associations between PA and MS have been published using the Aerobic Center Longitudinal Study (ACLS) data at the Cooper Clinic. It is important to note that these studies used middle-aged men and women of higher socio-economic status, thus not necessarily generalizeable to older adults. In cross-sectional analyses, Whaley (Whaley, Kambert et al. 1999) found that men in the lowest category of aerobic fitness (a by-product of regular PA) were ten times more likely to have MS compared to the highest fit group. The comparison between the least and moderately fit groups produced an odds ratio of 3.0. The large increase in odds of MS moving from the moderately to most fit groups could suggest a curvilinear association with a functional shape of the relationship resembling an exponential dose-response curve seen below.



The associations were not the same in women, with odds of MS comparing least fit to moderately and most fit at 2.7 and 4.9, respectively. These associations resemble a spaced, linear association between PA and MS. The role that gender plays in modifying the PA and MS relationship needs further examination. In a similar examination of the ACLS data in men only, Jurca et al. (Jurca, Lamonte et al. 2004) examined the potential modifying role of

muscle strength between the PA and MS association. They found muscular strength added to the protective effect of aerobic fitness in men with low and moderate fitness levels, indicating that engaging in strength training and even low levels of aerobic training can lower risk of MS in middle-aged men. The cross-sectional nature of these data cannot determine temporality, however. For example, it is plausible that having the factors of MS led to reduced levels of PA and subsequent low fitness levels in these men. Using prospective data from the ACLS, Katzmarzyk (Katzmarzyk, Church et al. 2004) reported that middle-aged men with MS were 30% more likely than healthy men to die of all causes before adjustment for fitness levels (Odds ratio=1.29), whereas after adjustment the association was non-significant (Odds ratio=0.98). Katzmarzyk also found a significant dose-response association between increasing fitness levels and reduced risk of CVD and all-cause mortality in men with MS at baseline. This indicates that, in men with MS, being moderately active can reduce the risk of death significantly, and engaging in higher levels of PA confers an even greater protective effect. In a similar study, Katzmarzyk studied the influence of obesity on the above mentioned associations (Katzmarzyk, Church et al. 2005). He found obesity levels, as determined by BMI, to have no added value in predicting mortality in men with MS. Since MS already has a measure of obesity (waist circumference), it is possible that adding BMI to the model added no further information due to the strong association between the two measures. Fitness persisted as a significant protective factor in this analysis, regardless of baseline MS status. The ACLS study adds a significant amount of information regarding the inter-relationships between MS, PA and mortality. Specifically, increasing levels of PA are associated with reduced prevalence of MS; however, not necessarily in a linear fashion. Very similar conclusions have been drawn in different middle-aged cohort studies (Carroll, Cooke

et al. 2000) (Ford, Kohl et al. 2005) (Rennie, McCarthy et al. 2003). Additionally, middle-aged men who regularly engage in strength training, but not necessarily endurance training, are less likely to have MS compared to men who do not participate in a regular program of strengthening. Lastly, middle aged men who are diagnosed with MS and engage in moderate to high levels of PA have substantially reduced risk of mortality compared to those who are sedentary. Of course epidemiologic data is subject to bias, confounding and temporality issues that randomized clinical trials can eliminate.

In the earliest such clinical trial found in the literature, Torjesen et al. (Torjesen, Hjermann et al. 1997) reported on the effect of a twelve-month endurance exercise intervention on individual MS factors in middle-aged adults. They showed a significant improvement in blood pressure and triglycerides with the exercise intervention, but no improvement in fasting glucose, BMI, and HDL cholesterol. Interestingly, another trial arm that participated in an exercise + diet intervention showed significant improvements in all MS factors. It was not reported what proportion of the participants, if any, had MS at baseline or how MS status was changed over the one year intervention.

Katzmarzyk and colleagues (Katzmarzyk, Leon et al. 2003) were the first to report the impact of exercise training on MS status in middle-aged adults. Reporting data from the Heritage study (621 white and black participants), they found that 20 weeks of three days per week aerobic training reduced the proportion of MS by approximately 30% in all subgroups (men/women; black/white). The MS factors most susceptible to change were triglycerides (43% improved this factor), blood pressure (38%), waist circumference (28%), HLD cholesterol (16%) and serum glucose (9%). This large intervention study demonstrated the efficacy of moderate-intensity (55-75% VO2max) aerobic training in reversing MS status in

otherwise healthy adults. Interestingly, serum glucose, the MS factor most closely tied to insulin resistance, which is postulated to be the underlying cause of MS, was least likely to be affected by the aerobic based intervention.

Based on the basic science evidence showing muscle strength as a potent means to improve muscle glucose uptake (Cartee 1994), Castaneda et al. tested the effect of 16 weeks of strength training on MS factors in older (mean age=66 years), Latino men and women with diabetes. This population was studied because Latinos have double the rate of diabetes compared to whites. Sixteen weeks of high resistance strength training produced improved systolic blood pressure, muscle glycogen stores (an indirect measure of insulin sensitivity), and lean mass and fat mass. This study indicated that strength training is a viable means of affecting not only glucose levels as an MS factor, but also blood pressure and obesity MS factors. This study adds to the previously mentioned study of Jurca et al. (Jurca, Lamonte et al. 2004), who reported associations between increased muscle strength and reduced MS prevalence.

Stewart conducted a 26-week exercise training study, with a strength training component, in older adults with elevated blood pressure (Stewart, Bacher et al. 2005). Individual MS factors and MS status were examined as outcome measures. At follow-up, there was a strong suggestion that the exercise group had reduced proportions of MS status compared to the control group (P=0.06). Also of interest was that, while strength and endurance improved significantly in the exercise group, the changes in individual MS factors were more strongly associated with changes in improved body fat and lean tissue measures in the exercise group (and blood glucose was not affected by the intervention). These results support the findings of Goodpastor (Goodpastor, Krishnaswami et al. 2005), who reported

body fat and its distribution to be strongly associated with MS status in older adults. Also, in a very recent clinical trial, Orchard found obesity (waist circumference) to be the MS factor most prevalent in older adults (>60 y.o.), and most likely to be attenuated by long-term PA intervention (three-years), which significantly lowered the risk of incident MS compared to metformin therapy and control groups.

In summary, there is epidemiologic evidence linking low levels of PA to higher prevalence and incidence of MS. Most interventions aimed at MS were in middle-aged adults or focused on individual MS factors rather than on attenuating MS status. PA interventions focused on older adults with MS report a strong association between changes in body composition and change in MS status with negligible changes in blood glucose levels, suggesting that 1) reduced insulin sensitivity may not be the common denominator driving MS in older adults, but body composition may be the driving factor, 2) Those factors that have linear associations with PA levels (blood pressure, HDL cholesterol, triglycerides, and obesity) may be more susceptible to change than glucose levels, which has a reported curvilinear association with PA. This could indicate that levels of PA above and beyond moderate levels may provide additional protective effects against the progression of development of MS in older adults. In fact, Whaley's data suggests an exponential type association between increasing levels of PA and reduced risk of MS. This review of literature provides further justification for studies examining the specific PA dose-MS response associations in older adults.

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APPENDIX B. Frailty Review of Literature

Frailty

As aging occurs there is a physiologic loss of the capacity of the body and its systems. While these losses are extremely heterogeneous and variable, all the available modern medicine and technology cannot stop some of the aging-related departures from our twenty year old bodies. The crux of gerontologic research for many decades has been in understanding why aging changes are so variable from one individual to the next. Why is it that one seventy year old is playing golf every day and enjoying retirement, while another seventy year old is struggling to maintain daily independence at home? Most, but not all, researchers focus there attention on the second seventy year old (or groups of similar people), and develop conceptual models to explain the accelerated loss in the body's functional capacity and reserves.

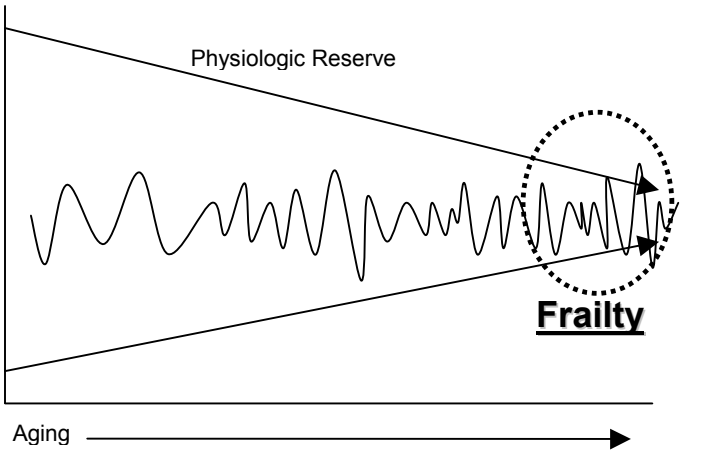
Geriatric clinicians have for many years tried to explain the pathways that lead to unsuccessful aging. The terms used for this concept have changed and morphed over the last twenty years. Earlier terms used were chronic sick, debilitated, incapacitated or functionally dependent (Hogan, MacKnight et al. 2003). Since these terms were first used to describe older adults with seemingly accelerated aging processes, the clinical and research communities have come together in an attempt to better describe a population of older adults who are on a "functional slippery slope." The first of these gatherings was the Task Force on the Frail Elderly, initiated by the Federal Council on Aging in 1974. The Task Force was charged with defining, characterizing and setting forth health policy guidelines for a group of

older adults who needed special attention by the medical community. The Task Force used the term "frail elderly" to identify a group of older adults who have physical debilities, emotional impairment, and debilitating physical and social environments (Tavani 1978). The purpose of identifying this special population of older adults was to develop services, care plans and case management in the health care systems. Interestingly, the reception to the Task Force's recommendation was met with criticism by the medical community, largely due to the overwhelming lack of evidence from which the recommendations were based.

Since the FCA's coining of the phrase "frail elderly" in the 1970s there has been a boom in research on frail older adults, albeit with numerous definitions and models of frailty. The MeSH heading "frail elderly" had 0 articles in the early 1980s and within fifteen years had grown to almost 800 articles using that MeSH term. Clearly there is interest in identifying and treating frail older adults, with the end purpose of making their lives better and preventing frailty in future populations of older adults.

This appendix will first introduce a conceptual model of frailty. In addition I will provide a review of frailty definitions and working models that have accumulated in the literature, synthesize the evidence for the use of the models in epidemiologic and clinical research, and discuss the advantages of distinguishing frailty from similar aging-related terms such as functional decline or disability.

Conceptualizing Frailty



The figure shown above provides a conceptual model of frailty, which is a result of decreased physiologic reserve and greater fluxuations in internal or environmental stressors (Fries 1980). When these fluxuations overtake physiologic reserve the individual could be considered impaired in that particular system. An example of this concept is demonstrated by considering that the fluxuations seen in the figure are daily walking habits of an individual. One of the physiologic systems needed to walk is strength, particularly in the lower body. Consider a loss of strength with aging (sarcopenia) to the point where the strength reserve needed to normally ambulate throughout the day is no longer sufficient. At this point the individual has an impairment in strength that places him/her at risk for mobility disability (a significant risk in the frail), and the individual would most likely adapt their behavior to compensate for the strength impairment, i.e. curtail mobility activities requiring sufficient strength reserves. This conceptual model is important to understand when further discussing the definitions and working models of frailty, which are detailed below.

Frailty Definitions

Three broad classes of frailty definitions have emerged from the literature over the last twenty years. These are 1) Dependency definitions, 2) Vulnerability definitions, and 3) Disease states definitions, as presented by the CIFA working group (Hogan, MacKnight et al. 2003). The importance of developing a working definition of frailty is its link between a conceptual and the working model. This is due to the fact that most well developed frailty definitions contain measurable aspects of the conceptual model that allow for structuring the methods of data collection for the working model. This definition link is where many of the above mentioned conceptual models fail to move beyond a theoretical concept to a working model in the clinical and research realm. For example, a biomedical/psychosocial model that states frailty occurs when medical, functional, and social dimensions become compromised may be conceptually sound, but a working definition of more specific medical, functional, and social constructs that should be measured is needed to put the model into use. As Rockwood states, "…the success of any definition of frailty will depend on it being useful to researchers and clinicians."(Rockwood 2005)

Definitions classes and their particular strengths and weaknesses will be discussed below. Specific examples within the three definition classes will be provided for further clarification. I will also discuss the importance of making a clear distinction between disability and frailty in this section of the paper.

Dependency Frailty Definitions

There are at least twelve definitions of frailty in the literature that are dependency driven. These definitions include a requirement of the frail individual to be dependent in one or more ADLs or IADLs, or to have an impairment in physical abilities that predispose him/her to disability. These definitions fit very well in the larger umbrella of functional

decline and are sometimes synonymous with functional limitations. This provides an initial opportunity for discussion on separating frailty from disability.

Dependency definitions for frailty inherently are very similar to disability definitions (also a term lacking in consensus of definition and measurement). For instance, Bowsher and colleagues(Bowsher, Bramlett et al. 1993)defined frailty as "…those over age 65 with one or more functional, cognitive or social impairments." Of course an impairment or inability to perform socially defined roles is the working definition of disability in the Nagi model (Nagi 1965). These overlaps are common in the frailty and disability literature and impede a clear understanding of either term. Risk factors common between frailty and disability in the literature are cognitive impairment, physical inactivity, smoking, social isolation, and comorbidities (Strawbridge, Shema et al. 1998; Stuck, Walthert et al. 1999). The working definition of frailty in this context is dependency driven and states frailty is "…involving problems or difficulties in two or more functional domains (physical, nutritive, cognitive, and sensory)." Similarly, disability is assumed to arise from functional decline, which is the outcome in exploring the above risk factors (Stuck, Walthert et al. 1999).

Perhaps the frailty/disability overlap is a result of researchers' liberal use of both terms, particularly disability. As stated previously, Nagi clearly defined disability as having a social component, thus moving beyond physical limitations to the interaction between these limitations and the individual's environment. The terms "mobility" or "functional" disability" are used in the literature with rather liberal definition (Chou and Chi 2005; Wang, Olson et al. 2005). Is difficulty in climbing stairs a disability? That question can only truly be answered on an individual basis. An older adult who resides in a first floor garden apartment may not feel disabled, while someone needing to climb twelve stairs to get to their bedroom

may feel disabled. That individual may be considered frail and susceptible to incident disability. However, difficulty or needing assistance with an ADL (bathing, dressing, toileting) may indeed infer disability, as ADL items are typically necessary for an individual to perform their normal role in society (Gill, Williams et al. 1995). Herein lies the distinction between frailty and disability, as frailty can be considered to be a "pre-disability" state before one loses independence in ADLs. In fact in a consensus paper written by leading researchers in frailty and disability (Fried, Ferrucci et al. 2004), it was clearly stated that frailty is a cause of disability, and that frailty should be defined and modeled without using disability items to assist in disentangling the two concepts. The current state of disability in the literature is that it is a process with multiple pathways(Jette 2003). Frailty can be considered a particular pathway to disability. Frail older adults are in fact more likely to become ADL disabled compared to non-frail older adults (Fried, Tangen et al. 2001).

For the purposes of this paper, frailty models with ADL dependency as a factor will not be discussed in depth, as these models capture a state of functional decline beyond frailty. For instance, Rockwood developed a frailty model referred to often in the literature (Rockwood, Stadnyk et al. 1999) and has very recently simplified his model for the clinician (Rockwood, Song et al. 2005); however, his frailty factors include overt disability (totally dependent on basic ADLs such as self-care and transferring). These individuals are severely disabled, and research indicates that this population would not respond to an intervention as favorably as the non-disabled (Ferrucci, Guralnik et al. 2004). However, focusing on identifying individuals who are in a pre-disabled state, and then intervening on those individuals, is an area in need of a focused effort (Fried, Ferrucci et al. 2004).

Vulnerability frailty definitions

The CIFA (Hogan, MacKnight et al. 2003) identified nineteen vulnerability definitions from the literature. Most of these definitions included the term "vulnerable" or "vulnerability/susceptibility" to functional loss, functional decline, environmental challenges, or disease. The mechanism responsible for this vulnerability is often at the impairment level, or deficits in the body's systems. For example, Ferrucci defined frailty as, "a pathologic condition that results in a constellation of signs and symptoms and is characterized by high *susceptibility*, impending decline in physical function and high risk of death." The quantity of research in the systems area lends these definitions to a general acceptance of their validity. Moreover, this class of definitions fits very well with the concurrent deficits in systems models described previously, and the result is well-constructed and measurable working models of frailty (discussed in detail below). There is still, however, a considerable amount of disagreement as to which model is superior in predicting poor health outcomes.

Disease states frailty definitions

The third and final definition class is disease states. This class is the least researched in the frailty literature, partly due to a preponderance of evidence in the broader medical literature that clearly establishes the link between disease and poor health outcomes. Researchers have established that disease is certainly a contributing factor to frailty (Newman, Gottdiener et al. 2001), particularly when severity (symptoms) of disease or concurrent diseases is considered. It is my opinion that disease states definitions are too restrictive, as not all diseases or even multiple diseases lead to frailty and subsequent decline. The sensitivity and specificity of these definitions alone are questionable, but certainly should be considered when considering a broader definition of frailty.

Working models of frailty

The working models of frailty are what allow clinicians and researchers to move from a theoretical model, to defining a population, to collecting information or intervening on that population using the working model. There are numerous working models of frailty in the literature, and their ability to detect individuals at risk for poor health outcomes vary greatly. The advantages and disadvantages of using these working models in epidemiologic and clinical research will be discussed in this section. Because of the inability to determine specifics of the model and its criteria, working frailty models in abstract form will not be discussed

Some of the first studies with working models of frailty were the FICSIT (Frailty and Injuries: Cooperative Studies of Intervention Techniques) studies, which were very well-designed and carried out collaborative studies. The working definition of frailty in these studies was "severely impaired strength, mobility, balance, and endurance." (Ory, Schechtman et al. 1993)Because each site targeted and recruited different populations for their interventions, the inclusion criteria varied from site to site. However a meta-analysis of the studies allowed for a cross-sectional snapshot of inclusion criteria and a "thematic" working model of frailty from similarities seen across studies. Five criteria for a working model of frailty appeared in the FICSIT studies. These criteria were 1) age ~75 y.o. 2) Community dwelling 3) Ambulatory (i.e. able to ambulate around the home) 4) history of/or risk for falls 5) no illnesses with impending, steep functional decline (i.e. Parkinson's, severe dementia, crippling arthritis) (Judge, Schechtman et al. 1996). When analyzing the pooled data from all studies, the use of the FICSIT model to identify frail elders who would most benefit from interventions resulted in reduced falls risk of 17% with balance training and

10% with exercise training (of varying modalities and intensities) (Province, Hadley et al. 1995). An interesting observation is that the five criteria listed represent a broad theoretical model spectrum. Of the theoretical models discussed previously, the aging model, concurrent systems model, biomedical/psychosocial model, and primary pathways model are represented in the FICSIT working model. The FICSIT studies demonstrate, at a relatively early stage in frailty research, that the strength of combining multiple theoretical models to develop a working frailty model are quite effective in affecting a multi-dimensional outcome such as falls.

Developed at about the same time as the FICSIT model was the model by Winograd and colleagues (Winograd, Gerety et al. 1991). The purpose of their model was to evaluate older, hospitalized adults for frailty and to refer these frail patients to a comprehensive geriatric evaluation clinic. Their working model for frailty included prevalence of one of a variety of illnesses, limitations, or functional deficits (physical and cognitive). After one year the frail group had increased length of stay at the hospital, nursing home admissions, and mortality compared to the independent group. The authors concluded that "geriatric syndromes" are of more utility than specific diagnoses for screening older adults for adverse outcomes. The underlying issues with this model are that most of the syndromes referred to are clinically detectable and are, in most cases, affecting an older adult who has already become disabled (i.e. prolonged bed-rest, pressure sores, dependence in ADLs). Similar to the Geriatric Evaluation and Management trials criteria (Cohen, Feussner et al. 2002), this specific model identifies older individuals who are beyond pre-clinically frail.

Because of the amount of literature on sarcopenia as a primary pathway to frailty, several investigators have advanced this concept to a working model of frailty. For instance,

knee extensor strength predicted four year mortality rates in community–dwelling older adults aged 75 and up (Laukkanen, Heikkinen et al. 1995). These investigators suggest that maximal isometric knee extensor force of less than ~27 kg (~60 lbs.) is a meaningful cut point for concern. Handgrip strength has also been shown to predict incident disability in older men. One study found that a handgrip strength measure of less than 30 kg in men greater than 77 years can be considered criteria for frailty and predictive of future disability (Giampaoli, Ferrucci et al. 1999). A low handgrip strength measure *in midlife* (<37 kg) is also predictive of future mobility limitations and ADL disability (Rantanen, Guralnik et al. 1999). This suggests that perhaps strength (or sarcopenia) is better conceptualized as a life course model (long-term disuse) in explaining frailty rather than a primary pathways model. Exercise advocates would undoubtedly agree with this notion.

Weight loss has been suggested as a primary pathways model of frailty. A 5% weight loss over three years was predictive of mortality in a group of community-dwelling older adults. Similarly, a low weight at baseline was also predictive of mortality (Newman, Yanez et al. 2001). Along similar lines, a low BMI has also been examined as a single frailty factor. A BMI less than 23 is one threshold point that has shown to be predictive of higher mortality in older adults (Deschamps, Astier et al. 2002). Weight loss as a stand-alone frailty factor is questionable as are most primary pathways models. Chin A Paw has used BMI or unintentional weight loss as factors in several frailty models (discussed below).

Owens and colleagues developed a seven-item model to detect frailty in older adults (75+) who were presenting to emergency rooms for treatment. Poor cognition, impaired mobility (unable to walk to across room), >6 lbs. weight loss in past year, four or more medications, overnight hospitalization in past 30 days, and age over 85 years old were

individually considered frailty factors and would thus initiate a consult by a geriatric pharmacist (Owens, Fretwell et al. 1994). Almost nine out of ten patients admitted to the hospital from the ER, over age 75, were positive for one of the frailty factors. This model is the only one to include multiple medications as frailty factor. It would be interesting to study the relevant strengths and weaknesses of multiple medications vs. multiple morbidities as frailty factors.

A relatively small study used balance and strength measures to delineate between frail and non-frail (as determined by the WHO functional capacity score) (Dayhoff, Suhrheinrich et al. 1998) . The results indicated that a postural sway measure with eyes closed on a compliant surface dorsiflexor strength were predictive of frailty in this group of community dwellers (mean age = 74). Specifically, cut –off scores were a sway score of 30% (using Smart Balance Master scoring) and a peak dorsiflexion force of ~ 40 pounds. These cut-points identified frail individuals 67% of the time and identified non-frail individuals 64% of the time. The sensitivity and specificity of these measures are quite good given the small sample size in the study. It appears that balance and strength may play key roles in working frailty models.

In a large study (6,928 persons) using data from the Alameda County Study (Strawbridge, Shema et al. 1998), Strawbridge identified a frailty model from four broad domains---physical functioning, nutritive functioning, cognitive functioning, and sensory functioning. Individual physical functioning items within the physical functioning domain were sudden loss of balance, weakness in arms or legs, and dizziness when standing up. Nutritive items were loss of appetite and unexplained weight loss. Cognitive functioning items were attentiveness, memory, forgetfulness, and speech recall. Finally, sensory items

consisted of visual and hearing loss. If an individual reported “often” or “very often” having problems in the last 12 months in any of the items, then the domain from which it represented was also classified as a positive frailty domain. If two domains were positive then that individual was classified as frail. In cross-sectional analyses, frailty was associated with decreases social activities (eating out, visiting friends), decreases life satisfaction, and poorer mental health and well-being. The major concern with this frailty model revolves around all the issues of self-report to determine frailty factors.

Stressing the importance of physical inactivity in the progression of functional decline, Chin A Paw (Chin A Paw, Dekker et al. 1999) developed and compared three frailty models, all with physical inactivity as a primary frailty factor, in predicting functional decline and mortality in older, community-dwelling, Dutch men. The three working frailty models were physical inactivity (<210 min/week + low energy intake (<7.6 MJ/day), physical inactivity + weight loss (>9 lbs. in last 5 years), and physical inactivity + low BMI (<23.5). The model that best predicted functional decline (incident dependency in ADLs) and mortality was physical inactivity and 5 yr. weight loss. The authors recognized that a 5 year weight loss measure may not be as sensitive as a one year measure, but the physical inactivity/weight loss frailty model had significant odds ratios nonetheless (OR of 4-5 for decline and mortality).

Chin A Paw later used this model to identify frail older adults with targeted exercise programs and nutritional supplementation. Two separate interventions aimed at improving physical function and well-being, respectively, in frail older adults (Chin A Paw, de Jong et al. 2002; Chin A Paw, de Jong et al. 2002). Interestingly, these two interventions used involuntary weight loss *or* low BMI (<25) in conjunction with physical inactivity to define

frailty. It is possible that the model was broadened to include more older adults in the study and reach a target number of participants not possible with just a 9 pound weight loss criterion. In the population used to develop their model, only 6% were identified as fitting the criterion of involuntary weight loss, however, by adding low BMI as an additional factor in the model, the percent frail doubled to 12%. This raises an issue when targeting frail older adults for an intervention using a CSV model, as prevalence rates of frailty using the model may be low (4-7%) and recruitment and sample size become issues. However, how does one balance using a scientifically grounded working model with tweaking the model to cast a wider net when conducting intervention trials?

Gill and colleagues developed a model in 1999 to predict incident functional dependence in community-dwelling older adults independent in ADLs at baseline (Gill, Williams et al. 1999). Frailty factors were defined as a fast gait speed <0.60 m/s, MMSE score <24, and age >85 years. In just one year ADL dependence developed in 40% of the frail group, compared to 7% in the non-frail group. However, in a validation group with similar baseline characteristics, only 28% of the frail group became disabled at one year, compared with 5% in the non-frail group.

Several years later Gill revised his frailty model to include only two factors, both physical performance measures, to identify frail older adults to participate in two separate home exercise intervention trials (Gill, Baker et al. 2002; Gill, Baker et al. 2003). In these trials Gill identified frailty by a fast gait speed of $\leq$0.60 m/sec (same as above) and inability to rise from a chair without arm assistance. Pre-frailty was identified by one of these factors being present. The interventions were affective in reducing functional decline over time, but

the impact of the intervention on the individual frailty factors (i.e. gait speed, chair rise score) was not reported. Thus it is not known how the exercise intervention affected frailty status.

Brown used scores from the modified physical performance test (PPT) to trichotomize community-dwelling older adults into not frail, mildly frail, and moderately frail groups (Brown, Sinacore et al. 2000). The splits in scores were determined as 32-26 not frail, 25-31 mildly frail, and 17-24 moderately frail. The moderately frail group had a fast gait speed of 1.00 m/sec, which is a velocity of concern for a normal gait speed (MJ Peterson (Abstract), Gerontologist, Nov. 2004). The moderately frail group also had poor balance as measured by the Berg balance test and a full tandem stand (mean time was 1.9 sec.). Brown later conducted a three-month randomized trial of exercise vs. home flexibility training in mildly frail groups (Brown, Sinacore et al. 2000). The exercise group had significant changes in PPT scores (29 to 31), compared to the home group who remained unchanged (29 to 29). Interestingly, on average the exercise group approached the not frail category by the end of the short intervention period. Long term sustained effects of the intervention were not reported.

Using a large, nationally representative sample of men and women (65+) from the Cardiovascular Health Study, Fried proposed a frailty "phenotype," an interaction between genetic and environmental factors that predispose functional decline (Fried, Tangen et al. 2001). Fried's model included five characteristics, 1) unintentional weight loss (>10 lbs. lost unintentionally in previous year), 2) poor endurance/ exhaustion (self-report from two items on CES-D), 3) slowness (gait velocity $\leq$0.65 m/s if ht. <173 cm.; $\leq$0.76 m/s if ht. >173 cm.), weakness (lowest 20% in sex and BMI adjusted grip strength) and, 5) low physical activity: (kcal expenditure/week from CHAMPS questionnaire; men <383 kcals/week, women <270

kcals/week). Presence of three or more factors constituted frailty, and presence of one or two factors deemed that individual as intermediate frail. Compared to the not frail group, intermediate frail and frail groups were more likely to fall, have worsening mobility, worsening ADL disability, be hospitalized, and die over three and seven years. A couple potential issues with the Fried model are that physical inactivity, weakness, and slowness are distribution dependent (i.e. 20^{th} percentile for that group). Using these cut-offs in sub-populations (oldest-old, minorities, low SES) may be difficult. Also, a fairly high prevalence of disability (~37%) was reported in the Cardiovascular Health Study cohort. A more precise model of frailty may have been developed by excluding those with disability at baseline, as Fried's frailty factors were developed using individuals further along the functional decline continuum.

Following Fried's research, we recently developed a proxy model to Fried's to determine the efficacy of a six-month telephone exercise counseling in affecting the frailty status of older veterans (Peterson, Sloane et al. In process). We substituted a BMI of <18 for weight loss, lowest 20% in chair stands for grip strength, and lowest 20% in 6-minute walk for poor endurance. Using our proxy model, we found an 18% relative reduction in the proportion of frail compared to the control groups. The frailty factor that was most likely to determine frailty status at baseline and follow-up was chair stands (lower body strength). This supports the large body of literature that exists in showing sarcopenia as an important frailty factor. Low BMI was a poor substitute for weight loss in our study, as no participants had a BMI <18. Fried and colleagues have recently reported that obesity, as opposed to weight loss, may be a superior frailty factor and better predictive of functional decline

(Blaum, Xue et al. 2005). More prospective work is needed to support the use of obesity as a frailty factor.

Timonen used gait mobility and balance limitations (dizziness or difficulty in walking independently) as frailty factors to target women hospitalized for acute illness for a post-hospitalization rehabilitation program(Timonen, Rantanen et al. 2002). Baseline maximal gait speed averaged near 0.80 m/s in both groups; however, after 3-months the exercise group had a mean increase in gait speed of 0.12 m/sec where the control group had no change. This intervention showed that the frailty factor can be affected by a targeted program of lower extremity strengthening and functional training (chair stands). The frailty factors were somewhat subjective in the study as difficulty with mobility was not defined, and an objective measure (timed gait speed) was not utilized.

Summary

Almost thirty years of research has resulted in many lines of thought on frailty and how it should be measured. Investigators in this area recently have convened to summarize the vast frailty literature and to make recommendations on defining frailty and designing trials aimed at frail older adults (Ferrucci, Guralnik et al. 2004). Interestingly, the end product of these consensus groups often results in more questions than answers. Needs for future research include continuing to develop a working model of frailty and the factors that should be included. Based one reviewing the models in existence and on consensus group opinion, physical factors should be measured with objective performance tests. The optimal measures of cognition and social factors remain unknown and in need of further study. Frailty investigators from varying disciplines need further collaboration to take advantage of the frailty knowledge that has accumulated in the fields of basic medicine, biostatistics,

applied physiology and geriatric medicine. Continued multi-disciplinary work will advance the taxonomy of frailty, with the end result of improving quality of life of the frail older adult.

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APPENDIX C. Secondary Analyses

Stability of Physical Activity Levels over Time

Secondary, exploratory analyses were conducted within the construct of this study, primarily for learning purposes compulsory with a dissertation project. First, stability and reliability of physical activity across time was tested using an intraclass correlation coefficient (ICC) test from all available waves for each participant. Because of the dramatic change in the format of the Health ABC physical activity questionnaire from year to year, the weekly time spent in physical activity (time spent walking of any intensity) was the only consistent variable collected at multiple time points (Years one, two, three and five). Results from this analyses indicated that there is a great deal of variability within individuals from year to year in their weekly time spent walking as a physical activity. The ICC value of 0.36 demonstrates a weak to moderate degree of stability in these older individuals walking patterns throughout their seventh decade. Further analyses with general linear modeling revealed that as a group, time spent walking steadily declined over time from an average of 138 minutes at baseline, to 128 minutes at year two, down to 100 minutes per week at year five. The drop in average time spent walking during the week from year one to year five (~38 minutes) was statistically significant ($P<0.05$). These results indicate that there is a substantial degree of variability within older individuals in their yearly physical activity patterns and that, on average, physical activity levels decline significantly over several years in older adults.

Homogeneity of Physical Activity Effects between Baseline Strata

We also wanted to determine if physical activity affected subsequent metabolic syndrome and frailty differently between those with and without the respective conditions at baseline. This information could be of significant public health interest if it is found that physical activity has differing effects on those with and without these conditions. To test this, a weight odds ratio was calculated by considering the size of the effect estimates in relation to the standard errors of the estimates in both strata. The equation to calculate the weight odds ratio is as follows:

$$\frac{\text{Beta}_1(1/\text{s.e.}_1) + \text{Beta}_2(1/\text{s.e.}_2)}{1/(\text{s.e.}_1)^2 + 1/(\text{s.e.}_2)^2}$$

With a variance of:

$$1/(1/\text{s.e.}_1)^2 + (1/\text{s.e.}_2)^2$$

From this information a 95% confidence interval is calculated for the weight odds ratio. Finally, to test for homogeneity of the effects a mantel-haentzel chi-square statistic is calculated and tested on one degree of freedom. This is synonymous with methods common in meta-analysis to determine homogeneity of effects sizes from multiple studies. If the chi-square statistic is significant (>3.84) then we must assume heterogeneity between the strata, indicating that physical activity has differing effects on long-term metabolic syndrome or frailty status in those with the condition. The tables below provide the weighted odds ratios and the test for homogeneity of the effects.

Table 1. Weighted odds ratios for incident metabolic syndrome in those with and without the condition at baseline.

	Weighted OR	95%CI	Test for homogeneity
	Men		
Time			
Low Dose	1.44	1.10-1.89	Yes
Recommended Dose	0.68	0.44-1.03	Yes
High Dose	1.00	reference	
Intensity			
Sedentary Dose	1.28	0.91-1.80	Yes
Light Dose	1.25	0.93-1.67	Yes
Moderate Dose	0.84	0.64-1.09	Yes
Vigorous Dose	1.00	reference	
Activity Types			
Sedentary	1.15	0.84-1.57	Yes
Lifestyle active	1.04	0.83-1.30	Yes
Exercise active	1.00	reference	
	Women		
Time			
Low Dose	0.95	0.74-1.23	Yes
Recommended Dose	0.93	0.62-1.39	Yes
High Dose	1.00	reference	
Intensity			
Sedentary Dose	0.82	0.57-1.18	Yes
Light Dose	0.81	0.64-1.03	No
Moderate Dose	1.17	0.84-1.63	Yes
Vigorous Dose	1.00	reference	
Activity Types			
Sedentary	0.73	0.54-0.97	Yes
Lifestyle active	1.11	0.90-1.38	Yes
Exercise active	1.00	reference	

Yes=homogeneity; No=heterogeneity

Table 2. Weighted odds ratios for incident frailty in those with and without the condition at baseline.

	Weighted OR	95%CI	Test for homogeneity
Time			
Low Dose	0.99	0.97-1.01	Yes
Recommended Dose	0.98	0.94-1.02	Yes
High Dose	1.00	reference	
Intensity			
Sedentary Dose	0.99	0.96-1.03	Yes
Light Dose	0.99	0.96-1.02	Yes
Moderate Dose	0.99	0.96-1.02	Yes
Vigorous Dose	1.00	reference	
Activity Types			
Sedentary	1.03	1.00-1.07	Yes
Lifestyle active	1.00	0.98-1.02	Yes
Exercise active	1.00	reference	

Yes=homogeneity; No=heterogeneity

In general the weighted odds ratios were very similar in magnitude and precision (95%CI) compared to the unweighted odds ratios presented in chapters two and three. The important finding in this analysis is the heterogeneity in the light intensity dose effect on metabolic syndrome in women with and without metabolic syndrome (Table 1). This indicates that light intensity doses were protective in healthy women from developing metabolic syndrome compared to vigorous intensity doses. These were the findings presented in chapter two. However, in women with metabolic syndrome at baseline, light intensity doses placed women at slightly higher risk for continuing to have metabolic syndrome at year six compared to vigorous intensity doses (OR=1.10). These results suggest that the status of metabolic syndrome may be an important determinant in the prescription of physical activity doses in women. Where higher intensity doses may be beneficial in reversing metabolic syndrome in those with it, and the same high intensity doses prescribed to an older woman

without metabolic syndrome may be inferior in effect to light intensity doses. Much work is needed to fully understand the differing effects of physical activity between disease states.

Volume of Physical Activity and Metabolic Syndrome/Frailty

Since volume of physical activity (PA volume) is a continuous variable (kcals/week), it was divided into quartiles, based on distribution, to allow for easier interpretation of the models. The quartiles were divided as follows:

Group 1: <25th percentile

Group 2: 25th-50th percentile

Group 3: 50th-75th percentile

Group 4 (referent group): >75th percentile

Table 3. Volume of physical activity by quartiles and subsequent metabolic syndrome in men and women.

	Odds Ratio	95% CI
Men (N=629)		
Quartile 1	0.83	0.48-1.42
Quartile 2	0.42	0.22-0.78
Quartile 3	0.83	0.49-1.43
Quartile 4	1.00	
P for trend	*0.19*	
Women (N=637)		
Quartile 1	0.48	0.27-0.84
Quartile 2	0.72	0.43-1.21
Quartile 3	0.80	0.48-1.33
Quartile 4	1.00	
P for trend	*0.01*	

In men, with the highest quartile as the referent group, the models indicated a U-shaped dose-response association between PA volume and incident metabolic syndrome. Men in the 25th-50th percentile range had an odds ratio of 0.42 (95%CI 0.22-0.78), indicating a significantly reduced odds of metabolic syndrome compared to men in the highest PA

volume group. Examination of the association between PA volume and metabolic syndrome within women showed that those in the lowest quartile had an odds ratio of 0.48 (95%CI 0.27-0.84) compared to women in the highest PA volume group. These findings are unexpected, as lower doses of PA volume have consistently been shown to be associated with higher rates of adverse health outcomes. Interim data in this cohort are needed to help explain these associations.

Table 4. Volume of physical activity by quartiles and any subsequent frailty over six years.

	Odds Ratio	95% CI
Quartile 1	1.85	1.44-2.38
Quartile 2	1.26	0.97-1.64
Quartile 3	1.09	0.84-1.42
Quartile 4	1.00	---------
P for trend	*<0.0001*	

Table 5. Volume of physical activity by quartiles and subsequent severe frailty over six years.

	Odds Ratio	95% CI
Quartile 1	1.11	0.10-12.6
Quartile 2	0.87	0.12-6.12
Quartile 3	1.01	0.24-4.29
Quartile 4	1.00	---------
P for trend	*0.83*	

PA volume had significant associations with the development of any frailty over six years (Table 4). First, those in the lowest quartile had significantly greater odds of frailty, with an 85% increased likelihood compared to the highest quartile (OR=1.85; 95%CI 1.44-2.38). There was also a dose-response association (P<0.0001) between increasing PA volume

and decreased likelihood of developing any frailty. Examination of PA volume and risk of developing severe frailty (Table 5) revealed no significant associations, indicating that PA volume did not predict subsequent severity of frailty over six years in this cohort.

Impact of Physical Activity on Individual Metabolic Syndrome Factors

Gender specific models were constructed to determine the physical activity categories' associations with the development of the five individual metabolic syndrome factors. The results displayed in Tables 6 and 7 indicate that overall there were few associations between physical activity doses and individual factors. Generally, in men, the lower doses of physical activities had higher odds of developing each factor compared to the highest doses, however the magnitude and precision of the odds ratios were unremarkable. There were two significant findings in men. First, those reporting low doses of time spent in physical activity were twice as likely to develop the waist circumference factor (OR=2.03; 95%CI 1.29-3.18), compared to the high time group. Second, men reporting low intensity physical activity doses were less likely to develop the fasting glucose factor compared to the vigorous intensity group (OR=0.53; 95%CI 0.29-0.97). The odds ratios in the intensity group when predicting development of a glucose factor were unlike any of the other dose-responses in men.

In women there were no significant findings (Table 7), however, dose-response associations in the intensity category when predicting development of elevated blood pressure as a factor does possibly provide insight into the significant findings in manuscript one, where light intensity doses were protective of metabolic syndrome compared to the vigorous intensity dose, and the highest incident factor at year six was blood pressure. These associations could have driven the significant findings detailed in manuscript one. Similarly, the dose response associations observed between the activity types and incident waist circumference factor resemble the findings seen when modeling the full metabolic syndrome incidence. These results indicate that, in women, it is possible that the association between

physical activity doses and one particularly prevalent metabolic syndrome factor could be responsible for the overall association between physical activity and metabolic syndrome. More work is needed to further explore this hypothesis.

Table 6. Baseline physical activity doses and incident metabolic syndrome factors in men.

Variable	Waist Circ.	Triglyc.	HDL	BP	Glucose
Time					
Low dose	**2.03 (1.29-3.18)**	1.08 (0.63-1.83)	1.09 (0.65-1.81)	1.08 (0.67-1.76)	1.14 (0.73-1.78)
Recommended dose	1.55 (0.71-3.38)	0.88 (0.34-2.29)	0.76 (0.29-1.96)	0.72 (0.33-1.56)	1.05 (0.48-2.32)
High dose	1.00	1.00	1.00	1.00	1.00
P for trend	*0.002*	*0.77*	*0.73*	*0.72*	*0.57*
Intensity					
Sedentary dose	1.15 (0.58-2.26)	1.34 (0.59-3.03)	1.35 (0.63-2.91)	1.35 (0.64-2.84)	0.72 (0.37-1.42)
Light dose	1.27 (0.71-2.27)	1.38 (0.67-2.82)	1.47 (0.75-2.88)	1.11 (0.59-2.10)	**0.53 (0.29-0.97)**
Moderate dose	1.31 (0.75-2.27)	1.19 (0.60-2.36)	0.99 (0.52-1.89)	1.06 (0.59-1.92)	0.82 (0.47-1.41)
Vigorous dose	1.00	1.00	1.00	1.00	1.00
P for trend	*0.69*	*0.40*	*0.23*	*0.44*	*0.12*
Activity types					
Sedentary	1.23 (0.65-2.32)	1.02 (0.48-2.17)	1.11 (0.52-2.38)	1.35 (0.66-2.76)	1.04 (0.56-1.94)
Lifestyle active	1.36 (0.87-2.13)	1.14 (0.66-1.96)	1.33 (0.79-2.23)	0.95 (0.59-1.55)	1.07 (0.68-1.69)
Exercise active	1.00	1.00	1.00	1.00	1.00
P for trend	*0.34*	*0.85*	*0.56*	*0.55*	*0.86*

*Adjusted for total kcals, age, percent body fat, gender, race, education, marital status, smoking status, drinking status, heart disease, and count of other diagnoses

Table 7. Baseline physical activity doses and incident metabolic syndrome factors in women.

Variable	Waist Circ.	Triglyc.	HDL	BP	Glucose
Time					
Low dose	1.01 (0.65-1.58)	0.78 (0.47-1.31)	0.83 (0.48-1.45)	1.05 (0.62-1.79)	1.60 (0.85-3.01)
Recommended dose	1.17 (0.55-2.51)	1.26 (0.56-2.87)	0.44 (0.12-1.56)	0.59 (0.26-1.34)	1.11 (0.34-3.60)
High dose	1.00	1.00	1.00	1.00	1.00
P for trend	*0.98*	*0.33*	*0.58*	*0.79*	*0.14*
Intensity					
Sedentary dose	1.27 (0.59-2.73)	0.90 (0.40-2.02)	0.72 (0.27-1.92)	0.44 (0.18-1.10)	1.35 (0.50-3.59)
Light dose	1.00 (0.56-1.79)	0.60 (0.32-1.10)	0.73 (0.38-1.41)	0.54 (0.26-1.12)	1.09 (0.53-2.26)
Moderate dose	0.98 (0.51-1.87)	0.71 (0.35-1.45)	0.97 (0.45-2.07)	0.55 (0.24-1.24)	1.06 (0.44-2.53)
Vigorous dose	1.00	1.00	1.00	1.00	1.00
P for trend	*0.63*	*0.37*	*0.30*	*0.08*	*0.62*
Activity types					
Sedentary	0.64 (0.33-1.24)	0.71 (0.32-1.56)	0.70 (0.31-1.60)	1.38 (0.65-2.93)	1.27 (0.54-2.96)
Lifestyle active	0.76 (0.45-1.26)	1.16 (0.65-2.06)	0.84 (0.46-1.55)	1.34 (0.76-2.35)	1.08 (0.54-2.14)
Exercise active	1.00	1.00	1.00	1.00	1.00
P for trend	*0.18*	*0.48*	*0.40*	*0.35*	*0.59*

*Adjusted for total kcals, age, percent body fat, gender, race, education, marital status, smoking status, drinking status, heart disease, and count of other diagnoses.

Reduced Models of Physical Activity and Subsequent Metabolic Syndrome/Frailty

Reduced models, via stepwise regression modeling, resulted in minimal differences from the fully adjusted models. Specifically, step-wise backward elimination was conducted, assessing whether dropping the variable of interest changed the main effect estimates by more than 10%. If the estimate did change by more than 10%, the variable was retained in the reduced model.

The models are provided below in Tables 8 through 11. Percent body fat was a confounder of the association between physical activity doses and incident metabolic syndrome in both genders. Additional confounders in men were education and age. In the frailty model number of diagnoses (comorbidities) was the only significant confounder of development of any frailty and transitioning to severe frailty

Table 8. Unadjusted, full adjusted, and reduced models of baseline physical activity and incident metabolic syndrome in men.

Variable	Unadjusted OR (95%CI)	Adjusted OR*(95% CI)	Reduced Model OR** (95%CI)
Time			
Low dose	1.92 (1.22-3.04)	1.67 (1.01-2.77)	1.64 (1.02-2.64)
Recommended dose	1.13 (0.47-2.75)	0.90 (0.35-2.31)	0.94 (0.37-2.38)
High dose	1.00	1.00	1.00
P for trend	*0.004*	*0.03*	*0.04*
Intensity			
Sedentary dose	1.76 (0.91-3.41)	2.00 (0.96-4.15)	1.76 (0.88-3.53)
Light dose	1.29 (0.71-2.34	1.39 (0.72-2.67)	1.28 (0.69-2.37)
Moderate dose	1.17 (0.65-2.11)	1.27 (0.68-2.39)	1.19 (0.65-2.20)
Vigorous dose	1.00	1.00	1.00
P for trend	*0.09*	*0.07*	*0.12*
Activity types			
Sedentary	1.49 (0.85-2.63)	1.46 (0.74-2.86)	1.33 (0.73-2.42)
Lifestyle active	1.37 (0.86-2.18)	1.33 (0.81-2.18)	1.32 (0.81-2.15)
Exercise active	1.00	1.00	1.00
P for trend	*0.13*	*0.19*	*0.30*

*Adjusted for total kcals, age, percent body fat, gender, race, education, marital status, smoking status, drinking status, heart disease, and count of other diagnoses.

**Adjusted for percent body fat, age and education.

Table 9. Unadjusted, full adjusted, and reduced models of baseline physical activity and incident metabolic syndrome in women.

Variable	Unadjusted OR (95%CI)	Adjusted OR* (95%CI)	Reduced Model OR** (95%CI)
Time			
Low dose	0.87 (0.58-1.30)	0.81 (0.51-1.27)	0.74 (0.49-1.13)
Recommended dose	0.53 (0.22-1.26)	0.63 (0.26-1.55)	0.56 (0.23-1.35)
High dose	1.00	1.00	1.00
P for trend	*0.57*	*0.25*	*0.20*
Intensity			
Sedentary dose	0.73 (0.38-1.42)	0.91 (0.44-1.88)	0.89 (0.45-1.78)
Light dose	0.47 (0.29-0.77)	0.48 (0.28-0.81)	0.48 (0.29-0.79)
Moderate dose	0.67 (0.37-1.21)	0.75 (0.40-1.39)	0.75 (0.41-1.38)
Vigorous dose	1.00	1.00	1.00
P for trend	*0.03*	*0.11*	*0.06*
Activity types			
Sedentary	0.53 (0.29-0.97)	0.55 (0.28-1.10)	0.55 (0.30-1.01)
Lifestyle active	0.90 (0.57-1.45)	0.84 (0.51-1.38)	0.81 (0.50-1.32)
Exercise active	1.00	1.00	1.00
P for trend	*0.04*	*0.08*	*0.05*

*Adjusted for total kcals, age, percent body fat, gender, race, education, marital status, smoking status, drinking status, heart disease, and count of other diagnoses.

**Adjusted for percent body fat.

Table 10. Unadjusted, full adjusted, and reduced models of baseline physical activity and development of any frailty.

	Unadjusted OR (95%CI)	Adjusted OR* (95%CI)	Reduced Model OR** (95%CI)
Time			
Low	1.25 (1.00 – 1.57)	0.99 (0.97 – 1.02)	1.02 (1.00-1.05)
Recommended	0.96 (0.62 – 1.48)	0.98 (0.94 – 1.03)	1.00 (0.96-1.04)
High	1.00	1.00	1.00
P for trend	*0.04*	*0.40*	*0.03*
Intensity			
Sedentary	1.14 (0.78 – 1.65)	1.01 (0.97 – 1.05)	1.03 (0.99-1.07)
Light	1.41 (1.06 – 1.88)	1.01 (0.99 – 1.04)	1.04 (1.02-1.07)
Moderate	0.88 (0.63 – 1.22)	0.99 (0.96 – 1.02)	1.00 (0.97-1.03)
Vigorous	1.00	1.00	1.00
P for trend	*0.02*	*0.26*	*0.002*
Activity Types			
Sedentary	1.92 (1.39 – 2.64)	1.04 (1.00 – 1.07)	1.08 (1.04-1.11)
Lifestyle active	1.38 (1.07 – 1.78)	1.00 (0.97 – 1.02)	1.03 (1.00-1.05)
Exercise active	1.00	1.00	1.00
P for trend	*<0.0001*	*0.08*	*<0.0001*

*Adjusted for test wave, total kcals, age, gender, race, education, marital status, smoking status, drinking status, waist circumference and count of diagnoses.

Table 11. Unadjusted, full adjusted, and reduced models of baseline physical activity and development of severe frailty.

	Unadjusted OR (95%CI)	Adjusted OR* (95%CI)	Reduced Model OR** (95%CI)
Time			
Low	0.88 (0.47 – 1.65)	0.96 (0.85 – 1.10)	1.00 (0.88-1.14)
Recommended	0.67 (0.23 – 1.94)	0.91 (0.75 – 1.11)	0.92 (0.75-1.13)
High	1.00	1.00	1.00
P for trend	*0.77*	*0.64*	*0.88*
Intensity			
Sedentary	2.83 (0.94 – 8.53)	1.23 (0.98 – 1.53)	1.23 (1.02-1.49)
Light	1.85 (0.77 – 4.45)	1.13 (0.96 – 1.34)	1.12 (0.98-1.29)
Moderate	1.23 (0.41 – 3.71)	1.05 (0.85 – 1.29)	1.04 (0.85-1.27)
Vigorous	1.00	1.00	1.00
P for trend	*0.06*	*0.06*	*0.03*
Activity Types			
Sedentary	2.67 (0.90 – 7.95)	1.24 (1.03 – 1.49)	1.24 (1.09-1.42)
Lifestyle active	2.37 (0.99 – 5.66)	1.19 (1.05 – 1.35)	1.19 (1.05-1.34)
Exercise active	1.00	1.00	1.00
P for trend	*0.09*	*0.02*	*0.01*

*Adjusted for test wave, total kcals, age, gender, race, education, marital status, smoking status, drinking status, waist circumference and count of diagnoses.

**Adjusted for count of diagnoses.

APPENDIX D: SAS PROGRAMS

Program for Metabolic Syndrome Analyses

```
OPTIONS PAGESIZE=50 LINESIZE=96 NODATE NONUMBER NOFMTERR;

*INITIATED 01-03-2006;
*UPDATED;

LIBNAME ABC V6 'C:\Documents and Settings\peter076\My
Documents\Dissertation\ABC DATA';
LIBNAME DEF V6 'C:\Documents and Settings\peter076\My
Documents\Dissertation\ABC DATA\FRAILTY';
RUN;



*IMPUTING MISSING VALUES HERE;

DATA MET1;
SET ABC.MS;

IF EDUC NOT IN(1,2,3) THEN EDUC=.;
IF EDUC =. THEN EDUC=3;
IF SMK1=. THEN SMK1=2;
IF CURDRNK1=. THEN CURDRNK1=1;
IF Y1PCBVD NOT IN(0,1,2) THEN Y1PCBVD=.;
IF Y1PCBVD=. THEN Y1PCBVD=0;
IF Y1PDIAB1 NOT IN(0,1) THEN Y1PDIAB1=.;
IF Y1PDIAB1=. THEN Y1PDIAB1=0;
IF Y1POAKN=. THEN Y1POAKN=0;
IF Y1POAHIP=. THEN Y1POAHIP=0;
IF Y1PHBP1 NOT IN(0,1,2) THEN Y1PHBP1=.;
IF Y1PHBP1=. THEN Y1PHBP1=0;
IF Y1PDEPR1 NOT IN(0,1,2,3) THEN Y1PDEPR1=.;
IF Y1PDEPR1=. THEN Y1PDEPR1=0;
IF Y1PPULCD NOT IN(0,1,2,3) THEN Y1PPULCD=.;
IF Y1PPULCD=. THEN Y1PPULCD=0;
IF TSMARSTA IN(0,2,3,4) THEN TSMARSTA=2;
IF Y1PCHD1 IN(1,2) THEN Y1PCHD1=1;
IF Y1PCHD1 NOT IN(0,1) THEN Y1PCHD1=.;
IF Y1PCHD1=. THEN Y1PCHD1=0;
IF Y1PPAD NOT IN(0,1) THEN Y1PPAD=.;
IF Y1PPAD=. THEN Y1PPAD=0;
RUN;
```

```
PROC MI DATA=MET1 OUT=IMPUT2 NIMPUTE=1 MINIMUM=0 MAXIMUM=1 NOPRINT;
VAR Y1PCHD1 Y1PPAD;
RUN;

DATA MET2;
MERGE MET1 IMPUT2;
BY HABCID;
RUN;


PROC LOGISTIC DATA=MET2;
OUTPUT OUT=OUTPUT P=PRED;
MODEL TSMARSTA=CV1AGE GENDER RACE EDUC SMK1
CURDRNK1 Y1PCHD1 Y1PCBVD Y1PPAD Y1PDIAB1 Y1POAKN Y1POAHIP Y1PHBP1 Y1PDEPR1
Y1PPULCD/
SELECTION=STEPWISE;
RUN;

DATA MARITAL;
SET OUTPUT;
IF TSMARSTA NOT IN(1,2) THEN NEWMAR=RANBIN(666,2,PRED);
ELSE NEWMAR=TSMARSTA;
RUN;

DATA MET3;
MERGE MET2 MARITAL;
BY HABCID;
IF NEWMAR=0 THEN NEWMAR=2;
RUN;


PROC FORMAT;

VALUE MINGROUP 1='LOW- 150 MIN/WEEK'
                        2='MOD- 150-200 MIN/WEEK'
                        3='XTRA- 200+ MIN/WEEK';

VALUE INTGROUP  0='ASEDENTARY'
                        1='LIGHT INTENSITY GROUP'
                        2='MODERATE INTENSITY GROUP'
                        3='VIGOROUS INTENTSITY GROUP';

VALUE BRACHGROUP 0='ASEDENTARY'
                                1='LIFESTYLE ACTIVE'
                                2='XERCISE ACTIVE';

RUN;

DATA CHECK1;
SET MET3;
IF Y1METSYN=1 THEN DELETE;
RUN;

DATA MET4;
SET MET3;
```

```
TOTMIN=Y1WKTIME+HIGHXMIN;
IF TOTMIN>=200 THEN MINGROUP=3;
IF 150<=TOTMIN<200 THEN MINGROUP=2;
IF TOTMIN<150 THEN MINGROUP=1;

DIFFWALK=Y6WKTIME-Y1WKTIME;
IF DIFFWALK<=-90 THEN WKGROUP=1;
IF DIFFWALK>-90 THEN WKGROUP=0;

IF Y6METSAB NOT IN(0,1) THEN DELETE;
IF Y6METSHD NOT IN(0,1) THEN DELETE;
IF Y6METSTG NOT IN(0,1) THEN DELETE;
IF Y6METSBP NOT IN(0,1)THEN DELETE;
IF Y6METSGL NOT IN(0,1) THEN DELETE;

IF Y1METSYN=1 THEN DELETE;

IF Y6METSAB +Y6METSHD+ Y6METSTG+ Y6METSBP+ Y6METSGL>=3 THEN Y6METS=1;
IF Y6METSAB+ Y6METSHD+ Y6METSTG+ Y6METSBP+ Y6METSGL<3 THEN Y6METS=0;

IF Y6METSAB +Y6METSHD+ Y6METSTG+ Y6METSBP+ Y6METSGL=0 THEN Y6NUMBER=0;
IF Y6METSAB +Y6METSHD+ Y6METSTG+ Y6METSBP+ Y6METSGL=1 THEN Y6NUMBER=1;
IF Y6METSAB +Y6METSHD+ Y6METSTG+ Y6METSBP+ Y6METSGL=2 THEN Y6NUMBER=2;
IF Y6METSAB +Y6METSHD+ Y6METSTG+ Y6METSBP+ Y6METSGL=3 THEN Y6NUMBER=3;
IF Y6METSAB +Y6METSHD+ Y6METSTG+ Y6METSBP+ Y6METSGL=4 THEN Y6NUMBER=4;
IF Y6METSAB +Y6METSHD+ Y6METSTG+ Y6METSBP+ Y6METSGL=5 THEN Y6NUMBER=5;

IF Y1METSAB+ Y1METSHD+ Y1METSTG+ Y1METSBP+ Y1METSGL=2 THEN METSRISK=2;
IF Y1METSAB+ Y1METSHD+ Y1METSTG+ Y1METSBP+ Y1METSGL=1 THEN METSRISK=1;

IF Y1METSAB=0 AND Y6METSAB=1 THEN CHANGEAB=1;
ELSE CHANGEAB=0;
IF Y1METSHD=0 AND Y6METSHD=1 THEN CHANGEHD=1;
ELSE CHANGEHD=0;
IF Y1METSTG=0 AND Y6METSTG=1 THEN CHANGETG=1;
ELSE CHANGETG=0;
IF Y1METSBP=0 AND Y6METSBP=1 THEN CHANGEBP=1;
ELSE CHANGEBP=0;
IF Y1METSGL=0 AND Y6METSGL=1 THEN CHANGEGL=1;
ELSE CHANGEGL=0;

GAITDIFF=SIXMPACE-Y16MPACE;

Y1OUTDRKK=FPPAKKWK*P2WTK;
Y1HEAVYKK=FPHCKKWK*P2WTK;
Y1HOUSEKK=FPLWKKWK*P2WTK;
Y1SHOPKK=FPGSKKWK*P2WTK;
Y1WASHKK=FPLDKKWK*P2WTK;
Y1STAIRSKK=FPFSKKWK*P2WTK;
Y1EXWLKKK=FPEWKKWK*P2WTK;
Y1NOEXWLKKK=FPOWKKWK*P2WTK;
Y1DANCEKK=FPACKKWK*P2WTK;
Y1LIFTKK=FPTRKKWK*P2WTK;
Y1MODEXKK=FPMIKKWK*P2WTK;
Y1PAYWRKKK=FPPWKKWK*P2WTK;
Y1VOLWRKKK=FPVWKKWK*P2WTK;
Y1CAREKK=FPCWKKWK*P2WTK;
```

```
Y1EXKK=EXKKWK*P2WTK;
TOTKCAL=TOTKKWK*P2WTK;
Y1LIFEKK=(HHKKWK+Y1WSKKWK+Y1WVCKKW)*P2WTK;
EXWLKKK=(FPEWKKWK+EXKKWK)*P2WTK;
IF Y1HEAVYKK+Y1STAIRSKK+Y1DANCEKK+Y1LIFTKK>=1000 THEN INTGROUP=3;
IF INTGROUP=3 THEN VIGGROUP=1;
IF Y1OUTDRKK+Y1EXWLKKK+Y1NOEXWLKKK+Y1MODEXKK>=1000 AND VIGGROUP=. THEN
INTGROUP=2;
IF INTGROUP=2 THEN MODGROUP=1;
IF Y1OUTDRKK+Y1EXWLKKK+Y1NOEXWLKKK+Y1MODEXKK<1000 AND VIGGROUP=1 THEN
INTGROUP=3;
IF Y1OUTDRKK+Y1EXWLKKK+Y1NOEXWLKKK+Y1MODEXKK>=1000 AND VIGGROUP=1 THEN
INTGROUP=3;
IF Y1HOUSEKK+Y1SHOPKK+Y1WASHKK+Y1PAYWRKKK+Y1VOLWRKKK+Y1CAREKK>=1000 AND
VIGGROUP=.
AND MODGROUP=. THEN INTGROUP=1;
IF Y1HOUSEKK+Y1SHOPKK+Y1WASHKK+Y1PAYWRKKK+Y1VOLWRKKK+Y1CAREKK>=1000 AND
VIGGROUP=.
AND MODGROUP=1 THEN INTGROUP=2;
IF Y1HOUSEKK+Y1SHOPKK+Y1WASHKK+Y1PAYWRKKK+Y1VOLWRKKK+Y1CAREKK>=1000 AND
VIGGROUP=1
THEN INTGROUP=3;
IF Y1HOUSEKK+Y1SHOPKK+Y1WASHKK+Y1PAYWRKKK+Y1VOLWRKKK+Y1CAREKK<1000 AND
VIGGROUP=1
THEN INTGROUP=3;
IF Y1HOUSEKK+Y1SHOPKK+Y1WASHKK+Y1PAYWRKKK+Y1VOLWRKKK+Y1CAREKK<1000 AND
MODGROUP=1
THEN INTGROUP=2;
IF Y1HEAVYKK+Y1STAIRSKK+Y1DANCEKK+Y1LIFTKK+
Y1OUTDRKK+Y1EXWLKKK+Y1NOEXWLKKK+
Y1MODEXKK+Y1HOUSEKK+Y1SHOPKK+Y1WASHKK+Y1PAYWRKKK+Y1VOLWRKKK+Y1CAREKK<1000
THEN INTGROUP=0;
IF EXWLKKK>=1000 THEN BRACHGROUP=2;
IF Y1LIFEKK>=2719 AND EXWLKKK<1000 THEN BRACHGROUP=1;
IF Y1LIFEKK<2719 AND EXWLKKK<1000 THEN BRACHGROUP=0;

IF MINGROUP IN (2,3) AND INTGROUP IN(2,3) THEN SUMGROUP=1;


FORMAT MINGROUP MINGROUP.;
FORMAT INTGROUP INTGROUP.;
FORMAT BRACHGROUP BRACHGROUP.;

RUN;


DATA METFINAL;
SET MET4;
IF CURDRNK1 IN(2,3) THEN CURDRNK1=2;
IF CURDRNK1 IN(4) THEN CURDRNK1=3;
IF SMK1 IN(1) THEN SMK1=4;
IF SMK1 IN(2) THEN SMK1=3;
IF Y1PCBVD IN(1,2) THEN Y1PCBVD=1;
IF Y1POAKN IN(1,2,3) THEN Y1POAKN=1;
IF Y1POAHIP IN(1,2,3) THEN Y1POAHIP=1;
IF Y1PDEPR1 IN(1,2,3) THEN Y1PDEPR1=1;
IF Y1PPULCD IN(1,2,3) THEN Y1PPULCD=1;
```

```
IF Y1PHBP1 IN(1,2) THEN Y1PHBP1=1;
IF Y1POAKN+Y1POAHIP=0 THEN LOWEROA=0;
ELSE LOWEROA=1;
COUNTDX=Y1PCBVD+LOWEROA+Y1PDEPR1+Y1PPULCD+Y1PPAD;
IF GENDER=1 AND TOTPF=. THEN TOTPF=28.3;
IF GENDER=2 AND TOTPF=. THEN TOTPF=39.9;
RUN;

PROC SORT DATA=METFINAL;
BY GENDER;
RUN;

PROC UNIVARIATE DATA=METFINAL;
BY GENDER;
VAR TOTPF;
RUN;

PROC MEANS DATA=METFINAL;
BY GENDER;
RUN;

PROC FREQ DATA=METFINAL;
BY GENDER;
TABLES MINGROUP INTGROUP BRACHGROUP;
RUN;

PROC FREQ DATA=METFINAL;
BY GENDER;
TABLES CV1AGE GENDER RACE EDUC NEWMAR SMK1 CURDRNK1 Y1PCHD1 Y1PCBVD Y1PPAD
Y1PDIAB1 LOWEROA Y1PHBP1 Y1PDEPR1 Y1PPULCD COUNTDX METSRISK Y6METSAB
Y6METSHD
Y6METSTG Y6METSBP Y6METSGL Y6METSYN Y6METS Y6NUMBER;
RUN;

PROC FREQ DATA=METFINAL;
BY GENDER;
TABLES CHANGEAB CHANGEHD CHANGETG CHANGEBP CHANGEGL;
RUN;

PROC FREQ DATA=METFINAL;
TABLES MINGROUP*Y6METS/CMH;
TABLES INTGROUP*Y6METS/CMH;
TABLES BRACHGROUP*Y6METS/CMH;
RUN;

*RUNNING LOGIT MODELS BY GENDER;

DATA MEN;
SET METFINAL;
IF GENDER=1;
RUN;

PROC FREQ DATA=MEN;
TABLES MINGROUP*Y6METS;
TABLES INTGROUP*Y6METS;
TABLES BRACHGROUP*Y6METS;
RUN;
```

```
*ALREADY LOOKED AT SATURATED MODELS. NOW NEED TO LOOK AT JUST PBF SINCE I
JUST ADDED IT IN
THE MODEL;

PROC LOGISTIC DATA=MEN DESCENDING;
MODEL Y6METS=TOTKCAL MINGROUP|TOTPF CV1AGE RACE EDUC NEWMAR SMK1 CURDRNK1
COUNTDX Y1PCHD1;
RUN;

PROC LOGISTIC DATA=MEN DESCENDING;
MODEL Y6METS= TOTKCAL INTGROUP|TOTPF CV1AGE RACE EDUC NEWMAR SMK1 CURDRNK1
COUNTDX Y1PCHD1;
RUN;

PROC LOGISTIC DATA=MEN DESCENDING;
MODEL Y6METS= TOTKCAL BRACHGROUP|TOTPF CV1AGE RACE EDUC NEWMAR SMK1
CURDRNK1 COUNTDX Y1PCHD1;
RUN;

*FINAL MODELS;

PROC LOGISTIC DATA=MEN DESCENDING;
CLASS MINGROUP;
MODEL Y6METS=MINGROUP TOTKCAL TOTPF CV1AGE RACE EDUC NEWMAR SMK1 CURDRNK1
COUNTDX Y1PCHD1;
RUN;

PROC LOGISTIC DATA=MEN DESCENDING;
CLASS INTGROUP;
MODEL Y6METS=INTGROUP TOTKCAL TOTPF CV1AGE RACE EDUC NEWMAR SMK1 CURDRNK1
COUNTDX Y1PCHD1;
RUN;

PROC LOGISTIC DATA=MEN DESCENDING;
CLASS BRACHGROUP;
MODEL Y6METS=BRACHGROUP TOTKCAL TOTPF CV1AGE RACE EDUC NEWMAR SMK1
CURDRNK1 COUNTDX Y1PCHD1;
RUN;

DATA WOMEN;
SET METFINAL;
IF GENDER=2;
IF Y6METSAB +Y6METSHD+ Y6METSTG+ Y6METSGL=0 THEN Y6WOBP=0;
IF Y6METSAB +Y6METSHD+ Y6METSTG+ Y6METSGL=1 THEN Y6WOBP=1;
IF Y6METSAB +Y6METSHD+ Y6METSTG+ Y6METSGL=2 THEN Y6WOBP=2;
IF Y6METSAB +Y6METSHD+ Y6METSTG+ Y6METSGL=3 THEN Y6WOBP=3;
IF Y6METSAB +Y6METSHD+ Y6METSTG+ Y6METSGL=4 THEN Y6WOBP=4;
IF Y6WOBP=>3 THEN Y6MSWOBP=1;
ELSE Y6MSWOBP=0;

RUN;

PROC FREQ DATA=WOMEN;
TABLES MINGROUP*Y6METS;
TABLES INTGROUP*Y6METS;
TABLES BRACHGROUP*Y6METS;
```

```
RUN;

PROC FREQ DATA=WOMEN;
TABLES MINGROUP*METSRISK/CMH;
TABLES INTGROUP*METSRISK/CMH;
TABLES BRACHGROUP*METSRISK/CMH;
RUN;

PROC FREQ DATA=WOMEN;
TABLES MINGROUP*METSRISK/CMH;
TABLES INTGROUP*METSRISK/CMH;
TABLES BRACHGROUP*METSRISK/CMH;
TABLES Y1PCHD1*BRACHGROUP/CMH;
TABLES Y1PCBVD*BRACHGROUP/CMH;
TABLES Y1PPAD*BRACHGROUP/CMH;
TABLES Y1PDIAB1*BRACHGROUP/CMH;
TABLES LOWEROA*BRACHGROUP/CMH;
TABLES Y1PHBP1*BRACHGROUP/CMH;
TABLES Y1PDEPR1*BRACHGROUP/CMH;
TABLES Y1PPULCD*BRACHGROUP/CMH;
TABLES COUNTDX*BRACHGROUP/CMH;
RUN;

DATA LIFTGUY;
SET MEN;
LIFTINT=Y1LIFTKK/(Y1HEAVYKK+Y1STAIRSKK+Y1DANCEKK+Y1LIFTKK);
LIFTBRACH=Y1LIFTKK/EXWLKKK;

RUN;

PROC MEANS DATA=LIFTGUY;
VAR LIFTINT LIFTBRACH;
RUN;

DATA LIFTGAL;
SET WOMEN;
LIFTINT=Y1LIFTKK/(Y1HEAVYKK+Y1STAIRSKK+Y1DANCEKK+Y1LIFTKK);
LIFTBRACH=Y1LIFTKK/EXWLKKK;

RUN;

PROC MEANS DATA=LIFTGAL;
VAR LIFTINT LIFTBRACH;
RUN;

*ALREADY LOOKED AT SATURATED MODELS. NOW NEED TO LOOK AT JUST PBF SINCE I
JUST ADDED IT IN
THE MODEL;

PROC LOGISTIC DATA=WOMEN DESCENDING;
MODEL Y6METS= TOTKCAL MINGROUP|TOTPF CV1AGE RACE EDUC NEWMAR SMK1 CURDRNK1
COUNTDX Y1PCHD1;
RUN;

PROC LOGISTIC DATA=WOMEN DESCENDING;
MODEL Y6METS= TOTKCAL INTGROUP|TOTPF CV1AGE RACE EDUC NEWMAR SMK1 CURDRNK1
COUNTDX Y1PCHD1;
```

```
RUN;

PROC LOGISTIC DATA=WOMEN DESCENDING;
MODEL Y6METS= TOTKCAL BRACHGROUP|TOTPF CV1AGE RACE EDUC NEWMAR SMK1
CURDRNK1 COUNTDX Y1PCHD1;
RUN;

*FINAL MODELS;

PROC LOGISTIC DATA=WOMEN DESCENDING;
CLASS MINGROUP;
MODEL Y6METS=MINGROUP METSRISK TOTKCAL TOTPF CV1AGE RACE EDUC NEWMAR SMK1
CURDRNK1 COUNTDX Y1PCHD1;
RUN;

PROC LOGISTIC DATA=WOMEN DESCENDING;
CLASS INTGROUP;
MODEL Y6METS=INTGROUP METSRISK TOTKCAL TOTPF CV1AGE RACE EDUC NEWMAR SMK1
CURDRNK1 COUNTDX Y1PCHD1;
RUN;

PROC LOGISTIC DATA=WOMEN DESCENDING;
CLASS BRACHGROUP;
MODEL Y6METS=BRACHGROUP METSRISK TOTKCAL TOTPF CV1AGE RACE EDUC NEWMAR
SMK1 CURDRNK1 COUNTDX Y1PCHD1;
RUN;

*LOOKING AT SEDENTARY AS REF GROUP;

PROC LOGISTIC DATA=WOMEN DESCENDING;
CLASS MINGROUP (REF=FIRST);
MODEL Y6METS=MINGROUP TOTKCAL TOTPF CV1AGE RACE EDUC NEWMAR SMK1 CURDRNK1
COUNTDX Y1PCHD1;
RUN;

PROC LOGISTIC DATA=WOMEN DESCENDING;
CLASS INTGROUP (REF=FIRST);
MODEL Y6METS=INTGROUP TOTKCAL TOTPF CV1AGE RACE EDUC NEWMAR SMK1 CURDRNK1
COUNTDX Y1PCHD1;
RUN;

PROC LOGISTIC DATA=WOMEN DESCENDING;
CLASS BRACHGROUP (REF=FIRST);
MODEL Y6METS=BRACHGROUP TOTKCAL TOTPF CV1AGE RACE EDUC NEWMAR SMK1
CURDRNK1 COUNTDX Y1PCHD1;
RUN;

*LOOKING AT MS WITHOUT BP AS A FACTOR;

PROC LOGISTIC DATA=WOMEN DESCENDING;
CLASS MINGROUP;
MODEL Y6MSWOBP=MINGROUP TOTKCAL TOTPF CV1AGE RACE EDUC NEWMAR SMK1
CURDRNK1 COUNTDX Y1PCHD1;
RUN;

PROC LOGISTIC DATA=WOMEN DESCENDING;
CLASS INTGROUP;
```

```
MODEL Y6MSWOBP=INTGROUP TOTKCAL TOTPF CV1AGE RACE EDUC NEWMAR SMK1
CURDRNK1 COUNTDX Y1PCHD1;
RUN;

PROC LOGISTIC DATA=WOMEN DESCENDING;
CLASS BRACHGROUP;
MODEL Y6MSWOBP=BRACHGROUP TOTKCAL TOTPF CV1AGE RACE EDUC NEWMAR SMK1
CURDRNK1 COUNTDX Y1PCHD1;
RUN;


*CHECKING TO SEE IF THERE ARE DIFFERENCES IN INCIDENCE OF MS FACTORS
BETWEEN LOW AND HIGH
INTENSITY GROUPS;

DATA LOWINT;
SET METFINAL;
IF GENDER=2;
IF INTGROUP=1;
IF METSRISK=2;
RUN;

PROC FREQ DATA=LOWINT;
TABLES CHANGEAB CHANGEHD CHANGETG CHANGEBP CHANGEGL;
RUN;

DATA HIGHINT;
SET METFINAL;
IF GENDER=2;
IF INTGROUP=3;
IF METSRISK=2;
RUN;

DATA X;
MERGE LOWINT HIGHINT;
BY HABCID;
RUN;

PROC LOGISTIC DATA=X DESCENDING;
CLASS MINGROUP;
MODEL Y6METS=MINGROUP TOTKCAL TOTPF CV1AGE RACE EDUC NEWMAR SMK1 CURDRNK1
COUNTDX Y1PCHD1;
RUN;

PROC LOGISTIC DATA=X DESCENDING;
CLASS INTGROUP;
MODEL Y6METS=INTGROUP TOTKCAL TOTPF CV1AGE RACE EDUC NEWMAR SMK1 CURDRNK1
COUNTDX Y1PCHD1;
RUN;

PROC LOGISTIC DATA=X DESCENDING;
CLASS BRACHGROUP;
MODEL Y6METS=BRACHGROUP TOTKCAL TOTPF CV1AGE RACE EDUC NEWMAR SMK1
CURDRNK1 COUNTDX Y1PCHD1;
RUN;

*TESTING FOR HOMOGENEITY BETWEEN STRATA;
```

```
*MODELS OF NO MS TO MS;

PROC LOGISTIC DATA=MEN DESCENDING;
CLASS MINGROUP;
MODEL Y6METS=MINGROUP TOTKCAL TOTPF CV1AGE RACE EDUC NEWMAR SMK1 CURDRNK1
COUNTDX Y1PCHD1;
RUN;

PROC LOGISTIC DATA=MEN DESCENDING;
CLASS INTGROUP;
MODEL Y6METS=INTGROUP TOTKCAL TOTPF CV1AGE RACE EDUC NEWMAR SMK1 CURDRNK1
COUNTDX Y1PCHD1;
RUN;

PROC LOGISTIC DATA=MEN DESCENDING;
CLASS BRACHGROUP;
MODEL Y6METS=BRACHGROUP TOTKCAL TOTPF CV1AGE RACE EDUC NEWMAR SMK1
CURDRNK1 COUNTDX Y1PCHD1;
RUN;

PROC LOGISTIC DATA=WOMEN DESCENDING;
CLASS MINGROUP;
MODEL Y6METS=MINGROUP METSRISK TOTKCAL TOTPF CV1AGE RACE EDUC NEWMAR SMK1
CURDRNK1 COUNTDX Y1PCHD1;
RUN;

PROC LOGISTIC DATA=WOMEN DESCENDING;
CLASS INTGROUP;
MODEL Y6METS=INTGROUP METSRISK TOTKCAL TOTPF CV1AGE RACE EDUC NEWMAR SMK1
CURDRNK1 COUNTDX Y1PCHD1;
RUN;

PROC LOGISTIC DATA=WOMEN DESCENDING;
CLASS BRACHGROUP;
MODEL Y6METS=BRACHGROUP METSRISK TOTKCAL TOTPF CV1AGE RACE EDUC NEWMAR
SMK1 CURDRNK1 COUNTDX Y1PCHD1;
RUN;

*MODELS OF MS TO MS;

DATA MET5;
SET MET3;
TOTMIN=Y1WKTIME+HIGHXMIN;
IF TOTMIN>=200 THEN MINGROUP=3;
IF 150<=TOTMIN<200 THEN MINGROUP=2;
IF TOTMIN<150 THEN MINGROUP=1;

DIFFWALK=Y6WKTIME-Y1WKTIME;
IF DIFFWALK<=-90 THEN WKGROUP=1;
IF DIFFWALK>-90 THEN WKGROUP=0;

IF Y6METSAB NOT IN(0,1) THEN DELETE;
IF Y6METSHD NOT IN(0,1) THEN DELETE;
IF Y6METSTG NOT IN(0,1) THEN DELETE;
IF Y6METSBP NOT IN(0,1)THEN DELETE;
IF Y6METSGL NOT IN(0,1) THEN DELETE;
```

```
IF Y1METSYN=0 THEN DELETE;

IF Y6METSAB +Y6METSHD+ Y6METSTG+ Y6METSBP+ Y6METSGL>=3 THEN Y6METS=1;
IF Y6METSAB+ Y6METSHD+ Y6METSTG+ Y6METSBP+ Y6METSGL<3 THEN Y6METS=0;

IF Y6METSAB +Y6METSHD+ Y6METSTG+ Y6METSBP+ Y6METSGL=0 THEN Y6NUMBER=0;
IF Y6METSAB +Y6METSHD+ Y6METSTG+ Y6METSBP+ Y6METSGL=1 THEN Y6NUMBER=1;
IF Y6METSAB +Y6METSHD+ Y6METSTG+ Y6METSBP+ Y6METSGL=2 THEN Y6NUMBER=2;
IF Y6METSAB +Y6METSHD+ Y6METSTG+ Y6METSBP+ Y6METSGL=3 THEN Y6NUMBER=3;
IF Y6METSAB +Y6METSHD+ Y6METSTG+ Y6METSBP+ Y6METSGL=4 THEN Y6NUMBER=4;
IF Y6METSAB +Y6METSHD+ Y6METSTG+ Y6METSBP+ Y6METSGL=5 THEN Y6NUMBER=5;

IF Y1METSAB+ Y1METSHD+ Y1METSTG+ Y1METSBP+ Y1METSGL=2 THEN METSRISK=2;
IF Y1METSAB+ Y1METSHD+ Y1METSTG+ Y1METSBP+ Y1METSGL=1 THEN METSRISK=1;



Y1OUTDRKK=FPPAKKWK*P2WTK;
Y1HEAVYKK=FPHCKKWK*P2WTK;
Y1HOUSEKK=FPLWKKWK*P2WTK;
Y1SHOPKK=FPGSKKWK*P2WTK;
Y1WASHKK=FPLDKKWK*P2WTK;
Y1STAIRSKK=FPFSKKWK*P2WTK;
Y1EXWLKKK=FPEWKKWK*P2WTK;
Y1NOEXWLKKK=FPOWKKWK*P2WTK;
Y1DANCEKK=FPACKKWK*P2WTK;
Y1LIFTKK=FPTRKKWK*P2WTK;
Y1MODEXKK=FPMIKKWK*P2WTK;
Y1PAYWRKKK=FPPWKKWK*P2WTK;
Y1VOLWRKKK=FPVWKKWK*P2WTK;
Y1CAREKK=FPCWKKWK*P2WTK;
Y1EXKK=EXKKWK*P2WTK;
TOTKCAL=TOTKKWK*P2WTK;
Y1LIFEKK=(HHKKWK+Y1WSKKWK+Y1WVCKKW)*P2WTK;
EXWLKKK=(FPEWKKWK+EXKKWK)*P2WTK;
IF Y1HEAVYKK+Y1STAIRSKK+Y1DANCEKK+Y1LIFTKK>=1000 THEN INTGROUP=3;
IF INTGROUP=3 THEN VIGGROUP=1;
IF Y1OUTDRKK+Y1EXWLKKK+Y1NOEXWLKKK+Y1MODEXKK>=1000 AND VIGGROUP=. THEN
INTGROUP=2;
IF INTGROUP=2 THEN MODGROUP=1;
IF Y1OUTDRKK+Y1EXWLKKK+Y1NOEXWLKKK+Y1MODEXKK<1000 AND VIGGROUP=1 THEN
INTGROUP=3;
IF Y1OUTDRKK+Y1EXWLKKK+Y1NOEXWLKKK+Y1MODEXKK>=1000 AND VIGGROUP=1 THEN
INTGROUP=3;
IF Y1HOUSEKK+Y1SHOPKK+Y1WASHKK+Y1PAYWRKKK+Y1VOLWRKKK+Y1CAREKK>=1000 AND
VIGGROUP=.
AND MODGROUP=. THEN INTGROUP=1;
IF Y1HOUSEKK+Y1SHOPKK+Y1WASHKK+Y1PAYWRKKK+Y1VOLWRKKK+Y1CAREKK>=1000 AND
VIGGROUP=.
AND MODGROUP=1 THEN INTGROUP=2;
IF Y1HOUSEKK+Y1SHOPKK+Y1WASHKK+Y1PAYWRKKK+Y1VOLWRKKK+Y1CAREKK>=1000 AND
VIGGROUP=1
THEN INTGROUP=3;
IF Y1HOUSEKK+Y1SHOPKK+Y1WASHKK+Y1PAYWRKKK+Y1VOLWRKKK+Y1CAREKK<1000 AND
VIGGROUP=1
THEN INTGROUP=3;
```

```
IF Y1HOUSEKK+Y1SHOPKK+Y1WASHKK+Y1PAYWRKKK+Y1VOLWRKKK+Y1CAREKK<1000 AND
MODGROUP=1
THEN INTGROUP=2;
IF Y1HEAVYKK+Y1STAIRSKK+Y1DANCEKK+Y1LIFTKK+
Y1OUTDRKK+Y1EXWLKKK+Y1NOEXWLKKK+
Y1MODEXKK+Y1HOUSEKK+Y1SHOPKK+Y1WASHKK+Y1PAYWRKKK+Y1VOLWRKKK+Y1CAREKK<1000
THEN INTGROUP=0;
IF EXWLKKK>=1000 THEN BRACHGROUP=2;
IF Y1LIFEKK>=2719 AND EXWLKKK<1000 THEN BRACHGROUP=1;
IF Y1LIFEKK<2719 AND EXWLKKK<1000 THEN BRACHGROUP=0;

IF MINGROUP IN (2,3) AND INTGROUP IN(2,3) THEN SUMGROUP=1;


FORMAT MINGROUP MINGROUP.;
FORMAT INTGROUP INTGROUP.;
FORMAT BRACHGROUP BRACHGROUP.;

RUN;

DATA METFINAL2;
SET MET5;
IF CURDRNK1 IN(2,3) THEN CURDRNK1=2;
IF CURDRNK1 IN(4) THEN CURDRNK1=3;
IF SMK1 IN(1) THEN SMK1=4;
IF SMK1 IN(2) THEN SMK1=3;
IF Y1PCBVD IN(1,2) THEN Y1PCBVD=1;
IF Y1POAKN IN(1,2,3) THEN Y1POAKN=1;
IF Y1POAHIP IN(1,2,3) THEN Y1POAHIP=1;
IF Y1PDEPR1 IN(1,2,3) THEN Y1PDEPR1=1;
IF Y1PPULCD IN(1,2,3) THEN Y1PPULCD=1;
IF Y1PHBP1 IN(1,2) THEN Y1PHBP1=1;
IF Y1POAKN+Y1POAHIP=0 THEN LOWEROA=0;
ELSE LOWEROA=1;
COUNTDX=Y1PCBVD+LOWEROA+Y1PDEPR1+Y1PPULCD+Y1PPAD;
IF GENDER=1 AND TOTPF=. THEN TOTPF=28.3;
IF GENDER=2 AND TOTPF=. THEN TOTPF=39.9;
RUN;

PROC SORT DATA=METFINAL2;
BY GENDER;
RUN;

DATA MEN2;
SET METFINAL2;
IF GENDER=1;
RUN;

PROC LOGISTIC DATA=MEN2 DESCENDING;
CLASS MINGROUP;
MODEL Y6METS=MINGROUP TOTKCAL TOTPF CV1AGE RACE EDUC NEWMAR SMK1 CURDRNK1
COUNTDX Y1PCHD1;
RUN;

PROC LOGISTIC DATA=MEN2 DESCENDING;
CLASS INTGROUP;
```

```
MODEL Y6METS=INTGROUP TOTKCAL TOTPF CV1AGE RACE EDUC NEWMAR SMK1 CURDRNK1
COUNTDX Y1PCHD1;
RUN;

PROC LOGISTIC DATA=MEN2 DESCENDING;
CLASS BRACHGROUP;
MODEL Y6METS=BRACHGROUP TOTKCAL TOTPF CV1AGE RACE EDUC NEWMAR SMK1
CURDRNK1 COUNTDX Y1PCHD1;
RUN;

DATA WOMEN2;
SET METFINAL2;
IF GENDER=2;
RUN;


PROC LOGISTIC DATA=WOMEN2 DESCENDING;
CLASS MINGROUP;
MODEL Y6METS=MINGROUP TOTKCAL TOTPF CV1AGE RACE EDUC NEWMAR SMK1 CURDRNK1
COUNTDX Y1PCHD1;
RUN;

PROC LOGISTIC DATA=WOMEN2 DESCENDING;
CLASS INTGROUP;
MODEL Y6METS=INTGROUP TOTKCAL TOTPF CV1AGE RACE EDUC NEWMAR SMK1 CURDRNK1
COUNTDX Y1PCHD1;
RUN;

PROC LOGISTIC DATA=WOMEN2 DESCENDING;
CLASS BRACHGROUP;
MODEL Y6METS=BRACHGROUP TOTKCAL TOTPF CV1AGE RACE EDUC NEWMAR SMK1
CURDRNK1
COUNTDX Y1PCHD1;
RUN;


data odds (keep=group est1 est2 est logest low_ci up_ci var Z  q);
input group $  est1 se1 est2 se2 ;

var1=se1** 2;
var2=se2** 2;
wt=(1 /var1) + (1 /var2);
logest= ((est1*(1 /var1)) + (est2*(1 /var2))) / wt ;
var=1 /wt;
z=logest/sqrt(var);
est=exp(logest);
up_ci=exp(logest +1.96 *sqrt(var));
low_ci=exp(logest -1.96 *sqrt(var));


* homogeneity;
q=(((est1-logest)** 2 )/var1) + (((est2-logest)** 2)/var2);



cards ;
```

```
Mlotime .3917 .1878 .3352 .2049
Mmodtime -.2433 .2990 -.5479 .3121
Msedint .3626 .2199 .0448 .2851
Mlightint .0355 .1876 .5423 .2447
Mmodint -.0938 .1797 -.2890 .2019
Msedbrach .1713 .2038 .0965 .2517
Mlifbrach .0682 .1530 .00301 .1748
Wlotime .00962 .1829 -.1110 .1836
Wmodtime -.2707 .2942 .1199 .2861
Wsedint .0674 .2455 -.5261 .2750
Wlightint -.4636 .1654 .0950 .1820
Wmodint .0164 .2072 .4439 .2903
Wsedbrach -.4277 .2060 -.2016 .2091
Wlifbrach .0540 .1478 .1699 .1611
;
proc print ;
run ;
```

Program for Metabolic Syndrome Analyses

```
OPTIONS PAGESIZE=50 LINESIZE=96 NODATE NONUMBER NOFMTERR;

*INITIATED 01-03-2006;
*UPDATED;

LIBNAME ABC V6 'C:\Documents and Settings\peter076\My
Documents\Dissertation\ABC DATA';
LIBNAME DEF V6 'C:\Documents and Settings\peter076\My
Documents\Dissertation\ABC DATA\FRAILTY';
RUN;

*IMPUTING MISSING VALUES HERE;

DATA A;
SET ABC.FRAILTY;
IF Y16MPACE=. THEN DELETE;
IF Y1ABL5CS=. THEN DELETE;
IF Y1ABL5CS IN(0,1);
IF EDUC NOT IN(1,2,3) THEN EDUC=.;
IF EDUC =. THEN EDUC=3;
IF SMK1=. THEN SMK1=2;
IF CURDRNK1=. THEN CURDRNK1=1;
IF Y1PCBVD NOT IN(0,1,2) THEN Y1PCBVD=.;
IF Y1PCBVD=. THEN Y1PCBVD=0;
IF Y1PDIAB1 NOT IN(0,1) THEN Y1PDIAB1=.;
IF Y1PDIAB1=. THEN Y1PDIAB1=0;
IF Y1POAKN=. THEN Y1POAKN=0;
IF Y1POAHIP=. THEN Y1POAHIP=0;
IF Y1PHBP1 NOT IN(0,1,2) THEN Y1PHBP1=.;
IF Y1PHBP1=. THEN Y1PHBP1=0;
IF Y1PDEPR1 NOT IN(0,1,2,3) THEN Y1PDEPR1=.;
IF Y1PDEPR1=. THEN Y1PDEPR1=0;
IF Y1PPULCD NOT IN(0,1,2,3) THEN Y1PPULCD=.;
IF Y1PPULCD=. THEN Y1PPULCD=0;
IF TSMARSTA IN(0,2,3,4) THEN TSMARSTA=2;
IF Y1PCHD1 IN(1,2) THEN Y1PCHD1=1;
RUN;

PROC FREQ DATA=A;
TABLES TSMARSTA;
RUN;

PROC LOGISTIC DATA=A NOPRINT;
MODEL Y1PCHD1=CV1AGE GENDER RACE EDUC SMK1
CURDRNK1 TSMARSTA Y1PCBVD Y1PPAD Y1PDIAB1 Y1POAKN Y1POAHIP Y1PHBP1
Y1PDEPR1 Y1PPULCD/
SELECTION=STEPWISE;
RUN;
```

```
PROC LOGISTIC DATA=A NOPRINT;
MODEL Y1PPAD=CV1AGE GENDER RACE EDUC SMK1
CURDRNK1 TSMARSTA Y1PCBVD Y1PCHD1 Y1PDIAB1 Y1POAKN Y1POAHIP Y1PHBP1
Y1PDEPR1 Y1PPULCD/
SELECTION=STEPWISE;
RUN;

*THESE MODELS INDICATE THAT HEART DISEASE AND PERIPHERAL ARTERY DISEASE
ARE CLOSELY LINKED.
SO I WILL NEED TO DO PROC MI METHODS FOR IMPUTING;

PROC MI DATA=A OUT=IMPUT NIMPUTE=1 MINIMUM=0 MAXIMUM=1 NOPRINT;
VAR Y1PCHD1 Y1PPAD;
RUN;

DATA FRAIL0;
MERGE A IMPUT;
BY HABCID;
RUN;

PROC UNIVARIATE DATA=FRAIL0 NOPRINT;
VAR Y1PCHD1 Y1PPAD;
RUN;

DATA FRAIL;
SET FRAIL0;
IF Y1PCHD1 NOT IN(0,1) THEN Y1PCHD1=0;
IF Y1PPAD NOT IN(0,1) THEN Y1PPAD=0;
RUN;

PROC LOGISTIC DATA=FRAIL;
OUTPUT OUT=OUTPUT P=PRED;
MODEL TSMARSTA=CV1AGE GENDER RACE EDUC SMK1
CURDRNK1 Y1PCHD1 Y1PCBVD Y1PPAD Y1PDIAB1 Y1POAKN Y1POAHIP Y1PHBP1 Y1PDEPR1
Y1PPULCD/
SELECTION=STEPWISE;
RUN;

PROC PRINT DATA=OUTPUT;
VAR HABCID PRED;
RUN;

DATA MARITAL;
SET OUTPUT;
IF TSMARSTA NOT IN(1,2) THEN NEWMAR=RANBIN(666,2,PRED);
ELSE NEWMAR=TSMARSTA;
RUN;

DATA COMPLETE;
MERGE FRAIL MARITAL;
BY HABCID;
IF NEWMAR=0 THEN NEWMAR=2;
RUN;

PROC FREQ DATA=COMPLETE;
TABLES NEWMAR;
RUN;
```

```
PROC FORMAT;

VALUE MINGROUP 1='LOW- 150 MIN/WEEK'
                        2='MOD- 150-200 MIN/WEEK'
                        3='XTRA- 200+ MIN/WEEK';

VALUE INTGROUP  0='ASEDENTARY'
                        1='LIGHT INTENSITY GROUP'
                        2='MODERATE INTENSITY GROUP'
                        3='VIGOROUS INTENTSITY GROUP';

VALUE BRACHGROUP 0='ASEDENTARY'
                                1='LIFESTYLE ACTIVE'
                                2='XERCISE ACTIVE';

VALUE FRAIL6Y  1='NOT FRAIL'
                        2='MODERATELY FRAIL'
                        3='SEVERELY FRAIL';

VALUE FRAIL4Y  1='NOT FRAIL'
                        2='MODERATELY FRAIL'
                        3='SEVERELY FRAIL';

VALUE FRAIL1Y  1='NOT FRAIL'
                        2='MODERATELY FRAIL'
                        3='SEVERELY FRAIL';

VALUE BMICAT 1='HEALTHY WEIGHT'
                  2='OVERWEIGHT'
                  3='OBESE';
RUN;

DATA FRAIL;
SET COMPLETE;
TOTMIN=Y1WKTIME+HIGHXMIN;
IF TOTMIN>=200 THEN MINGROUP=3;
IF 150<=TOTMIN<200 THEN MINGROUP=2;
IF TOTMIN<150 THEN MINGROUP=1;

IF (Y2BWTIME+Y2WKTIME)>=200 THEN Y2MINGROUP=3;
IF 150<=(Y2BWTIME+Y2WKTIME)<200 THEN Y2MINGROUP=2;
IF (Y2BWTIME+Y2WKTIME)<150 THEN Y2MINGROUP=1;

IF (Y3BWTIME+Y3WKTIME)>=200 THEN Y3MINGROUP=3;
IF 150<=(Y3BWTIME+Y3WKTIME)<200 THEN Y3MINGROUP=2;
IF (Y3BWTIME+Y3WKTIME)<150 THEN Y3MINGROUP=1;

IF (Y5BWTIME+Y5WKTIME)>=200 THEN Y5MINGROUP=3;
IF 150<=(Y5BWTIME+Y5WKTIME)<200 THEN Y5MINGROUP=2;
IF (Y5BWTIME+Y5WKTIME)<150 THEN Y5MINGROUP=1;

IF Y6ABL5CS=1 AND Y66MPACE>0.60 THEN FRAILY6=1;
IF Y6ABL5CS=0 AND Y66MPACE>0.60 THEN FRAILY6=2;
IF Y6ABL5CS=1 AND Y66MPACE<=0.60 THEN FRAILY6=2;
IF Y6ABL5CS=0 AND Y66MPACE<=0.60 THEN FRAILY6=3;
IF Y4ABL5CS=1 AND Y46MPACE>0.60 THEN FRAILY4=1;
```

```
IF Y4ABL5CS=0 AND Y46MPACE>0.60 THEN FRAILY4=2;
IF Y4ABL5CS=1 AND Y46MPACE<=0.60 THEN FRAILY4=2;
IF Y4ABL5CS=0 AND Y46MPACE<=0.60 THEN FRAILY4=3;
IF Y1ABL5CS=1 AND Y16MPACE>0.60 THEN FRAILY1=1;
IF Y1ABL5CS=0 AND Y16MPACE>0.60 THEN FRAILY1=2;
IF Y1ABL5CS=1 AND Y16MPACE<=0.60 THEN FRAILY1=2;
IF Y1ABL5CS=0 AND Y16MPACE<=0.60 THEN FRAILY1=3;
Y1OUTDRKK=FPPAKKWK*P2WTK;
Y1HEAVYKK=FPHCKKWK*P2WTK;
Y1HOUSEKK=FPLWKKWK*P2WTK;
Y1SHOPKK=FPGSKKWK*P2WTK;
Y1WASHKK=FPLDKKWK*P2WTK;
Y1STAIRSKK=FPFSKKWK*P2WTK;
Y1EXWLKKK=FPEWKKWK*P2WTK;
Y1NOEXWLKKK=FPOWKKWK*P2WTK;
Y1DANCEKK=FPACKKWK*P2WTK;
Y1LIFTKK=FPTRKKWK*P2WTK;
Y1MODEXKK=FPMIKKWK*P2WTK;
Y1PAYWRKKK=FPPWKKWK*P2WTK;
Y1VOLWRKKK=FPVWKKWK*P2WTK;
Y1CAREKK=FPCWKKWK*P2WTK;
Y1EXKK=EXKKWK*P2WTK;
TOTKCAL=TOTKKWK*P2WTK;
Y1LIFEKK=(HHKKWK+Y1WSKKWK+Y1WVCKKW)*P2WTK;
EXWLKKK=(FPEWKKWK+EXKKWK)*P2WTK;
IF Y1HEAVYKK+Y1STAIRSKK+Y1DANCEKK+Y1LIFTKK>=1000 THEN INTGROUP=3;
IF INTGROUP=3 THEN VIGGROUP=1;
IF Y1OUTDRKK+Y1EXWLKKK+Y1NOEXWLKKK+Y1MODEXKK>=1000 AND VIGGROUP=. THEN
INTGROUP=2;
IF INTGROUP=2 THEN MODGROUP=1;
IF Y1OUTDRKK+Y1EXWLKKK+Y1NOEXWLKKK+Y1MODEXKK<1000 AND VIGGROUP=1 THEN
INTGROUP=3;
IF Y1OUTDRKK+Y1EXWLKKK+Y1NOEXWLKKK+Y1MODEXKK>=1000 AND VIGGROUP=1 THEN
INTGROUP=3;
IF Y1HOUSEKK+Y1SHOPKK+Y1WASHKK+Y1PAYWRKKK+Y1VOLWRKKK+Y1CAREKK>=1000 AND
VIGGROUP=.
AND MODGROUP=. THEN INTGROUP=1;
IF Y1HOUSEKK+Y1SHOPKK+Y1WASHKK+Y1PAYWRKKK+Y1VOLWRKKK+Y1CAREKK>=1000 AND
VIGGROUP=.
AND MODGROUP=1 THEN INTGROUP=2;
IF Y1HOUSEKK+Y1SHOPKK+Y1WASHKK+Y1PAYWRKKK+Y1VOLWRKKK+Y1CAREKK>=1000 AND
VIGGROUP=1
THEN INTGROUP=3;
IF Y1HOUSEKK+Y1SHOPKK+Y1WASHKK+Y1PAYWRKKK+Y1VOLWRKKK+Y1CAREKK<1000 AND
VIGGROUP=1
THEN INTGROUP=3;
IF Y1HOUSEKK+Y1SHOPKK+Y1WASHKK+Y1PAYWRKKK+Y1VOLWRKKK+Y1CAREKK<1000 AND
MODGROUP=1
THEN INTGROUP=2;
IF Y1HEAVYKK+Y1STAIRSKK+Y1DANCEKK+Y1LIFTKK+
Y1OUTDRKK+Y1EXWLKKK+Y1NOEXWLKKK+
Y1MODEXKK+Y1HOUSEKK+Y1SHOPKK+Y1WASHKK+Y1PAYWRKKK+Y1VOLWRKKK+Y1CAREKK<1000
THEN INTGROUP=0;
IF EXWLKKK>=1000 THEN BRACHGROUP=2;
IF Y1LIFEKK>=2719 AND EXWLKKK<1000 THEN BRACHGROUP=1;
IF Y1LIFEKK<2719 AND EXWLKKK<1000 THEN BRACHGROUP=0;
```

```
IF MINGROUP IN (2,3) AND INTGROUP IN(2,3) THEN SUMGROUP=1;

IF BMI<=25 THEN BMICAT=1;
IF 25<BMI<30 THEN BMICAT=2;
IF BMI>=30 THEN BMICAT=3;

FORMAT FRAILY6 FRAIL6Y.;
FORMAT FRAILY4 FRAIL4Y.;
FORMAT FRAILY1 FRAIL4Y.;
FORMAT MINGROUP MINGROUP.;
FORMAT INTGROUP INTGROUP.;
FORMAT BRACHGROUP BRACHGROUP.;
FORMAT BMICAT BMICAT.;
RUN;


DATA FINALFRAIL;
SET FRAIL;
IF CURDRNK1 IN(2,3) THEN CURDRNK1=2;
IF CURDRNK1 IN(4) THEN CURDRNK1=3;
IF SMK1 IN(1) THEN SMK1=4;
IF SMK1 IN(2) THEN SMK1=3;
IF Y1PCBVD IN(1,2) THEN Y1PCBVD=1;
IF Y1POAKN IN(1,2,3) THEN Y1POAKN=1;
IF Y1POAHIP IN(1,2,3) THEN Y1POAHIP=1;
IF Y1PDEPR1 IN(1,2,3) THEN Y1PDEPR1=1;
IF Y1PPULCD IN(1,2,3) THEN Y1PPULCD=1;
IF Y1PHBP1 IN(1,2) THEN Y1PHBP1=1;
IF Y1POAKN+Y1POAHIP=0 THEN LOWEROA=0;
ELSE LOWEROA=1;
COUNTDX=Y1PCHD1+Y1PCBVD+LOWEROA+Y1PDEPR1+Y1PPULCD+Y1PHBP1+Y1PPAD+Y1PDIAB1;
RUN;


PROC SORT DATA=FINALFRAIL;
BY GENDER;
RUN;

PROC FREQ DATA= FINALFRAIL;
BY GENDER;
TABLES SUMGROUP MINGROUP INTGROUP BRACHGROUP FRAILY1 FRAILY4 FRAILY6
CV1AGE GENDER RACE EDUC
NEWMAR SMK1 CURDRNK1 Y1PCHD1 Y1PCBVD Y1PPAD Y1PDIAB1 LOWEROA Y1PHBP1
Y1PDEPR1 Y1PPULCD COUNTDX;
RUN;

PROC MEANS DATA=FINALFRAIL;
BY GENDER;
RUN;

PROC FREQ DATA=FINALFRAIL;
TABLES MINGROUP*FRAILY6/CMH;
TABLES INTGROUP*FRAILY6/CMH;
TABLES BRACHGROUP*FRAILY6/CMH;
TABLES CV1AGE*FRAILY6/CMH;
TABLES GENDER*FRAILY6/CMH;
TABLES RACE*FRAILY6/CMH;
```

```
TABLES EDUC*FRAILY6/CMH;
TABLES NEWMAR*FRAILY6/CMH;
TABLES SMK1*FRAILY6/CMH;
TABLES CURDRNK1*FRAILY6/CMH;
TABLES Y1PCHD1*FRAILY6/CMH;
TABLES Y1PCBVD*FRAILY6/CMH;
TABLES Y1PPAD*FRAILY6/CMH;
TABLES Y1PDIAB1*FRAILY6/CMH;
TABLES LOWEROA*FRAILY6/CMH;
TABLES Y1PHBP1*FRAILY6/CMH;
TABLES Y1PDEPR1*FRAILY6/CMH;
TABLES Y1PPULCD*FRAILY6/CMH;
TABLES COUNTDX*FRAILY6/CMH;
RUN;

PROC GLM DATA=FINALFRAIL;
CLASS MINGROUP;
MODEL TOTKCAL=MINGROUP;
LSMEANS MINGROUP;
RUN;

PROC GLM DATA=FINALFRAIL;
CLASS INTGROUP;
MODEL TOTKCAL=INTGROUP;
LSMEANS INTGROUP;
RUN;

PROC GLM DATA=FINALFRAIL;
CLASS BRACHGROUP;
MODEL TOTKCAL=BRACHGROUP;
LSMEANS BRACHGROUP;
RUN;

*TESTING PROPORTIONALITY ASSUMPTION WITH THE FOLLOWING LOGISTIC MODELS;
DATA FRAIL2;
SET FINALFRAIL;
IF FRAILY1 IN(2,3) THEN DELETE;

PROC LOGISTIC DATA=FRAIL2;
CLASS MINGROUP;
MODEL FRAILY6=MINGROUP;
RUN;

PROC LOGISTIC DATA=FRAIL2;
WHERE INTGROUP NOT=.;
CLASS INTGROUP;
MODEL FRAILY6=INTGROUP;
RUN;

PROC LOGISTIC DATA=FRAIL2;
CLASS BRACHGROUP;
MODEL FRAILY6=BRACHGROUP;
RUN;

*PROPORTIONALITY ASSUMPTION NOT MET SO I AM DO ORTHOGANOL OR'S NOW. THIS
IS ODDS OF BECOMING
```

```
EITHER MODERATELY OR SEVERELY FRAIL AT YEAR 6. FIRST UNADJUSTED THEN
ADJUSTED MODELS;

DATA FRAIL3;
SET FINALFRAIL;
IF FRAILY1 IN(2,3) THEN DELETE;
IF FRAILY6 IN (2,3) THEN FRAILY6=2;
RUN;


*UNADJUSTED MODELS;
PROC LOGISTIC DATA=FRAIL3;
CLASS MINGROUP;
MODEL FRAILY6=MINGROUP TOTKCAL;
RUN;

PROC LOGISTIC DATA=FRAIL3;
MODEL FRAILY6=INTGROUP TOTKCAL;
RUN;

PROC LOGISTIC DATA=FRAIL3;
MODEL FRAILY6=BRACHGROUP TOTKCAL;
RUN;

*SATURATED MODELS LOOKING FOR INTERACTIONS FIRST WITH CV1AGE GENDER RACE
EDUC NEWMAR SMK1
CURDRNK1 Y1PCHD1 Y1PCBVD Y1PPAD Y1PDIAB1 LOWEROA Y1PHBP1 Y1PDEPR1
Y1PPULCD;
PROC LOGISTIC DATA=FRAIL3;
MODEL FRAILY6=  MINGROUP|CV1AGE MINGROUP|GENDER MINGROUP|RACE
MINGROUP|EDUC
MINGROUP|NEWMAR MINGROUP|SMK1 MINGROUP|CURDRNK1
MINGROUP|Y1PCHD1 MINGROUP|Y1PCBVD MINGROUP|Y1PPAD MINGROUP|Y1PDIAB1
MINGROUP|LOWEROA
MINGROUP|Y1PHBP1 MINGROUP|Y1PDEPR1 MINGROUP|Y1PPULCD;
RUN;

PROC LOGISTIC DATA=FRAIL3;
MODEL FRAILY6= INTGROUP|CV1AGE INTGROUP|GENDER INTGROUP|RACE INTGROUP|EDUC
INTGROUP|NEWMAR INTGROUP|SMK1 INTGROUP|CURDRNK1
INTGROUP|Y1PCHD1 INTGROUP|Y1PCBVD INTGROUP|Y1PPAD INTGROUP|Y1PDIAB1
INTGROUP|LOWEROA
INTGROUP|Y1PHBP1 INTGROUP|Y1PDEPR1 INTGROUP|Y1PPULCD;
RUN;

PROC LOGISTIC DATA=FRAIL3;
MODEL FRAILY6=  BRACHGROUP|CV1AGE BRACHGROUP|GENDER BRACHGROUP|RACE
BRACHGROUP|EDUC
BRACHGROUP|NEWMAR BRACHGROUP|SMK1 BRACHGROUP|Y1PPAD BRACHGROUP|Y1PDIAB1
BRACHGROUP|LOWEROA
BRACHGROUP|Y1PHBP1 BRACHGROUP|Y1PDEPR1 BRACHGROUP|Y1PPULCD;
RUN;

*FINAL ADJUSTED MODELS WITH REDUCED FIT TO ONLY INCLUDE SIGNIFICANT
INTERACTIONS-
WHICH WERE NONE WHEN REDUCING THE MODEL BACK DOWN- AND OTHER A PRIORI
COVARIATES. ALSO
```

```
ADDED COUNTDX INSTEAD OF INDIVIDUAL DX;
PROC LOGISTIC DATA=FRAIL3;
CLASS MINGROUP;
MODEL FRAILY6= MINGROUP TOTKCAL CV1AGE GENDER RACE EDUC NEWMAR SMK1
CURDRNK1 COUNTDX;
RUN;

PROC LOGISTIC DATA=FRAIL3;
CLASS INTGROUP;
MODEL FRAILY6= INTGROUP TOTKCAL Y1PCHD1  CV1AGE GENDER RACE EDUC
NEWMAR SMK1 CURDRNK1 COUNTDX;
RUN;

PROC LOGISTIC DATA=FRAIL3;
CLASS BRACHGROUP;
MODEL FRAILY6= BRACHGROUP TOTKCAL CV1AGE GENDER RACE EDUC NEWMAR SMK1
COUNTDX;
RUN;


*TESTING ODDS OF LEVEL OF FRAILTY IN THOSE NOT FRAIL AT BASELINE. THIS IS
ODDS OF
INCIDENT LEVEL OF SEVERITY OF FRAILTY;

DATA FRAIL4;
SET FINALFRAIL;
IF FRAILY1 IN(2,3) THEN DELETE;
IF FRAILY6=1 THEN DELETE;
RUN;


*UNADJUSTED MODELS;
PROC LOGISTIC DATA=FRAIL4 DESCENDING;
CLASS MINGROUP;
MODEL FRAILY6=MINGROUP TOTKCAL;
RUN;

PROC LOGISTIC DATA=FRAIL4 DESCENDING;
CLASS INTGROUP;
MODEL FRAILY6=INTGROUP TOTKCAL;
RUN;

PROC LOGISTIC DATA=FRAIL4 DESCENDING;
CLASS BRACHGROUP;
MODEL FRAILY6=BRACHGROUP TOTKCAL;
RUN;

*SATURATED MODELS LOOKING FOR INTERACTIONS FIRST WITH CV1AGE GENDER RACE
EDUC NEWMAR SMK1
CURDRNK1 Y1PCHD1 Y1PCBVD Y1PPAD Y1PDIAB1 LOWEROA Y1PHBP1 Y1PDEPR1
Y1PPULCD;
PROC LOGISTIC DATA=FRAIL4;
MODEL FRAILY6=  MINGROUP|CV1AGE MINGROUP|GENDER MINGROUP|RACE
MINGROUP|EDUC
MINGROUP|NEWMAR MINGROUP|SMK1 MINGROUP|CURDRNK1
MINGROUP|Y1PCHD1 MINGROUP|Y1PCBVD MINGROUP|Y1PPAD MINGROUP|Y1PDIAB1
MINGROUP|LOWEROA
```

```
MINGROUP|Y1PHBP1 MINGROUP|Y1PDEPR1 MINGROUP|Y1PPULCD;
RUN;

PROC LOGISTIC DATA=FRAIL4;
MODEL FRAILY6= INTGROUP|CV1AGE INTGROUP|GENDER INTGROUP|RACE INTGROUP|EDUC
INTGROUP|NEWMAR INTGROUP|SMK1 INTGROUP|CURDRNK1
INTGROUP|Y1PCHD1 INTGROUP|Y1PCBVD INTGROUP|Y1PPAD INTGROUP|Y1PDIAB1
INTGROUP|LOWEROA
INTGROUP|Y1PHBP1 INTGROUP|Y1PDEPR1 INTGROUP|Y1PPULCD;
RUN;

PROC LOGISTIC DATA=FRAIL4;
MODEL FRAILY6=  BRACHGROUP|CV1AGE BRACHGROUP|GENDER BRACHGROUP|RACE
BRACHGROUP|EDUC
BRACHGROUP|NEWMAR BRACHGROUP|SMK1 BRACHGROUP|Y1PPAD BRACHGROUP|Y1PDIAB1
BRACHGROUP|LOWEROA
BRACHGROUP|Y1PHBP1 BRACHGROUP|Y1PDEPR1 BRACHGROUP|Y1PPULCD;
RUN;

*FINAL ADJUSTED MODELS WITH REDUCED FIT TO ONLY INCLUDE SIGNIFICANT
INTERACTIONS-
WHICH WERE NONE WHEN REDUCING THE MODEL BACK DOWN- AND OTHER A PRIORI
COVARIATES. ALSO
ADDED COUNTDX INSTEAD OF INDIVIDUAL DX;
PROC LOGISTIC DATA=FRAIL4;
CLASS MINGROUP;
MODEL FRAILY6= MINGROUP TOTKCAL CV1AGE GENDER RACE EDUC NEWMAR SMK1
CURDRNK1 COUNTDX;
RUN;

PROC LOGISTIC DATA=FRAIL4;
CLASS INTGROUP;
MODEL FRAILY6= INTGROUP TOTKCAL Y1PCHD1  CV1AGE GENDER RACE EDUC
NEWMAR SMK1 CURDRNK1 COUNTDX;
RUN;

PROC LOGISTIC DATA=FRAIL4;
CLASS BRACHGROUP;
MODEL FRAILY6= BRACHGROUP TOTKCAL GENDER CV1AGE RACE EDUC NEWMAR SMK1
CURDRNK1 COUNTDX;
RUN;

*-------------------------------------------------------------------------
--------------;

*TESTING ODDS OF LEVEL OF FRAILTY USING GEE MODELING. THIS IS SETTING UP
ODDS OF
BECOMING NOT FRAIL V. MODERATELY/SEVERELY FRAIL;

DATA FRAIL5;
SET FINALFRAIL;
IF FRAILY1 IN(2,3) THEN DELETE;
IF FRAILY4 IN (2,3) THEN FRAILY4=2;
IF FRAILY6 IN(2,3) THEN FRAILY6=2;
RUN;

DATA FRAIL6;
```

```
  SET FRAIL5;
  WAVE=4;
  FRAILGROUP=FRAILY4;
  OUTPUT;
  WAVE=6;
  FRAILGROUP=FRAILY6;
  OUTPUT;
  KEEP HABCID WAVE MINGROUP INTGROUP BRACHGROUP FRAILY1 FRAILGROUP COUNTDX
TOTKCAL CV1AGE GENDER
RACE EDUC NEWMAR SMK1 CURDRNK1 Y1PCHD1 Y1PCHF Y1PCBVD Y1PPAD Y1PDIAB1
LOWEROA Y1PHBP1 Y1PDEPR1 Y1PPULCD Y1PCANCR P3ABI;
RUN;

*UNADJUSTED MODELS-ALREADY TESTED FOR PA X WAVE INTERACTIONS AND THEY WERE
NONSIGNIFICANT
IN ALL MODELS;
PROC GENMOD DATA=FRAIL6 DESCENDING;
      CLASS HABCID MINGROUP WAVE;
      MODEL FRAILGROUP=MINGROUP WAVE TOTKCAL/DIST=BIN;
      REPEATED SUBJECT=HABCID /TYPE=EXCH COVB CORRW;
   run;

PROC GENMOD DATA=FRAIL6 DESCENDING;
      CLASS HABCID INTGROUP WAVE;
      MODEL FRAILGROUP=INTGROUP WAVE TOTKCAL/DIST=BIN;
      REPEATED SUBJECT=HABCID /TYPE=EXCH COVB CORRW;
   run;

PROC GENMOD DATA=FRAIL6 DESCENDING;
      CLASS HABCID BRACHGROUP WAVE;
      MODEL FRAILGROUP=BRACHGROUP WAVE TOTKCAL/DIST=BIN;
      REPEATED SUBJECT=HABCID /TYPE=EXCH COVB CORRW;
   run;

*SATURATED MODELS LOOKING FOR INTERACTIONS FIRST WITH CV1AGE GENDER RACE
EDUC NEWMAR SMK1
CURDRNK1 Y1PCHD1 Y1PCBVD Y1PPAD Y1PDIAB1 LOWEROA Y1PHBP1 Y1PDEPR1
Y1PPULCD;
PROC GENMOD DATA=FRAIL6 DESCENDING;
CLASS HABCID;
MODEL FRAILGROUP=  WAVE MINGROUP|CV1AGE MINGROUP|GENDER MINGROUP|RACE
MINGROUP|EDUC
MINGROUP|NEWMAR MINGROUP|SMK1 MINGROUP|CURDRNK1
MINGROUP|Y1PCHD1 MINGROUP|Y1PCBVD MINGROUP|Y1PPAD MINGROUP|Y1PDIAB1
MINGROUP|LOWEROA
MINGROUP|Y1PHBP1 MINGROUP|Y1PDEPR1 MINGROUP|Y1PPULCD;
REPEATED SUBJECT=HABCID/TYPE=EXCH COVB CORRW;
RUN;

PROC GENMOD DATA=FRAIL6 DESCENDING;
CLASS HABCID;
MODEL FRAILGROUP= WAVE INTGROUP|CV1AGE INTGROUP|GENDER INTGROUP|RACE
INTGROUP|EDUC
INTGROUP|NEWMAR INTGROUP|SMK1 INTGROUP|CURDRNK1
INTGROUP|Y1PCHD1 INTGROUP|Y1PCBVD INTGROUP|Y1PPAD INTGROUP|Y1PDIAB1
INTGROUP|LOWEROA
INTGROUP|Y1PHBP1 INTGROUP|Y1PDEPR1 INTGROUP|Y1PPULCD;
```

```
REPEATED SUBJECT=HABCID/TYPE=EXCH COVB CORRW;
RUN;

PROC GENMOD DATA=FRAIL6 DESCENDING;
CLASS HABCID;
MODEL FRAILGROUP= WAVE BRACHGROUP|CV1AGE BRACHGROUP|GENDER BRACHGROUP|RACE
BRACHGROUP|EDUC
BRACHGROUP|NEWMAR BRACHGROUP|SMK1 BRACHGROUP|Y1PPAD BRACHGROUP|Y1PDIAB1
BRACHGROUP|LOWEROA
BRACHGROUP|Y1PHBP1 BRACHGROUP|Y1PDEPR1 BRACHGROUP|Y1PPULCD;
REPEATED SUBJECT=HABCID/TYPE=EXCH COVB CORRW;
RUN;

*FINAL ADJUSTED MODELS WITH REDUCED FIT TO ONLY INCLUDE SIGNIFICANT
INTERACTIONS-
WHICH WERE NONE WHEN REDUCING THE MODEL BACK DOWN- AND OTHER A PRIORI
COVARIATES. ALSO
ADDED COUNTDX INSTEAD OF INDIVIDUAL DX;
PROC GENMOD DATA=FRAIL6 DESCENDING;
CLASS HABCID WAVE;
MODEL FRAILGROUP= MINGROUP WAVE TOTKCAL CV1AGE GENDER RACE EDUC NEWMAR
SMK1 CURDRNK1 P3ABI
COUNTDX;
REPEATED SUBJECT=HABCID/TYPE=EXCH COVB CORRW;
RUN;

PROC GENMOD DATA=FRAIL6 DESCENDING;
CLASS HABCID WAVE;
MODEL FRAILGROUP= INTGROUP TOTKCAL CV1AGE GENDER RACE EDUC
NEWMAR SMK1 CURDRNK1 P3ABI COUNTDX;
REPEATED SUBJECT=HABCID/TYPE=EXCH COVB CORRW;
RUN;

PROC GENMOD DATA=FRAIL6 DESCENDING;
CLASS HABCID WAVE;
MODEL FRAILGROUP= BRACHGROUP TOTKCAL GENDER CV1AGE RACE EDUC NEWMAR SMK1
CURDRNK1
P3ABI COUNTDX;
REPEATED SUBJECT=HABCID/TYPE=EXCH COVB CORRW;
RUN;


*LOOKING TO SEE IF PA GROUPS PREDICT SEVERITY OF FOLLOW UP FRAILTY STATUS;
DATA FRAIL7;
  SET FINALFRAIL;
  IF FRAILY1 IN (2,3) THEN DELETE;
  IF FRAILY4=1 THEN DELETE;
  IF FRAILY6=1 THEN DELETE;
  WAVE=4;
  FRAILGROUP=FRAILY4;
  OUTPUT;
  WAVE=6;
  FRAILGROUP=FRAILY6;
  OUTPUT;
  KEEP HABCID WAVE MINGROUP INTGROUP BRACHGROUP FRAILY1 FRAILGROUP TOTKCAL
CV1AGE GENDER
RACE EDUC NEWMAR SMK1 CURDRNK1 Y1PCHD1 Y1PCHF Y1PCBVD Y1PPAD Y1PDIAB1
```

```
LOWEROA COUNTDX Y1PHBP1 Y1PDEPR1 Y1PPULCD Y1PCANCR P3ABI;
RUN;

PROC GENMOD DATA=FRAIL7 DESCENDING;
      CLASS HABCID MINGROUP WAVE;
      MODEL FRAILGROUP=MINGROUP WAVE TOTKCAL/DIST=BIN;
      REPEATED SUBJECT=HABCID/TYPE=EXCH COVB CORRW;
   run;

PROC GENMOD DATA=FRAIL7 DESCENDING;
      CLASS HABCID INTGROUP WAVE;
      MODEL FRAILGROUP=INTGROUP WAVE TOTKCAL/DIST=BIN;
      REPEATED SUBJECT=HABCID /TYPE=EXCH COVB CORRW;
   run;

PROC GENMOD DATA=FRAIL7 DESCENDING;
      CLASS HABCID BRACHGROUP WAVE;
      MODEL FRAILGROUP=BRACHGROUP WAVE TOTKCAL/DIST=BIN;
      REPEATED SUBJECT=HABCID /TYPE=EXCH COVB CORRW;
   run;

*SATURATED MODELS LOOKING FOR INTERACTIONS FIRST WITH CV1AGE GENDER RACE
EDUC NEWMAR SMK1
CURDRNK1 Y1PCHD1 Y1PCBVD Y1PPAD Y1PDIAB1 LOWEROA Y1PHBP1 Y1PDEPR1
Y1PPULCD;
PROC GENMOD DATA=FRAIL7 DESCENDING;
CLASS HABCID;
MODEL FRAILGROUP=  WAVE MINGROUP|CV1AGE MINGROUP|GENDER MINGROUP|RACE
MINGROUP|EDUC
MINGROUP|NEWMAR MINGROUP|SMK1 MINGROUP|CURDRNK1
MINGROUP|Y1PCHD1 MINGROUP|Y1PCBVD MINGROUP|Y1PPAD MINGROUP|Y1PDIAB1
MINGROUP|LOWEROA
MINGROUP|Y1PHBP1 MINGROUP|Y1PDEPR1 MINGROUP|Y1PPULCD;
REPEATED SUBJECT=HABCID/TYPE=EXCH COVB CORRW;
RUN;

PROC GENMOD DATA=FRAIL7 DESCENDING;
CLASS HABCID;
MODEL FRAILGROUP= WAVE INTGROUP|CV1AGE INTGROUP|GENDER INTGROUP|RACE
INTGROUP|EDUC
INTGROUP|NEWMAR INTGROUP|SMK1 INTGROUP|CURDRNK1
INTGROUP|Y1PCHD1 INTGROUP|Y1PCBVD INTGROUP|Y1PPAD INTGROUP|Y1PDIAB1
INTGROUP|LOWEROA
INTGROUP|Y1PHBP1 INTGROUP|Y1PDEPR1 INTGROUP|Y1PPULCD;
REPEATED SUBJECT=HABCID/TYPE=EXCH COVB CORRW;
RUN;

PROC GENMOD DATA=FRAIL7 DESCENDING;
CLASS HABCID;
MODEL FRAILGROUP= WAVE BRACHGROUP|CV1AGE BRACHGROUP|GENDER BRACHGROUP|RACE
BRACHGROUP|EDUC
BRACHGROUP|NEWMAR BRACHGROUP|SMK1 BRACHGROUP|Y1PPAD BRACHGROUP|Y1PDIAB1
BRACHGROUP|LOWEROA
BRACHGROUP|Y1PHBP1 BRACHGROUP|Y1PDEPR1 BRACHGROUP|Y1PPULCD;
REPEATED SUBJECT=HABCID/TYPE=EXCH COVB CORRW;
RUN;
```

```
*FINAL ADJUSTED MODELS WITH REDUCED FIT TO ONLY INCLUDE SIGNIFICANT
INTERACTIONS-
WHICH WERE NONE WHEN REDUCING THE MODEL BACK DOWN- AND OTHER A PRIORI
COVARIATES. ALSO
ADDED COUNTDX INSTEAD OF INDIVIDUAL DX;
PROC GENMOD DATA=FRAIL7 DESCENDING;
CLASS HABCID MINGROUP WAVE;
MODEL FRAILGROUP= MINGROUP WAVE TOTKCAL CV1AGE GENDER RACE EDUC NEWMAR
SMK1 CURDRNK1
P3ABI COUNTDX;
REPEATED SUBJECT=HABCID/TYPE=EXCH COVB CORRW;
RUN;

PROC GENMOD DATA=FRAIL7 DESCENDING;
CLASS HABCID INTGROUP WAVE;
MODEL FRAILGROUP= INTGROUP SMK1 TOTKCAL CV1AGE GENDER RACE EDUC
NEWMAR CURDRNK1 P3ABI COUNTDX;
REPEATED SUBJECT=HABCID/TYPE=EXCH COVB CORRW;
RUN;

PROC GENMOD DATA=FRAIL7 DESCENDING;
CLASS HABCID BRACHGROUP WAVE;
MODEL FRAILGROUP= BRACHGROUP SMK1 TOTKCAL GENDER CV1AGE RACE EDUC NEWMAR
CURDRNK1
P3ABI COUNTDX;
REPEATED SUBJECT=HABCID/TYPE=EXCH COVB CORRW;
RUN;


*THESE ANALYSES ARE TESTING DIFFERENCES IN PA EFFECT BETWEEN SRATA. IN
OTHER WORDS,
DO THOSE WHO ARE FRAIL AT BASELINE CHANGE TO NOT FRAIL WITH HIGH PA
LEVELS?;
DATA FRAIL8;
  SET FINALFRAIL;
  IF FRAILY1 IN (1) THEN DELETE;
  IF FRAILY1 IN(2,3) THEN FRAILY1=2;
  IF FRAILY4 IN(2,3) THEN FRAILY4=2;
  IF FRAILY6 IN(2,3) THEN FRAILY6=2;
  WAVE=4;
  FRAILGROUP=FRAILY4;
  OUTPUT;
  WAVE=6;
  FRAILGROUP=FRAILY6;
  OUTPUT;
  KEEP HABCID WAVE MINGROUP INTGROUP BRACHGROUP FRAILY1 FRAILGROUP TOTKCAL
CV1AGE GENDER
RACE EDUC NEWMAR SMK1 CURDRNK1 Y1PCHD1 Y1PCHF Y1PCBVD Y1PPAD Y1PDIAB1
LOWEROA COUNTDX Y1PHBP1 Y1PDEPR1 Y1PPULCD Y1PCANCR P3ABI;
RUN;

*MODELS ESTIMATING ODDS OF CHANGING FRAILTY STATUS IN THOSE FRAIL AT
BASELINE;
PROC GENMOD DATA=FRAIL8;
CLASS HABCID MINGROUP WAVE;
MODEL FRAILGROUP= MINGROUP WAVE TOTKCAL CV1AGE GENDER RACE EDUC NEWMAR
SMK1 CURDRNK1
```

```
P3ABI COUNTDX;
REPEATED SUBJECT=HABCID/TYPE=EXCH COVB CORRW;
RUN;

PROC GENMOD DATA=FRAIL8;
CLASS HABCID INTGROUP WAVE;
MODEL FRAILGROUP= INTGROUP SMK1 TOTKCAL CV1AGE GENDER RACE EDUC
NEWMAR CURDRNK1 P3ABI COUNTDX;
REPEATED SUBJECT=HABCID/TYPE=EXCH COVB CORRW;
RUN;

PROC GENMOD DATA=FRAIL8;
CLASS HABCID BRACHGROUP WAVE;
MODEL FRAILGROUP= BRACHGROUP SMK1 TOTKCAL GENDER CV1AGE RACE EDUC NEWMAR
CURDRNK1
P3ABI COUNTDX;
REPEATED SUBJECT=HABCID/TYPE=EXCH COVB CORRW;
RUN;

*AND MODELS ESTIMATING ODDS OF CHANGING FRAILTY STATUS IN THOSE NOT FRAIL
AT BASELINE;
DATA FRAIL9;
SET FINALFRAIL;
IF FRAILY1 IN(2,3) THEN DELETE;
IF FRAILY4 IN (2,3) THEN FRAILY4=2;
IF FRAILY6 IN(2,3) THEN FRAILY6=2;
RUN;

DATA FRAIL10;
  SET FRAIL9;
  WAVE=4;
  FRAILGROUP=FRAILY4;
  OUTPUT;
  WAVE=6;
  FRAILGROUP=FRAILY6;
  OUTPUT;
  KEEP HABCID WAVE MINGROUP INTGROUP BRACHGROUP FRAILY1 FRAILGROUP COUNTDX
TOTKCAL CV1AGE GENDER
RACE EDUC NEWMAR SMK1 CURDRNK1 Y1PCHD1 Y1PCHF Y1PCBVD Y1PPAD Y1PDIAB1
LOWEROA Y1PHBP1 Y1PDEPR1 Y1PPULCD Y1PCANCR P3ABI;
RUN;

PROC GENMOD DATA=FRAIL10 DESCENDING;
CLASS HABCID MINGROUP WAVE;
MODEL FRAILGROUP= MINGROUP WAVE TOTKCAL CV1AGE GENDER RACE EDUC NEWMAR
SMK1 CURDRNK1
P3ABI COUNTDX;
REPEATED SUBJECT=HABCID/TYPE=EXCH COVB CORRW;
RUN;

PROC GENMOD DATA=FRAIL10 DESCENDING;
CLASS HABCID INTGROUP WAVE;
MODEL FRAILGROUP= INTGROUP TOTKCAL CV1AGE GENDER RACE EDUC
NEWMAR SMK1 CURDRNK1 P3ABI COUNTDX;
REPEATED SUBJECT=HABCID/TYPE=EXCH COVB CORRW;
RUN;
```

```
PROC GENMOD DATA=FRAIL10 DESCENDING;
CLASS HABCID BRACHGROUP WAVE;
MODEL FRAILGROUP= BRACHGROUP TOTKCAL GENDER CV1AGE RACE EDUC NEWMAR SMK1
CURDRNK1
P3ABI COUNTDX;
REPEATED SUBJECT=HABCID/TYPE=EXCH COVB CORRW;
RUN;

data odds (keep=group est1 est2 est logest low_ci up_ci var Z  q);
input group $  est1 se1 est2 se2 ;

var1=se1** 2;
var2=se2** 2;
wt=(1 /var1) + (1 /var2);
logest= ((est1*(1 /var1)) + (est2*(1 /var2))) / wt ;
var=1 /wt;
z=logest/sqrt(var);
est=exp(logest);
up_ci=exp(logest +1.96 *sqrt(var));
low_ci=exp(logest -1.96 *sqrt(var));


* homogeneity;
q=(((est1-logest)** 2 )/var1) + (((est2-logest)** 2)/var2);



cards ;
lotime .1896 .1364 -.0107 .0120
modtime -.2065 .2257 -.0163 .0214
sedint .1668 .1626 -.0091 .0194
lightint .1662 .1437 -.0138 .0148
modint -.1191 .1806 -.0096 .0152
sedbrach .1256 .1880 .0348 .0178
lifbrach .0968 .1578 -.0021 .0121


;
proc print ;
run ;

*-------------------------------------------------------------------------
------------;

*TESTING TO SEE WHAT CHARACTERISTICS DROP-OUTS HAD COMPARED TO THOSE THAT
REMAINED IN THE STUDY;

DATA DROP;
SET FINALFRAIL;
IF FRAILY6=.;
GROUP=2;
RUN;

DATA NOTDROP;
SET FINALFRAIL;
IF FRAILY6 NOT=.;
```

```
GROUP=1;
RUN;

PROC SORT DATA=NOTDROP;
BY HABCID;
RUN;

PROC SORT DATA=DROP;
BY HABCID;
RUN;

DATA DROPALL;
MERGE DROP NOTDROP;
BY HABCID;
RUN;


PROC FREQ DATA=DROPALL;
TABLES CV1AGE*GROUP/CMH;
TABLES COUNTDX*GROUP/CMH;
TABLES GENDER*GROUP/CMH;
TABLES FRAILY1*GROUP/CMH;
TABLES MINGROUP*GROUP/CMH;
TABLES INTGROUP*GROUP/CMH;
TABLES BRACHGROUP*GROUP/CMH;
RUN;


*ANALYSIS OF THE STABILITY OF THE EXERCISE TIME GROUP OVER TIME;

DATA PAWAVE1;
SET FINALFRAIL;
DROP MINGROUP;
TOTMIN=Y1WKTIME+HIGHXMIN;
IF TOTMIN>=200 THEN MINGROUP1=3;
IF 150<=TOTMIN<200 THEN MINGROUP1=2;
IF TOTMIN<150 THEN MINGROUP1=1;

IF (Y2BWTIME+Y2WKTIME)>=200 THEN MINGROUP2=3;
IF 150<=(Y2BWTIME+Y2WKTIME)<200 THEN MINGROUP2=2;
IF (Y2BWTIME+Y2WKTIME)<150 THEN MINGROUP2=1;

IF (Y3BWTIME+Y3WKTIME)>=200 THEN MINGROUP3=3;
IF 150<=(Y3BWTIME+Y3WKTIME)<200 THEN MINGROUP3=2;
IF (Y3BWTIME+Y3WKTIME)<150 THEN MINGROUP3=1;

IF (Y5BWTIME+Y5WKTIME)>=200 THEN MINGROUP5=3;
IF 150<=(Y5BWTIME+Y5WKTIME)<200 THEN MINGROUP5=2;
IF (Y5BWTIME+Y5WKTIME)<150 THEN MINGROUP5=1;

DATA PAWAVE2;
SET PAWAVE1;
IF MINGROUP1=. THEN DELETE;
IF MINGROUP2=. THEN DELETE;
IF MINGROUP3=. THEN DELETE;
IF MINGROUP5=. THEN DELETE;
RUN;
```

```
DATA PAWAVE3;
  SET PAWAVE2;
  WAVE=1;
  MINGROUP=MINGROUP1;
WALKMIN=Y1WKTIME;
  OUTPUT;
  WAVE=2;
  MINGROUP=MINGROUP2;
  WALKMIN=Y2WKTIME;
  OUTPUT;
  WAVE=3;
  MINGROUP=MINGROUP3;
  WALKMIN=Y3WKTIME;
  OUTPUT;
  WAVE=5;
  MINGROUP=MINGROUP5;
  WALKMIN=Y5WKTIME;
  OUTPUT;

  KEEP HABCID WAVE MINGROUP WALKMIN;
RUN;

PROC VARCOMP DATA=PAWAVE3 METHOD=TYPE1;
CLASS HABCID;
MODEL MINGROUP=HABCID;
RUN;

PROC GLM DATA=PAWAVE3;
CLASS WAVE;
MODEL WALKMIN=WAVE;
MEANS WAVE/tukey;
RUN;

PROC VARCOMP DATA=PAWAVE3 METHOD=TYPE1;
CLASS HABCID WAVE;
MODEL MINGROUP=HABCID WAVE;
RUN;

PROC VARCOMP DATA=PAWAVE3 METHOD=TYPE1;
CLASS HABCID WAVE;
MODEL MINGROUP=HABCID WAVE/FIXED=1;;
RUN;
```