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IRB Proposal
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CRC

A. Study Purpose and Rationale

Cardiovascular disease, including coronary heart disease, cerebrovascular disease and peripheral vascular disease, remains one of the largest contributors to the burden of disease worldwide. Regular exercise has been shown to significantly reduce the risk of cardiovascular disease morbidity. This observation is drawn from the results of large prospective studies that use self-reported assessments of physical activity, which are subject to random and systematic reporting bias, do not account for free-living activity, and provide inaccurate estimates of absolute measures of activity.

Doubly labeled water (DLW) emerged as an effective non-invasive method that uses indirect calorimetry to determine activity patterns objectively in free-living individuals (Westerterp, 2009). However DLW remains prohibitively expensive, has a high participant burden, and requires special technical expertise for implementation that limits its use in most large studies. As such, the capacity to measure the association between objective activity patterns and cardiovascular disease in large populations has remained elusive.

Recent technologies such as pedometers and accelerometers are now relatively inexpensive and feasible for use to objectively measure activity patterns in large epidemiologic studies (Colbert, 2011). In a validation study evaluating daily energy expenditure and physical activity energy expenditure in 45 subjects over a 10 day period simultaneously with a portable armband and DLW, a significant level of concordance between armband and DLW methods was shown (St-Onge, 2007).

Accelerometers have been utilized by several large studies to show associations between decreased levels of objectively measured physical activity and increase in cardiovascular risk factors. Using data from the National Health and Nutrition Examination Survery (NHANES), negative associations were observed between accelerometer-measured minutes of combined moderate and vigorous activity and systolic blood pressure, blood glucose, diabetes, hypertension, body mass index and obesity (Luke, 2011). A cross-sectional study of children from Denmark, Estonia, and Portugal similarly demonstrated that lower levels physical activity as measured by accelerometry were associated with increased systolic blood pressure, triglycerides, and insulin resistance (Anderson, 2006). However, none of these studies have examined the relationship of objectively measured activity level and incident development of cardiovascular disease. Thus, it remains uncertain whether portable activity monitors are capable of accurately predicting incidence of cardiovascular disease.

Recent studies using the present database have shown significant inverse associations between the objectively measured physical activity variables total energy expenditure, time in moderate activity, time in sedentary behavior and CVD mortality. However lack of association between these variables and incident CVD event was observed. In this study we plan to further examine this relationship between objectively measured physical activity and CVD by assessing the association of peak and sustained physical activity with CVD events and mortality. We hypothesize that higher daily peak activity and days in sustained activity are associated with decreased cardiovascular incidence and mortality in older men.

B. Study Design and Statistical Analysis

Study Sample

In 2000-2003, 5994 men joined the Osteoporotic Fractures in Men Study (MrOS), in six US clinical centers, (Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Monongahela Valley, near Pittsburgh, PA; Portland, OR and San Diego, CA). At the baseline visit, men were aged ≥65 years and able to walk independently. Men were invited to a third visit between 2007-2009 to wear an accelerometer. Of 4,681 active men, 3,354 (72%) wore the activity monitor. For these analyses, we excluded 283 men who wore the activity monitor for <90% of the time; and an additional 153 who wore the activity monitor <5 days, leaving 2,918 men with complete accelerometry data. Written informed consent was obtained from each participant and was approved by the institutional review boards at each institution.

Accelerometry

Participants were instructed to wear the SenseWear Pro Armband (Body Media, Inc; Pittsburgh, PA) over the right triceps muscle at all times, including while sleeping, over a typical 7-day period. Data were sampled in 1-minute epochs from several sensors: a heat flux sensor, a galvanic skin response sensor, a skin temperature sensor, a near body sensor and body movement sensor (2-axis accelerometer). These data were used in proprietary algorithms (Innerview Professional 5.1 software) along with height, weight, handedness and smoking status to estimate energy expenditure in kilocalories per day. Resting metabolic rate (RMR) was estimated using the Harris Benedict Equation (REF). Available accelerometry measurements were: total energy expenditure (TEE): average total amount of energy (kcal) expended per 24 hrs; physical activity energy expenditure (PAEE): average amount of energy (kcal) that was expended per 24 hrs at a MET≥1.5 ; minutes of moderate activity: average number of minutes per day spent in activity with MET≥3.0; minutes of sedentary activity: average number of minutes per day spent at MET≤1.5. Acceptable levels of agreement for TEE and PAEE comparing Sensewear Pro Armband with doubly labeled water were observed in older adults.

Other Measurements

All participants completed a standard self-administered questionnaire that included queries about race/ethnicity, education level, smoking, number of alcoholic drinks per week, self-reported disease, and self-rated health. Available blood pressure (BP) measurements include ankle-arm BP, pulse pressure, and resting BP. Mobility limitation was defined as self-reported difficulty walking 2-3 blocks or climbing 10 steps. Height (cm) was measured on Harpenden stadiometers, and weight (kg) was measured on standard balance beam or digital scales using standard protocols, with participants wearing light clothing without shoes. Body mass index (BMI) was calculated as kg/m^2. Lipid profiles were unavailable.

Statistical Analyses
Primary measures of activity level will be analyzed as continuous variables (peak METS or number minutes in sustained activity >3 METS, per SD increase) and expressed in quintiles. Primary measures of energy expenditure (peak and sustained energy expenditure, peak and sustained physical activity energy expenditure) will be analyzed as continuous variables (kcal/day, per SD increase) and expressed in quintiles. Cox proportional hazards models will be used to analyze the association between activity level and/or energy expenditure measure and risk of cardiovascular disease and mortality. Hazard ratios and 95% CI will be calculated. The base model will adjust for age, race, site, and season. A candidate covariate will be selected as a potential confounder based on evidence of an association with activity level or energy expenditure measure and risk of cardiovascular risk factor independent of age. Multivariate models will adjust for base + confounders (eg., total cholesterol, HDL cholesterol, smoking status, systolic blood pressure). Using 80% power and alpha 0.05, with 1500 subjects in each group this study will be able to detect a case-control difference of one-tenth of an SD in each continuous characteristic to be significant.

C. Study Procedure.
There will be no additional study procedures that are outside of those already received by patients prior to study enrollment.

D. Study Drugs*
N/A

E. Medical Device.*
N/A

F. Study Questionnaires
No further questionnaires will be administered.

G. Study Subjects
Inclusion criteria: Men aged $\geq$65 years and able to walk independently who were part of the Osteoporotic Fractures in Men Study (MrOS) and wore an accelerometer between 2007-2009.

Exclusion criteria: Accelerometer worn <90% time or <5 days

This study was limited to men only, as women were not included in the original

(2000-2003) MrOS cohort.

H. Recruitment of Subjects
All subjects have already been recruitment and no further recruitment will be taking place.

I. Confidentiality of Study Data
All study data have been de-identified and personal identifiers are unavailable. All data are stored in a secured location.

J. Potential Conflict of Interest
None of the study investigators have any conflicts of interest to disclose or stand to benefit financially or in any other way from the results of the investigation.

K. Location of the Study
The study is located in six clinical centers throughout the US, (Birmingham, AL; Minneapolis, MN; Palo Alto, CA; Monongahela Valley, near Pittsburgh, PA; Portland, OR and San Diego, CA). IRB approval has been obtained by all remote clinical centers. The CUMC sponsor with access to study data is Dr. Tien Dam.

L. Potential Risks
There are no potential risks identified in this study.

M. Potential Benefits
The potential benefits of this study are discovering a potential association between higher levels of objectively measured physical activity and reduced cardiovascular disease, which could potentially lead to future development of therapeutic exercise regimens or treatments.

N. Alternative Therapies
N/A

O. Compensation to Subjects
N/A

P. Costs to Subjects
N/A

Q. Minors as Research Subjects
N/A

R. Radiation or Radioactive Substances
N/A