The Role of Physical Activity and Obesity in the Occurrence of Major Cardiovascular Events and Mortality among a Low-Income Population with Diabetes

By

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To my faithful and ever-present Savior, the Lord Jesus Christ, who guides my footsteps and brings me strength with peace. This process has taught me how to know You for myself;

To my family who have always loved and accepted me, my ambitions, and my strong resolve. Thank you for never leaving me;

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CHAPTER 1

Literature Review

Introduction

Diabetes is a major public health problem in the United States, with 25.6 million people with the disease(1). Strategies to reduce adverse outcomes among those with diabetes and delay mortality are important to provide to patients and structure for healthcare providers. Physical activity has long been a neglected aspect of the type 2 diabetes treatment regimen. Increasing physical activity is simple and relatively free for patients, and may provide significant benefits to insulin sensitivity, glycemic control, and overall health(2). However, most studies that have researched the association between physical activity, sedentary behaviors, and cardiovascular disease in those with diabetes have been among primarily white or male populations (3-16). This leaves the literature with little to no information about this association in other racial groups, like blacks, and women – both populations disproportionately affected by diabetes.

Descriptive Epidemiology of Diabetes and Associated Racial Disparities

Type 2 diabetes mellitus, often referred to as adult-onset or non-insulin-dependent diabetes, is a chronic disease that results from a progressive insulin secretory defect on the background of insulin resistance(17). Insulin resistance is a condition in which the body is unable to properly use the insulin it produces. In this stage, the pancreatic β-cells try to compensate by increasing the levels of insulin in the blood leading to hyperinsulinemia. The patient may be asymptomatic during this stage but mild hyperglycemia is still present. When β-cell function decreases, the production of insulin

also decreases while blood glucose levels and insulin resistance increase(18) (**Figure 1**).

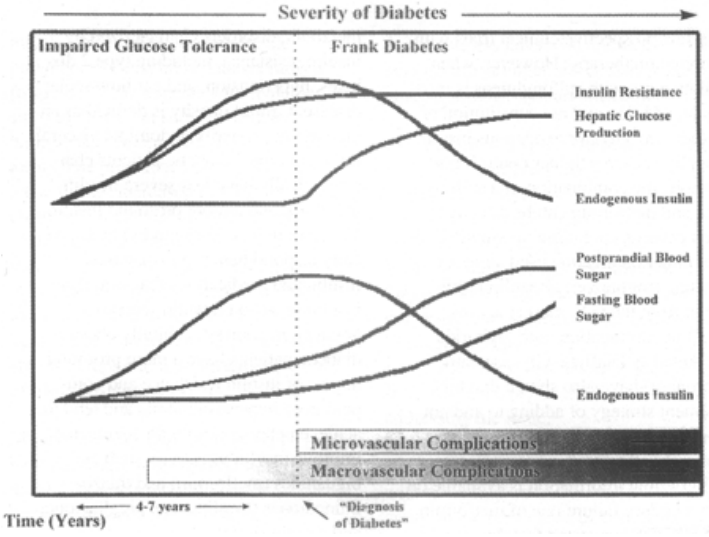


Figure 1. The natural history of insulin resistance. (Figure from Ramlo-Halsted & Edelman, 2000)(18)

Figure 2 below shows the increase in the prevalence of diagnosed diabetes across the United States from 2004-2009(19). In five years, the age-adjusted prevalence of diagnosed diabetes rose from 5.2% to 6.3% nationwide. The National Diabetes Fact Sheet from 2011 reported that in 2010, an estimated 13.0 million men and 12.6 million women aged 20 years or older had been diagnosed with diabetes(20).

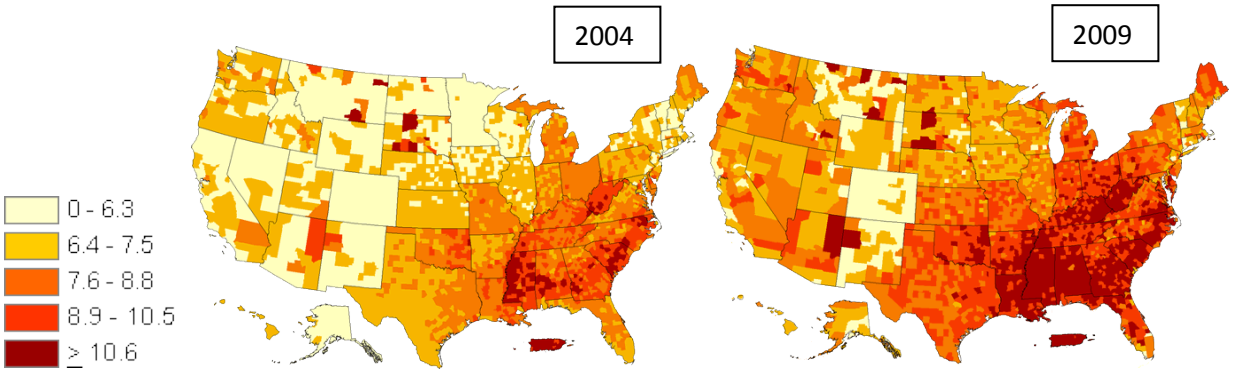


Figure 2. Age-adjusted estimates of the prevalence of diagnosed diabetes among U.S. adults aged 20 years and older(21), 2004 and 2009.

Blacks are disproportionately affected by diabetes, with a consistently observed higher prevalence of diabetes compared to whites (12.6% vs. 7.1% for 2007-2009)(20). Echoing the prevalence rates, blacks are at increased risk of developing incident diabetes when compared to whites (13.0 vs. 7.7 per 1,000 persons diagnosed in 2010)(19). Blacks are also younger, on average, than whites when diagnosed with diabetes (51.4 vs. 53.2 years old)(19). In the Southern Community Cohort Study (SCCS), a large prospective epidemiologic cohort study examining racial differences in cancer and other chronic diseases in the southeastern United States (described in detail in the *Methods* section), which will serve as the parent cohort for the research, no significant difference was observed in the prevalence of diagnosed diabetes among blacks when compared to whites of similar (predominantly low) socioeconomic status and after adjustment for pertinent confounding factors(22, 23). The Atherosclerosis Risk in Communities (ARIC) Project reported similar results among over 15,000 black and white men and women(24), suggesting that socioeconomic and other lifestyle or social environment factors may play a contributory role in racial disparities in diabetes occurrence.

Summary of Epidemiologic Risk Factors Associated with Diabetes

Health disparities in diabetes risk are hypothesized to be attributable to differences in risk factors such as diet, physical activity, obesity, and socioeconomic status between blacks and whites(25, 26). In particular, with low socioeconomic status and obesity both disproportionately affecting blacks and both being positively associated with diabetes, much of the reported higher risk of diabetes among blacks can likely be accounted for by to these two confounding factors. Other research has suggested a role for genetic predispositions to diabetes and diabetes-related risk factors, as discussed later(27). Several identified genetic variants only explain a small proportion of excess risk of diabetes in certain subpopulations (blacks, for instance)(28, 29).

Many risk factors for diabetes have been identified, including poor diet, obesity and sedentary lifestyle, smoking, and socioeconomic status. Obesity, particularly central or abdominal obesity, and weight gain are positively associated with the risk of diabetes (30-32). A cross-sectional study conducted in the SCCS population reported a strong positive association between adult weight gain and diabetes that persisted across genders and racial groups(33).

A positive association between smoking and incident diabetes has been reported in several prospective cohort studies (34-38). Collectively, these studies have demonstrated that persons smoking 20 or more cigarettes per day had up to a two-fold greater risk of developing type 2 diabetes compared to non-smokers, after adjustment for body mass index (BMI), alcohol consumption, physical activity and other factors(38-

40). Diabetes has been associated with measures of socioeconomic status such as poverty income ratio, education and occupational status(41-43).

Physical activity and sedentary behaviors have been consistently associated with incident type 2 diabetes in both men and women (44-50). A recent case-cohort study reported that increased physical activity was associated with a 13% and 7% reduction in diabetes risk in men and women, respectively(51). Among women, another study found that for every 2 hour/day increase in time spent watching television, the risk of diabetes increases by 14%. Two hour/day increases in sitting resulted in a 7% increase in diabetes risk.(52)

Cardiovascular Disease and its Relationship with Diabetes

Chronic cardiovascular complications, also known as macrovascular complications, include conditions such as coronary heart disease (CHD), peripheral artery disease (PAD), congestive heart failure (CHF), and stroke. Diabetes usually occurs in the setting of metabolic syndrome, which is comprised of abdominal obesity, hypertension, hyperlipidemia, hyperglycemia, and increased coagulability(53). Although factors included in metabolic syndrome are also risk factors for cardiovascular disease (CVD), diabetes is believed to act as an independent risk factor for CVD.

Atherosclerosis is the hardening and narrowing of the arteries and the main mechanism in the processes that lead to macrovascular disease. It is also believed to be the result of chronic inflammation and injury to the arterial wall in the peripheral or coronary vascular system (53). In response to this injury, oxidized lipids from low-density lipoprotein (LDL) particles accumulate in the endothelial wall of the arteries. Monocytes differentiate into macrophages after infiltrating the arterial wall, and then accumulate oxidized lipids to create foam cells. The foam cells promote macrophage proliferation and attract of T-lymphocytes. The growing amounts of T-lymphocytes prompt smooth muscle proliferation in the arterial walls and collagen buildup. This process results in the formation a lipid-rich atherosclerotic lesion (atheroma).(54)

In individuals with diabetes, increased platelet adhesion and hypercoagulability occur in addition to the atheroma formation(54). Increased levels of plasminogen activator inhibitor type 1 may also impair fibrinolysis in patients with diabetes. Hypercoagulability and impaired fibrinolysis increases the risk of vascular obstruction and cardiovascular

events among diabetics(55). Although the precise mechanisms are not defined, the association between diabetes and plaque formation is strong (54, 56).

CVD is the leading cause of death among diabetics and CVD morbidity accounts for the greatest proportion of healthcare expenditures for diabetics (57, 58). In 2010, heart disease and stroke were listed as contributing causes of death on 68% and 16%, respectively, of diabetes-related death certificates in people aged 65 years or older(20). In previous work conducted in the SCCS, Conway et al reported that CHD was among the leading causes of death among pharmaceutically-treated young-onset diabetics (59). Another study conducted by Conway et al among SCCS participants reported a greater risk of mortality among diabetics with CVD, hypertension and stroke compared to non-diabetics(60).

Racial Disparities in Cardiovascular Disease and Mortality among those with Diabetes

A systematic review of the literature published in 2005 revealed that blacks, Hispanic Americans, and Asian Americans had a lower risk for developing cardiovascular complications of diabetes compared to whites(61). Although blacks have a lower or equal incidence of CVD related to diabetes, the mortality rate among blacks from CVD is higher(62). The mortality difference between blacks and whites may be due, in part, to differences in glucose metabolism, insulin resistance, obesity, and related genetic factors(63).

CHAPTER 2

Study Population

All subjects for this study were participants in the SCCS, an ongoing, prospective, population-based study designed to examine health disparities in the incidence and mortality of chronic conditions. The study population is unique, with over two-thirds black and both black and white participants having similar socioeconomic characteristics. Details of the study design, including recruitment and sampling methods, were described in detail elsewhere(23). In short, approximately 85% of participants were recruited from community health centers (CHCs), which are federally funded healthcare facilities primarily servicing low-income individuals, in 12 southeastern states (Figure 3; Alabama, Arkansas, Florida, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee, Virginia, and West Virginia)(64). CHC personnel conducted the recruitment of participants and facilitated the provision of informed consent. Individuals who appeared to be 40 to 79 years of age were approached by CHC personnel and study eligibility was determined (age criterion, English-speaking, and had not undergone treatment for any cancer except non-melanoma skin cancer within the preceding year).(64)

The remaining 15% of the SCCS population was recruited from the general population in order to provide more diversity in the income and educational backgrounds of SCCS participants. Government rosters, such as driver's license registries and Medicare databases, as well as organizational listings and commercial mailing files for residents of the study states were used for this process. A randomly selected age-, sex-, and

race-stratified sample of persons aged 40-79 was contacted for potential participation. The sampling frame for the general population recruitment had a similar black-white proportion as for those recruited from CHCs, but higher percentages of whites than blacks were enrolled through this method.

Figure 3. Locations of participating community health centers of the Southern Community Cohort Study (Cohen et al, 2013)

Recruitment began in March 2002 and was completed in September 2009 (Table 1). Institutional Review Boards at Vanderbilt University Medical Center and Meharry Medical College have approved the study and all research protocols. All participants signed written informed consent forms and since April 14, 2003, participants also signed Health Insurance Portability and Accountability (HIPAA) authorization forms.

Table 1. Characteristics of the Southern Community Cohort Study participants by sex and race, March 2002-September 2009						
	Black		White		Other race/ethnicity	
	Women	Men	Women	Men	Women	Men
N (%)	32,406 (58.3)	23,159 (41.7)	15,459 (60.9)	9,918 (39.1)	3,202 (63.2)	1,866 (36.8)
Mean age at enrollment (years)	51.7	50.8	53.9	54.1	53.0	52.9
% enrolled at community health center	91.2	91.1	80.9	64.5	79.9	70.1

*Adapted from *The SCCS Cohort* table reported at http://southerncommunitystudy.org/Cohort/SCCSCohort.htm. Numbers do not add up to 100% due to rounding.

SCCS participants were administered a baseline questionnaire (http://www.southerncommunitystudy.org/InfoResearch/SCCS-questionnaire.pdf) which ascertained information on demographics; anthropometry; personal medical history; family medical history; tobacco use; medication use; reproductive history (women only); alcohol consumption; diet; physical activity; emotional wellness; social support; religion/spirituality; health insurance; use of medical and cancer screening services; occupational history; and other factors(23). For CHC participants, the questionnaire was administered in person using a laptop computer and a computer-assisted personal interview (CAPI) with logic-checking and skip pattern technology. Trained interviewers administered the questionnaires with the assistance of handheld cards to facilitate responses, and abstracted anthropometric and other clinical information (weight, height, blood pressure) from participants' medical records if those measurements were also collected on the day of data collection. If not, the measures of height and weight were collected via self-report on the questionnaire. (23, 64) General population participants completed and mailed in a paper version of the study questionnaire. The paper version

was identical to the CAPI used at the CHCs and informed consent was obtained by a form included in the questionnaire booklet.

Analyses for the association between physical activity, sedentary time, and mortality were conducted among all SCCS participants with diabetes who were followed through December 31, 2011. The study period ended at this time because of the linkage with the National Death Index (NDI) was through December 31, 2011. Participants for analyses of the relationship between physical activity, sedentary time, and CVD were selected from among SCCS participants with diabetes at cohort enrollment who are 65 years old or greater, and thus eligible for Medicare, on or before January 1, 2008 ("Medicare"), and/or SCCS participants with diabetes at cohort enrollment recruited in Tennessee under the age of 65 ("TN HDDS"). Participants who self-reported diabetes (responded yes to the question "have you ever been told by a doctor that you had diabetes or high blood sugar or were treated for diabetes or high blood sugar?") and were enrolled between March 1, 2002 and January 1, 2008 were included in the analyses. The study period ended on this date because the SCCS linkage to the HDDS and the Medicare data was up-to-date through 2008 at the time that this study proposal began. As discussed later, those enrolled during 2008 may not have had sufficient opportunity to have a complication so additional sensitivity analyses were conducted including those participants to ensure the robustness of the observed estimates.

SCCS investigators confirmed 96% of self-reported diabetes diagnoses in two validation studies – one reviewing medical records (n = 124) and the other evaluating A1C percentages(23). For other variables self-reported at baseline (time of study enrollment), a series of validation studies have been conducted on subsets of the SCCS

population (150-800 SCCS participants) for sections of the food frequency questionnaire (FFQ), physical activity patterns, tobacco use, and biometric measurements (height/weight)(65, 66). These validation studies reported satisfactory reliabilities and validities.

Participants were included in all analyses if they were diagnosed with diabetes after the age of 18 years old and self-reported race as either “black” or “white”. If participants were missing information regarding the age of diabetes diagnosis (“what was your age at first diagnosis for diabetes or high blood sugar?”), medication use (“are you currently taking prescription medication, including insulin, to lower your blood sugar?”), or demographics (age, sex, or race) they were also excluded from all analyses, as these variables were essential to the models constructed. Participants were excluded from all analyses of CVD outcomes if they reported a history of myocardial infarction or stroke (heart disease) at baseline (“have you ever been told by a doctor that you had a heart attack…or stroke?”).

CHAPTER 3

Major Cardiovascular Disease Risk among Blacks and Whites with Diabetes

Methods

Outcome Ascertainment

The primary outcome measure, a composite CVD endpoint, was defined as the time from study enrollment to the first recorded CVD diagnosis or death with CVD as the primary cause or underlying cause of death (**Table 2**).

Table 2. Major cardiovascular events of interest and associated diagnostic codes

	Outcome	*Diagnostic Codes*
Cardiovascular Events (ICD-9)	Myocardial infarction(67)	410, 411, 413, 414
	Coronary artery bypass surgery(68)	36.10, 36.11, 36.12, 36.13, 36.14, 36.15, 36.16, 36.19 (procedure codes)
	Angioplasty	36.01, 36.02, 36.05, 36.03, 36.04, 36.06, 36.07, 36.08, 36.09 (procedure codes)
	Congestive heart failure(69)	402.01, 402.11, 402.91, and 428
	Stroke(70)	431.x, 433.x, 434.x, 436.x
	Carotid endarterectomy	38.11, 38.12 (procedure codes)
	Peripheral vascular disease	250.7, 440.x, 441.x, 442.x, 443.9, 444.x
Fatal Cardiovascular Events (ICD-10)	Myocardial infarction	I21.0-I21.4, I21.9-122.1, I22.8-I23.6, I23.8
	Heart failure	I11.0, I13.0, I42.0-I42.9, I50.0, I50.1, I50.9, I51.7
	Stroke	I60.0-I60.9, I61.0-I61.9, I63.0-I63.9, I64, I65.0-I65.9
	Coronary artery disease	I20.0, I20.8, I20.9, I21.0-I25.9, I516

Non-fatal events and the date of first recorded occurrence among SCCS participants with diabetes who did not turn 65 on or before January 1, 2008 (“TN HDDS” group) were identified via the Tennessee Hospital Discharge Data System, based on previously validated algorithms using diagnostic (International Classification of Diseases Ninth Edition: ICD-9-CM) codes or the underlying cause of death on the death certificate

using the International Classification of Diseases Tenth Edition (ICD-10) codes used in previous SCCS studies on mortality among diabetics(23, 69, 71-74). In addition to the composite CVD endpoint, more common events were examined individually, where the sample size allowed.

The TN HDDS information became available in 1997 after the revision of Tennessee Code Annotate (T.C.A.), Section 68-1-108 which required each licensed hospital to report all claims data from the UB-92 form or any successor forms on every inpatient, outpatient, emergency room, or ambulatory surgery discharge to the commissioner of health(67). The Division of Health Statistics at the Tennessee Department of Health is responsible for compiling the TN HDDS on an annual basis. The UB-92 form was the billing form for handling health care claims until the updated UB-04 form was instituted in 2007. The data for the analyses were collected using the UB-92 form. The HDDS was established also for the purposes of collecting, aggregating, and disseminating patient level data.(67)

At minimum, each reported discharge includes, but is not limited to, the following data elements: patient control number, type of bill, the period the statement covers, patient's date of birth, patient's sex, admission date, medical/health record number, revenue codes, date(s) of service, certificate number/identification number/social security number, insurance group number, principal diagnosis codes, other diagnosis codes, E code, principal procedure code and date, other procedure codes and date, and patient's race/ethnicity(75). Data are reported quarterly to the Tennessee Department of Health. Those who fail to report or report late are sent correspondence to advise of the

penalties associated with failure to report and are given a determined period of time to submit the records (76).

The SCCS cohort was linked to the HDDS by submitting the participants' names, dates of birth, and social security numbers. The Tennessee Department of Health sent the returned probabilistic matches back to the International Epidemiology Institute (IEI) where the SCCS cohort data are housed. IEI then evaluated the returns to confirm the matches by examining the dates of birth, sex, and social security number of the participants. We used HDDS outcome data from March 1, 2001 through December 31, 2008, the latest date for which such data were available when the linkage was performed. Participants' data in the TN HDDS from before their enrollment in SCCS were used to adjust for the previous number of cardiovascular complications experienced by the participant. For each participant, the number of previous hospitalizations in the year prior to their study enrollment were counted and used for adjustment. We limited the timeframe for the number of previous hospitalizations because we did not want to bias our analyses by allowing those who entered the study at later dates to have a longer time frame to collect previous hospitalizations compared to those who entered at earlier dates. We recognize that previous hospitalizations accrued outside of Tennessee may not have been represented in these data, and may have resulted in an under-adjustment for this confounding.

CVD outcomes among SCCS participants with diabetes who turned 65 on or before January 1, 2008 ("Medicare" group) were ascertained by linkage, using social security number, date of birth, and gender, with the National Centers for Medicare and Medicaid Services (CMS) Research Identifiable Files from January 1, 1999 through December

31, 2008, the last date for which data were available. CVD among those aged 65 years or older was defined as having one or more medical claims with an ICD-9 code for a major cardiovascular event (**Table 2**) within the MEDPAR (inpatient) file or two or more medical claims in the Medicare outpatient base claims files from the date of enrollment to December 31, 2008.

Diagnosis code algorithms for the identification of major cardiovascular events were selected using previously validated algorithms (**Table 3**). The use of diagnostic codes in administrative data, particularly Medicare claims data, have been reported to have a high positive predictive value (PPV) for the diagnosis of acute myocardial infarctions (ICD-9 codes 410 and 411; 69.5%-95.4%) with the inclusion of diagnosis-related group (DRG) codes not appreciably increasing that value(77-79). It has also been noted that that the PPV was significantly lower for subjects with a history of myocardial infarction compared to those without previous myocardial infarctions (88.1%)(77). A review of the detection of heart failure in administrative claims data included 8 studies conducted among Medicare beneficiaries that reported PPVs between 76% and 99%, with the majority of the studies reporting PPVs over 90%(80). Among studies of hospital discharge records among general populations (diabetes status not specified) included in that review, the PPVs were similarly high (82-97%). A similar review was conducted on the detection of stroke in administrative claims data and included one study conducted specifically among individuals ≥65 (PPV = 90%). This review found that the studies that validated codes as a part of a composite endpoint reported PPVs ranging from 71% to 96%(81). The high PPVs observed among general populations has also been observed

among diabetics (myocardial infarction, 95.2%; stroke, 91.2%; ischemic heart disease, 90.3%)(82).

In the present study, an event was counted if it was noted as the primary diagnosis, any of the other diagnoses (a maximum of 18 other diagnoses can be reported in the record for TN HDDS; a maximum of 10 can be reported in the record for Medicare), or any of the procedure codes (a maximum of six procedures can be reported in the record for both Medicare and TN HDDS). The events were categorized dichotomously (present/not present).

Deaths were ascertained through linkage of the SCCS cohort with the National Death Index (NDI). NDI is a national, computerized registry of all death record information on file in the State vital statistics offices(70). The National Center of Health Statistics (NCHS) established NDI to aid medical and health research concerned with mortality statistics. NDI data were available for the years from 1979 to 2011, although only deaths related to CVD occurring on or before December 31, 2008 were included to match the follow up time for incident CVD events identifiable in CMS and TN HDDS files. The full period of follow-up through 2011 was used for the analyses evaluating the relationship between physical activity, sedentary time, and all-cause mortality. (70, 83). Previous evaluations of the NDI have reported that the sensitivity of cause-specific death ascertainment ranged from 87% to 97% (84-86). Sensitivity tends to vary by race (more sensitive for whites compared to non-whites; 93% vs. 84%), sex (more sensitive for males compared to female; 95% vs. 91%), and availability of social security number (sensitivity increases from 93% to 97%)(86). First, ascertainment of death status was provided through linkage of the SCCS cohort with the Social Security Administration

(SSA) through February 4, 2011. SCCS participants' personal information was then linked to NDI death records through December 31, 2011 to ascertain cause of death by submitting an application to NCHS, thus encompassing the entire follow-up period for the study. To qualify as a possible match, SCCS information had to match at least one of seven matching criteria specified by NDI standards for each participant. (87).

From the NDI, information on date of death, primary cause of death and contributing causes of death were obtained.

Table 3. Algorithm used for the determination of a CVD event

	Ages Included	Non-Fatal CVD Events	Fatal CVD Events	Algorithm for Incident CVD
"TN HDDS" group	40-64 years old	Tennessee Hospital Discharge Data System (ICD-9 codes)	National Death Index	≥1 discharge records with an ICD-9 code for CVD between the date of enrollment and December 31, 2008 OR An ICD-10 code for CVD as the primary or underlying cause of death
"Medicare" group	≥65 years old	Medicare inpatient and outpatient files (ICD-9 codes)	National Death Index	Between the date of enrollment and December 31, 2008: (a) ≥1 inpatient medical claim(s) with an ICD-9 code for CVD, OR (b) ≥2 outpatient CVD medical claims with an ICD-9 code for CVD, OR (c) An ICD-10 code for CVD as the primary or underlying cause of death

The person-time of follow-up began on the date of enrollment into the SCCS cohort (prior to January 1, 2008) and concluded with the first occurrence of a CVD event, death, or the end of the study period (December 31, 2008).

Statistical Analysis

The HDDS data were originally in case-based form (also known as long format) where there were multiple observations per participant. The dataset was converted from long format to wide format by reshaping. The reshaping procedure associated the principal diagnosis, other diagnoses, procedures and other visit-specific information to the date of the admission. For each participant, the occurrence and date of the cardiovascular events were determined individually.

Prior to conducting any of the following analyses, all variables were screened for inconsistent or abnormal values, and continuous variables were assessed for skewness and outliers. If a value appeared to be incorrectly reported (implausible), the observation to which the value belonged was to be removed because other measures for that participant may have been incorrect as well, but no observations were removed for those reasons.

Proportions of the population missing data for each covariate were assessed by race. Reasons for missingness were examined as well (e.g. missing value for pack-years because participant was a non-smoker). If the missingness was not at random, the observation was preserved in the dataset for analysis. When possible the missing value was recoded to a non-missing value that represents the reason for missingness (e.g. non-smokers had their missing values recoded as 0 for pack-years and the pack-years for smokers were categorized in ranges).

Descriptive statistics included counts and frequencies (or means with standard deviations for continuous variables) of each potential covariate by race. The number of

events per category and person-time for each category by race were also calculated. Descriptive comparisons between black and white race, and between quartiles of physical activity and sedentary time, were made using Pearson's chi-squared tests or ANOVA tests for categorical variables and Wilcoxon rank sum test for continuous variables.

Incidence calculations and regression analyses were conducted separately for the "TN HDDS" group (n = 498) and the "Medicare" group (n = 1,880). Events and person-time contributed by participants recruited in Tennessee who turned 65 during the study period were considered as a part of the "TN HDDS" group until they turned 65. After that point, their events and person-time were considered under the "Medicare" group. Since Medicare collects data from both inpatient and outpatient medical claims, while TN HDDS primarily collects data from inpatient discharges, sensitivity analyses were conducted with only inpatient claims and discharges from both systems. The number of participants who experienced a cardiovascular event during follow-up and the person-years accrued were calculated by race. Incidence rates were age-adjusted and standardized directly to the United States 2000 Census population over the age ranges of those over the course of follow-up.

Unadjusted and adjusted Cox proportional hazards models, using age as the timescale, were specified to determine the association between race and cardiovascular events, generating hazards ratios (HR) and 95% confidence intervals (CI). Those who self-reported their race as "black" were compared to those who self-reported their race as "white" (referent). The proportionality assumptions were tested for Cox proportional

hazards model using the goodness-of-fit testing and the log-log survival plots. The results did not indicate a violation of the proportional hazards assumption.

Unadjusted models only included cardiovascular events as the outcome and race as the explanatory variable (Model 1). The minimally adjusted model added only age and sex as covariates (Model 2). Model 3 added covariates selected based on the directed acyclic graph (DAG; see **Appendix 1.1**). The DAG was constructed based on previous literature and biological plausibility. A sufficient set of confounders were selected that close all open, backdoor pathways of the association between race and cardiovascular disease among SCCS participants with diabetes and represent commonly included confounders from similar studies.

Such confounders considered in the multivariate analysis were BMI, education, annual household income, insurance status, smoking, alcohol consumption, first degree family history of CVD death before the age of 65, medical history (hypertension, hyperlipidemia, depression), previous hospitalizations in the past year, diabetes medication type, diabetes self-management behaviors (frequency of blood glucose monitoring and medication adherence) and duration of diabetes. The number of covariates included in the model was limited based on the rule that a minimum of 10 outcome events per explanatory variable may be added.

Age and sex were chosen as variables for which the association between race and CVD would be adjusted because of the non-modifiable, biological differences between the old and the young, and males and female. As age increases, the risk of cardiovascular disease increases because of vascular changes over time. Males also are at an

increased risk of CVD compared to females so controlling for the biological factors that explain these differences is essential(88). The variables that represent differences in socioeconomic status between blacks and whites are necessary to include in adjusted models because socioeconomic status can determine healthcare access and treatment opportunities, as well as other factor that influence health(89). Body mass index (BMI) is a commonly used measure for general obesity and has also been reported as a risk factor for CVD. Blacks in the SCCS are more likely to have higher BMI than whites, and this difference may confound the relationship between race and CVD among diabetics. CVD risk has been partially explained by genetic factors(90). Including first-degree family history of CVD death at an early age in the adjusted models attempts to control for some of the confounding presented by genetic predisposition to CVD.

Smoking was included in adjustments because it is positively associated with CVD risk through several established biological mechanisms and black-white differences in these factors have been reported.

Hypertension and high cholesterol have been previously reported as risk factors for CVD and reported to be more prevalent among blacks and those of low SES(91-98). Hypertension also places those with diabetes at an increased risk for microvascular diseases such as diabetic retinopathy and renal failure (96, 99-116). Microvascular disease is a risk factor in itself for cardiovascular disease (macrovascular disease) and is also more common among blacks with diabetes (70, 117-125).

Diabetes has been deemed an independent risk factor for CVD so the characteristics of diabetes are important to adjust for in multivariate models. The longer one has

diabetes, the more likely complications become (71, 126, 127). Blacks are usually younger when diagnosed with diabetes and it has been proposed that the onset of diabetes is earlier in blacks as well (126, 128). Based on duration of diabetes and glycemic control, medication is prescribed to lower blood glucose levels. Insulin is an aggressive treatment for Type 2 diabetes and is associated with an increased risk of CVD and microvascular disease (129-132). Insulin treatment usually occurs individuals with more severe diabetes or uncontrolled diabetes either alone or in concert with an oral medication. Since we did not have information regarding HbA1c levels or fasting glucose, we used insulin and duration of diabetes as a proxy for the severity of diabetes. This assumes that diabetes severity increases the longer one has the disease and those who use insulin have more severe diabetes. Previous SCCS studies have reported a higher proportion of blacks use insulin as a part of their glucose-lowering medication(59, 60).

Fully adjusted models included age at enrollment (years; continuous), sex, BMI (kg/m^2; continuous), education level (less than high school, high school, beyond high school), annual household income (< $15,000, $15,000-49,000, and ≥ $50,000), insulin use (yes/no), smoking status (current, former, never), prevalent hypertension and high cholesterol (yes/no), parental history of CVD death (yes/no), and duration of diabetes (years; continuous).

All analyses were conducted using SAS software, version 9.3 (SAS Institute Inc, Cary, NC) and all tests were two-sided.

Results

During follow-up (median follow-up time: 4.1 years, range = 0.06-7.6 years), 362 CVD events or CVD-related deaths occurred in the “Medicare” group (19.3%, with 19.8% among blacks). The 1,880 SCCS participants with diabetes in the “Medicare” group (73.7% black, 26.3% white, 70.9% female) had an average age at enrollment of 67.1 (4.6) years (**Table 4**). More than 60% of the population had a high school education or less, and approximately 62% reported an annual household income of less than $15,000. Whites were more likely to have an annual household income of $15,000 or more. Higher proportions of whites than blacks had prevalent high cholesterol. There were no significant differences observed in population characteristics captured at baseline between “TN HDDS” whites and blacks in the study.

Table 4. Baseline characteristics of SCCS participants with diabetes who turned 65 on or before January 1, 2008, by race				
	Total (n=1,880)	***Black (n=1,385)***	***White (n=495)***	***p***
Age at Enrollment (mean, SD)	67.1 (4.6)	67.1 (4.7)	67.2 (4.4)	0.70
Age at Diabetes Diagnosis (mean, SD)	55.6 (10.4)	54.8 (10.6)	57.8 (9.4)	<0.0001
Time Since Diabetes Diagnosis (n, %)				
- < 5 years	691 (36.8)	471 (34.0)	220 (44.4)	<0.0001
- 5-10 years	385 (20.5)	271 (19.6)	114 (23.0)	
- 11-19 years	406 (21.6)	310 (22.4)	96 (19.4)	
- ≥ 20 years	398 (21.2)	333 (24.0)	65 (13.1)	
Female (n, %)	1,333 (70.9)	1,024 (73.9)	309 (62.4)	<0.0001
Education (n, %)				
- Less than High School	881 (46.9)	722 (52.1)	159 (32.1)	<0.0001
- High School	512 (27.2)	362 (26.1)	150 (30.3)	
- Beyond High School	487 (25.9)	301 (21.7)	186 (37.6)	
Household Income (n, %)				
- Less than $15K	1,233 (65.6)	965 (69.7)	268 (54.1)	<0.0001
- $15K-$49K	556 (29.6)	378 (27.3)	178 (36.0)	
- $50K or Greater	91 (4.8)	42 (3.0)	49 (9.9)	
Body Mass Index (BMI; n, %)				
- 18.5-24.9	191 (10.3)	129 (9.4)	62 (12.7)	0.06
- 25-29.9	560 (30.2)	406 (29.7)	154 (31.6)	
- 30-39.9	854 (46.1)	648 (47.4)	206 (42.2)	
- ≥ 40	249 (13.4)	183 (13.4)	66 (13.5)	
Prevalent Conditions (n, %)				
- Hypertension	1,608 (85.5)	1,211 (87.4)	397 (80.2)	<0.0001
- High Cholesterol	1,078 (57.4)	755 (54.6)	323 (65.3)	<0.0001
Family History of CVD Death	478 (25.4)	283 (20.4)	195 (39.4)	<0.0001
Smoking Status (n, %)				
- Current	247 (13.3)	180 (13.1)	67 (13.8)	0.02
- Former	706 (37.9)	499 (36.3)	207 (42.6)	
- Never	908 (48.8)	696 (50.6)	212 (43.6)	
Glucose-Lowering Medication				
- Oral Medication Only	1,142 (60.7)	836 (60.4)	306 (61.8)	<0.0001
- Insulin Use	522 (27.8)	421 (30.4)	101 (20.4)	
- No Medication	216 (11.5)	128 (9.2)	88 (17.8)	
Physical Activity (MET-h/d; n, %)				
- < 5.7	397 (21.1)	302 (21.8)	95 (19.2)	0.14
- 5.8-11.0	465 (24.7)	343 (24.8)	122 (24.7)	
- 11.1-18.8	511 (27.2)	378 (27.3)	133 (26.9)	
- ≥ 18.9	507 (27.0)	362 (26.1)	145 (29.3)	
Sedentary Time (h/d; n, %)				
- < 5.2	465 (24.7)	364 (26.3)	101 (20.4)	0.06
- 5.2-7.9	485 (25.8)	348 (25.1)	137 (27.7)	
- 8.0-10.6	485 (25.8)	352 (25.4)	133 (26.9)	

- ≥ 10.7	445 (23.7)	321 (23.2)	124 (25.1)

The overall age-adjusted rates for CVD events were 91.7 and 154.4 in the "TN HDDS" group and "Medicare" group, respectively. Age-adjusted rates of CVD were similar for whites compared to blacks in the "TN HDDS" group but higher for whites for the "Medicare" group (**Table 5 and Table 8**).

TABLE 5. Incidence Rates for CVD Events among Black and White SCCS Participants who turned 65 on or before January 1, 2008

	Total Person-Years of Follow-Up	CVD Events (n)	Age-Adjusted Incidence Rate per 1,000 Person-Years (95% CI)
Black (n = 1,385)	6,023	274	142.5 (103.5-181.5)
White (n = 495)	1,879	88	245.7 (111.9-379.6)
Total (n = 1,880)	7,038	362	154.4 (116.6-192.2)

HRs and 95% CIs for the association between race and CVD risk among those with diabetes in the "Medicare" group can be found in **Table 6**. Blacks were at lower, but not significantly so, risk of CVD compared to whites (HR, 0.88; 95% CI: [0.68-1.15]). When only inpatient records were considered, the results did not vary significantly (HR, 0.86; 95% CI: [0.54-1.39]).

TABLE 6. Hazard ratios (95% confidence intervals) for CVD risk for blacks with diabetes compared to whites with diabetes in the "Medicare" group

	# of Events	Model 1	Model 2	Model 3
Black vs. White Race	362	0.96 (0.75-1.22)	0.98 (0.77-1.25)	0.88 (0.68-1.15)

[a]Model 1: unadjusted; [b]Model 2: age at enrollment and sex; [c]Model3: age at enrollment, sex, BMI, education, annual household income, insulin use, smoking status (former/current/never), prevalent hypertension or high cholesterol, family history of premature death from myocardial infarction, and duration of diabetes.

During follow-up (median follow-up time: 4.2 years, range = 0.01-7.5 years), 188 CVD events or CVD-related deaths occurred in the "TN HDDS" group (37.8%; 38.6% among

blacks and 33.7% among whites). The 498 SCCS participants with diabetes in the "TN HDDS" group (83.7% black, 16.3% white, 61.9% female) had an average age at enrollment of 50.1 (6.2) years (**Table 7**). More than 60% of the population had a high school education or less, and 61.9% reported an annual household income of less than $15,000. Whites were more likely to have an annual household income of $15,000 or greater and have prevalent high cholesterol. No other significant differences in characteristics collected at baseline were observed between the "TN HDDS" blacks and whites.

Table 7. Baseline characteristics of SCCS participants with diabetes who were recruited in Tennessee at ages 40-64 years old, by race				
	Total (n=498)	***Black (n=412)***	***White (n=86)***	***p***
Age at Enrollment (mean, SD)	50.1 (6.2)	50.0 (6.2)	50.5 (6.5)	0.58
Age at Diabetes Diagnosis (mean, SD)	42.7 (8.4)	42.5 (8.4)	43.8 (8.4)	0.18
Time Since Diabetes Diagnosis (n, %)				
- < 5 years	261 (52.4)	214 (51.9)	47 (54.7)	0.63
- 5-10 years	106 (21.3)	88 (21.4)	18 (20.9)	
- 11-19 years	91 (18.3)	74 (18.0)	17 (19.8)	
- ≥ 20 years	40 (8.0)	36 (8.7)	4 (4.7)	
Female (n, %)	308 (61.9)	253 (61.4)	55 (64.0)	0.66
Education (n, %)				
- Less than High School	144 (28.9)	124 (30.1)	20 (23.2)	0.36
- High School				
- Beyond High School	168 (33.7)	139 (33.7)	29 (33.7)	
	186 (37.4)	149 (36.2)	37 (43.0)	
Household Income (n, %)				
- Less than $15K	308 (61.9)	254 (61.7)	54 (62.8)	0.0002
- $15K-$49K	163 (32.7)	143 (34.7)	20 (23.3)	
- $50K or Greater	27 (5.4)	15 (3.6)	12 (14.0)	
Body Mass Index (BMI; n, %)				
- 18.5-24.9	59 (11.9)	54 (13.2)	5 (5.8)	0.08
- 25-29.9	100 (20.2)	82 (20.1)	18 (20.9)	
- 30-39.9	220 (44.5)	184 (45.1)	36 (41.9)	
- ≥ 40	115 (23.3)	88 (21.6)	27 (31.4)	
Prevalent Conditions (n, %)				
- Hypertension	358 (71.9)	300 (72.8)	58 (67.4)	0.31
- High Cholesterol	178 (35.9)	133 (32.4)	45 (52.3)	0.0005
Family History of CVD Death	170 (34.1)	134 (32.5)	36 (41.9)	0.10
Smoking Status (n, %)				
- Current	235 (47.4)	197 (47.9)	38 (44.7)	0.66
- Former	101 (20.4)	85 (20.7)	16 (18.8)	
- Never	160 (32.3)	129 (31.4)	31 (36.5)	
Glucose-Lowering Medication				
- Oral Medication Only	270 (54.2)	222 (53.9)	48 (55.8)	0.61
- Insulin Use	130 (30.7)	130 (31.6)	23 (26.7)	
- No Medication	75 (15.1)	60 (14.6)	15 (17.4)	
Physical Activity (MET-h/d; n, %)				
- < 5.7	120 (24.1)	93 (22.6)	27 (31.4)	0.30
- 5.8-11.0	105 (21.1)	90 (21.8)	15 (17.4)	
- 11.1-18.8	100 (20.1)	86 (20.9)	14 (16.3)	
- ≥ 18.9	173 (34.7)	143 (34.7)	30 (34.9)	
Sedentary Time (h/d; n, %)				
- < 5.2	91 (18.3)	78 (18.9)	13 (15.1)	0.74
- 5.2-7.9	99 (19.9)	82 (19.9)	17 (19.8)	
- 8.0-10.6	114 (22.9)	91 (22.1)	23 (26.7)	

-	≥ 10.7	194 (39.0)	161 (39.1)	33 (38.4)

TABLE 8. Incidence rates for CVD events among black and white SCCS participants with diabetes who were recruited in Tennessee at ages 40-64 years old

	Total Person-Years of Follow-Up	CVD Events (n)	Age-Adjusted Incidence Rate per 1,000 Person-Years (95% CI)
Black (n = 412)	1,996	159	91.7 (68.0-115.5)
White (n = 86)	386	29	88.4 (38.6-138.3)
Total (n = 498)	2,382	188	91.1 (69.7-112.6)

Table 9 displays the HRs and 95% CIs for the association between race and CVD risk among those with diabetes in the "TN HDDS" group. Blacks did not have a significantly different risk of CVD compared to whites (HR, 1.01; 95% CI: [0.67-1.52]) after adjustment of selected covariates. When only inpatient records (n = 97) were considered, blacks were at lower risk, but not significantly so (HR, 0.62; 95% CI: [0.22-1.70]).

Table 9. Hazard ratios (95% confidence intervals) for CVD risk for blacks with diabetes compared to whites with diabetes in the "TN HDDS" group

	# of Events	Model 1[a]	Model 2[b]	Model 3[c]
Black vs. White Race	188	1.12 (0.75-1.66)	1.19 (0.80-1.77)	1.01 (0.67-1.52)

[a]Model 1: unadjusted; [b]Model 2: age at enrollment and sex; [c]Model3: age at enrollment, sex, BMI, education, annual household income, insulin use, smoking status (former/current/never), prevalent hypertension or high cholesterol, family history of premature death from myocardial infarction, and duration of diabetes.

Conclusions

The results of the current study do not support a significant association between race and CVD risk among individuals with diabetes. Although blacks had a higher prevalence of CVD risk factors like hypertension and obesity that difference did not translate into

increased CVD risk among that population in either the “Medicare” or “TN HDDS” group. Indeed, the only suggested differences were non-significantly lower mortality risks among blacks than whites. Diabetes itself is a strong risk factor for CVD and any racial differences in CVD risk may be overwhelmed by the influence of diabetes.

Our results were consistent with other studies that reported no significant difference between blacks and whites with diabetes in respect to CVD risk(70). Most of these studies presented condition-specific (myocardial infarction, stroke, etc.) estimates while our study presented risk estimates for a composite endpoint that includes CVD-related death. Although our study results represented those for a composite CVD endpoint rather than single endpoints, the results similarly reported no increased risk of CVD among blacks compared to whites.

Major strengths of the current study are the racial diversity of the sample, with blacks representing more than two-thirds of the study population, the systematic and standardized collection of extensive baseline data on the cohort participants and the systematic follow-up of the cohort via linkage with the Tennessee HDDS and Medicare files. By design, black and white SCCS participants are of generally similar socioeconomic status, which allows us to evaluate risk of cardiovascular complications with minimal confounding presented by differences in socioeconomic factors. We also have extensive information collected in our baseline in-person interview to enable further statistical adjustment for socioeconomic status as well as for risk factors such as tobacco and alcohol use, medical history, medication use, family history of chronic conditions, psychosocial factors, and various other characteristics of study participants. The current study adjusted for important confounders that have not always been

included in previous studies and could have a significant impact on the estimates generated.

The analyses were limited by several factors. All questionnaire data were collected at baseline and we do not have follow-up data for any of the covariates included in multivariate analyses. Also, the questionnaire data are self-reported and may introduce bias. Adjustment for covariates rendered residual confounding due to imperfect measurement, which is inherent to studies of this kind. Our study relies on self-reported diabetes diagnosis and did not conduct chart reviews or biological testing to confirm diabetes in our sample population. Previous validation studies, however, conducted within the SCCS using medical records for 124 participants reported that 96% of the self-reported diagnoses were validated using ICD-9 codes, HbA1c levels, treatment, or physicians' notes(133, 134). Therefore, we do not believe this is a significant concern in our study.

We also relied on self-reported age of diagnosis and used it to determine the duration of diabetes in this study. Recall errors may have caused the participant to be misclassified into a different duration category. To our knowledge, no studies have validated self-reported date or age of diabetes diagnosis but we do not believe it is a significant issue in our study because diabetes is a major chronic disease with significant lifestyle changes associated with it. However, the onset of diabetes and its symptoms may be gradual and date of diagnosis may not necessarily reflect date of onset. For these reasons we used broad 5 and 10-year categories to group individuals by time since diagnosis of the condition.

CVD events were ascertained through hospital discharge data for the “TN HDDS” population, capturing only CVD events severe enough for the participant to seek care. However, the TN HDDS included discharges from both outpatient and ambulatory care departments, minimizing the potential for under-ascertainment. Another concern specific to administrative billing data is that there may have been preferential coding since the data are intended for billing purposes and the coding is conducted by hospital personnel. We do not believe that is a substantial concern in our analyses for several reasons. First, we took into account all of the conditions diagnosed in each admission – not only the principal diagnosis. Second, there are 18 positions in which conditions can be coded during an admission. In the “TN HDDS” population less than 3% of the participants had the 18^{th} field completed for any of their admissions, so the majority of the participants had the availability of a coding position if other diagnosed conditions occurred during that admission. Third, we have no reason to believe that any errors or prioritization in coding occurred differentially between blacks and whites.

Our study did not have a method to definitively distinguish between type 1 and type 2 diabetics. In an effort to remove those likely to be type 1 diabetics, we only included those who reported diagnosis after 18 years of age. We understand that all participants with type 1 diabetes may not have been excluded due to some participants with type 1 diabetes being diagnosed in their early twenties. There has been evidence of a biologically different type of diabetes that is usually diagnosed before age 30 with overlapping clinical features of both type 1 and type 2 diabetes(135). This is an important limitation because these types may differ significantly in several ways (daily

management of the disease, duration, risk of complications). Our estimates are not diabetes type-specific, but they represent the estimates for a combined group.

The lack of evidence to support a strong racial disparity in CVD risk among those with diabetes reinforces the validity of managing the risk of CVD in this population, regardless of race.

Chapter 4

Evaluation of the Independent Association between Physical Activity or Sedentary Time and the Risk of Cardiovascular Disease or All-Cause Mortality

Physical Activity and Sedentary Behaviors as Risk Factors for Cardiovascular Complications and Mortality

Diabetes is the seventh leading cause of death in the United States(20). When compared with those without diabetes, people with diabetes have a two-fold increase in relative risk of death(20, 136). Previous research conducted in SCCS reported that mortality risk was approximately 80% higher for those with versus without diabetes, and that blacks with diabetes had a slightly lower mortality risk compared with whites with diabetes of similarly low socioeconomic status(60).

Strategies to reduce premature death related to diabetes have important public health implications. Along with self-management behaviors such as dietary alterations and medication adherence, healthcare providers often recommend increased physical activity to those with diabetes (17, 137). Increased levels of physical activity have been found to increase insulin sensitivity and glucose tolerance, as well as positively impact serum lipid levels among individuals with type 2 diabetes(138). A review of 47 randomized controlled clinical trials that assessed the associations of structured exercise training programs that included aerobic exercise, resistance training, or both found that these programs were associated with a significant reduction in A1C levels(139). The magnitude of these reductions has varied across studies, but it is most important to note that reductions have occurred and when paired with other lifestyle

interventions (e.g. dietary interventions), the gains in glycemic control may be magnified appreciably (15, 140).

Physical activity has been historically linked with better general health and positive health outcomes. According to the 2008 Physical Activity Guidelines for Americans, adults are recommended to engage in at least 150 minutes/week of moderate to intense aerobic activity to obtain health benefits and more than 300 minutes/week of aerobic activity to obtain further benefits(141). The National Health Interview Survey found that in 2008, while 43.5% of U.S. adults could be considered active, only 28.4% of U.S. adults were highly active. The United States Health and Retirement Study surveyed 1,811 adults aged 50 years or more who responded to the 2003 Diabetes Supplement. They concluded that adults with diabetes who had heart disease were less likely to meet physical activity guidelines compared to those without heart disease (OR: 0.69; 95% CI: 0.51-0.94)(142). The relatively small proportion of highly active adults, and thus eligible to receive the extensive health benefits from that level of activity, demonstrated a need for more improvement in achieving increased levels of physical activity among Americans.

A recent meta-analysis examined cohort studies of the association between physical activity and risk of all-cause mortality and CVD in patients with diabetes. Pooled results from the 17 included studies reported the highest physical activity category was associated with lower relative risk (RR) for all-cause mortality (0.61, 95% CI: 0.52-0.70) and CVD (0.71, 95% CI: 0.60-0.84)(143). The strength of the association across studies varies with the measure of physical activity as well as with the population, but the direction of the effect has been consistent among these study populations of

diabetics. A majority of the aforementioned results, however, were reported among males, all-white populations, and populations with a low prevalence or absent of CVD risk factors (hypertension, obesity, hyperlipidemia, poor glycemic control). In studies including both men and women, the observed effect estimates were generally not as strong among women with diabetes compared to men with diabetes. Not only is the SCCS population over two-thirds black and two-thirds female, the cohort has a high prevalence of CVD risk factors like obesity and hypertension.

Diabetes may attenuate the disparity in CVD risk between males and females(144). Evidence exists suggesting that females with diabetes have a greater relative risk of CVD, CVD mortality, and ACM than males with diabetes, especially with advanced age(145). This increase in risk conferred by diabetes makes physical activity as a strategy to decrease the risk of CVD among females even more important. Hu et al. studied self-reported total physical activity, including walking, among 5,125 women with diabetes from the Nurses' Health Study. The authors reported that increased physical activity and walking were associated with a non-significant reduction in all CVD events risk (highest vs. lowest categories of activity, relative risk: 0.55; 95% CI: 0.26-1.14)(6). Statistically significant reductions in CVD were only observed between the second highest quintile of physical activity compared to the lowest quintile. Coronary heart disease, pulmonary embolism, and stroke incidence were investigated in relation to self-reported physical activity in 25,915 women with diabetes of the Million Women Study in the United Kingdom. The results suggested a reduced 5-year incidence of these particular CVD events among active women compared to inactive women (inactive women HR: 2.4, 95% CI: 1.8-3.2)(146).

Though no published studies have presented race-specific effect estimates for the association between physical activity and CVD events among blacks and whites, several studies have included non-white participants in their study populations. The previously mentioned study by Ford and colleagues also studied coronary heart disease mortality in conjunction with ACM. In this 21.5% black population, leisure-time physical inactivity was not significantly associated with a reduction in coronary heart disease mortality among participants with diabetes (inactive compared to most active HR: 0.74, 95% CI: 0.27-2.03; moderately active compared to most active HR: 0.59, 95% CI: 0.21-1.64). However, the previously discussed NHIS study determined that those with diabetes who walked at least 2 hours per week had a 34% lower CVD mortality rate compared to inactive participants with diabetes(5). The width of the confidence intervals calculated does support the possibility of the differences in these effect estimates may be functions of measurement error and differences in measurement of physical activity, the breadth of CVD conditions included as outcomes, and the characteristics of each study population.

The disparity among blacks compared to whites in the participation in leisure-time physical activity has been consistently reported, despite the Healthy People 2010 recommendations (147-150). The 2007 Behavioral Risk Factor Surveillance System (BRFSS) reported that non-Hispanic whites (45.7%) had a substantially greater proportion of highly active individuals compared with non-Hispanic blacks (37.5%) and Hispanics (37.6%), based on the 2008 Physical Activity Guidelines for Americans(151). Numerous studies suggested that socioeconomic status and environmental influence (e.g. access to parks and recreational centers, sidewalks, crime/community safety) play

a key role in creating and exacerbating that disparity (152-155). Much of the research regarding racial differences in physical activity has been conducted among adolescents. One study found that black girls spent more time watching television, had higher BMIs, were less active, and more likely to be overweight than white girls(156). A racially-diverse national, longitudinal study of over 14,000 US adolescents reported that minority adolescents had consistently higher levels of inactivity, with females having the lowest levels of physical activity(157).

An SCCS study examined the association between physical activity and sedentary time and BMI among black and white adult women. The study found that among white women, high levels of sedentary time were strongly associated with moderate or severe obesity, while the association was weaker among black women(158). The significant racial differences in physical activity, sedentary behaviors, and BMI among women suggest that the impact of activity and sedentary behaviors may vary by race.

Sedentary lifestyles are a risk factor for overweight and obesity, and are associated with an increased risk of insulin resistance, CVD, and mortality (52). Most studies estimate that adults spend more than half of their time sitting, doing sedentary activities (screen-based activities like computers, television [TV] watching)(159). Sedentary lifestyles have been associated with abnormal glucose metabolism and high blood glucose levels(47). Time spent in sedentary behaviors is more nuanced than simply the inverse of physically active time. Several studies have found independent associations between sedentary time and physical activity with outcomes such as obesity, abnormal glucose metabolism, and mortality(47).

Recently, a meta-analysis was conducted to examine sedentary time (primarily in TV viewing time) among adults and the association with diabetes, CVD and mortality. The study found that increased sedentary time was associated with a 112% increase in the risk for diabetes (RR: 2.12, 95% CI: 1.61-2.78) and a 147% increase in CVD event risk (RR: 2.47, 95% CI: 1.44-2.24)(160). This study provides support for the association between sedentary time and the biological process that leads to adverse outcomes. However, we do not yet understand fully how those who have prevalent diabetes are impacted by sedentary behaviors and whether the adverse effects seen in initially healthy populations are similar for those with diabetes.

Methods

The analysis was conducted separately in the "TN HDDS" group (n = 498) and the "Medicare" group (n = 1,880). Participants were included in this analysis if, on the baseline questionnaire, they self-reported race as "black" or "white", self-reported ever being diagnosed with diabetes, responded to questions regarding duration of diabetes and medication type, and were not missing information on body mass index, physical activity and sedentary time.

Physical activity was assessed using the SCCS physical activity questionnaire (PAQ), which was specifically developed for the SCCS to assess physical activities at home, work and for leisure at enrollment during the interview (see **Appendix 2**). Time spent conducting light, moderate, and strenuous activity at home and work were assessed for weekdays and weekends, both separately and combined using weighted averages. Interviewers asked participants about how much time the participant they spent doing

an activity “typically”. Hand cards were used to assist the interviewer in showing examples of light work (i.e. standing at work, light office work, cooking, and child care), moderate work (i.e. cleaning house, gardening, and mowing lawn), and strenuous work (i.e. construction work or farming). Two questions were asked about time spent doing moderate sports like bowling, dancing, softball, or golf, and vigorous sports like jogging, aerobics, bicycling, tennis, swimming, or basketball. Sedentary time was also assessed in the PAQ and measured by asking the participant how much time per day was typically spent sitting in a car or bus, at work, watching television or movies, using a computer, or other sitting activities (i.e. talking on the phone, reading, or sitting at meals).

Physically active times were converted from hours per day into a summary measure of metabolic equivalent tasks (MET) – hours per day (MET-hours/day). MET-hours were chosen as the measurement of physical activity frequency and intensity because it is independent of weight(161). MET values were based on the values suggested by the Compendium of Physical Activities(162). The exposures for the analysis were calculated as total physical activity (total of light, moderate, and strenuous household/occupational work and moderate and vigorous leisure-time physical activity in MET-hours/day).

Participants were categorized by quartiles of total physical activity, in MET-hours/day, as calculated from the distribution among all participants that met the inclusion criteria for these analyses. All sitting times were summarized into total hours per day spent in sedentary time. Participants were categorized in quartiles of sedentary activity as calculated from the distribution among all included participants.

Cox proportional hazards models, using age as the timescale, were constructed to estimate hazards ratios (HR) and 95% confidence intervals (CI) for major cardiovascular events in relation to total physical activity. Models were constructed separately for total physical activity and sedentary time, and then adjusted for one another to determine whether each association is independent of the other measure. Cohen et al.(163) demonstrated the independence of the sedentary time and physical activity measures in their recent report relating those two metrics to breast cancer risk in the SCCS cohort. In particular, they showed that, among cases and controls, sedentary time was not simply the inverse of physically active time. Also, when models with physical activity as the exposure variable were adjusted for total sedentary time, the confidence intervals for the estimates remained consistent and did not widen substantially.(164) Thus, we have considered total activity and total sedentary time as independent measures related to CVD.

Unadjusted models included only physical activity or sedentary time. Minimally adjusted models added age and sex only. Fully adjusted model (Model A) included age, sex, and selected covariates. Fully adjusted (Model B) added physical activity or sedentary time, as appropriate, to the model. Variables considered in the DAG of the association between physical activity and the risk of major cardiovascular events were based on previous literature and biological plausibility (see **Appendix 1.2**). Such confounders considered in the multivariate analysis are BMI, education, annual household income, insurance status, smoking, alcohol consumption, first degree family history of CVD death before the age of 65, total energy intake, medical history (hypertension, hyperlipidemia, microvascular disease, and depression), medication type, other

medication use (statins, anti-hypertensive medications, and aspirin), and duration of diabetes.

To explore the possibility of reverse causation, whereby decreased levels of physical activity in some participants may be due to illness, secondary analyses excluding participants who died within the first year of follow-up were conducted. Decreased The results were compared for similarity in the magnitude and the direction of the effect.

Age and sex were chosen as variables for which the association between physical activity and CVD, and sedentary time and CVD, were adjusted. The variables that represented differences in socioeconomic status between those who are active and those who are less active are necessary to include in adjusted models because socioeconomic status can determine healthcare access and treatment opportunities, as well as other factor that influence health(89). SES also strongly ties together neighborhood structure and ability to be physically active. Low SES neighborhoods are more likely to have higher crime rates and a built environment not conducive to regular, outdoor exercise (149, 152, 154, 165).

Smoking behavior for those who are active versus those who are not active may differ. Usually, those who participate in healthy behaviors such as physical activity may also be less likely to smoke or may have quit smoking (166, 167).

Hypertension may place those with diabetes at an increased risk for microvascular diseases such as diabetic retinopathy and renal failure (96, 99-116). Vigorous physical activity can have a negative impact on diabetic retinopathy and is sometimes contraindicated in those with hypertension (168, 169). Therefore, those individuals may

be among the less active individuals who are at an increased risk of CVD. High cholesterol is a risk factor for CVD and physical activity is often suggested to those with high cholesterol in addition to treatment. Those with high cholesterol may be more physically active, due to those recommendations, and those who are not active would be at an increased risk of CVD incidence and death. Including high cholesterol in the models as a covariate will adjust for the possible differences in risk that may exist between those with and without the condition.

Full models were adjusted for age at enrollment, sex and race (except for in race- and sex-specific analyses), body mass index (kg/m^2, continuous), educational attainment (less than high school, high school graduate, beyond high school), annual household income (< $15, $15-$50K, ≥$50K), insulin use (yes/no), smoking (current, former, never), family history of premature CVD-related death (yes/no), hypertension, high cholesterol, duration of diabetes, and physical activity or sedentary time.

All analyses were conducted using SAS software, version 9.3 (SAS Institute, Cary, NC) and all tests were two-sided.

Results

During follow-up (median follow-up time: 4.1 years, range = 0.06-7.6 years), 362 CVD events or CVD-related deaths occurred among the 1,880 participants in the “Medicare” group (19.3%, with 19.8% among blacks and 17.8% among whites; 18.6% among females; 20.8% among males) (**Tables 10 and 11**). **Table 12** shows the HRs (95% CI) for CVD risk across quartiles of physical activity in the SCCS cohort participants with diabetes in the “Medicare” group, overall and stratified by race. Increased physical

activity was not significantly associated with CVD (highest vs. lowest quartile: HR, 0.92; 95% CI: 0.67-0.1.25). The highest level of physical activity corresponds to doing moderate exercise for one hour, five days per week. These associations were not significantly different for blacks and whites (p-for interaction by race = 0.75), or for women and men (p-for interaction by sex = 0.61). The estimates did not appreciably change when participants who died within the first year of follow-up were excluded (highest compared with lowest level of physical activity, HR 0.90; 95% CI: 0.66-1.23).

Table 13 shows HRs (95% CIs) for the association between quartiles of sedentary time and CVD, overall and stratified by race in the "Medicare" group. Sedentary time in the highest quartile corresponds to spending more than half of the 24-hour day or ¾ of usual waking hours (16 hours) in sedentary behaviors. Among participants with diabetes, those in the highest quartile of sedentary time had a non-significantly higher CVD risk than those in the lowest quartile (HR, 1.21; 95% CI 0.89-1.64). Race-specific analyses showed that these results did not differ significantly among blacks compared to whites (p-for interaction by race = 0.18), although a significant trend of increasing risk with increasing sedentary time was observed among whites. Similarly, sex did not modify the association between sedentary time and CVD risk (p-for interaction by sex = 0.27), but a significant trend of rising risk with rising sedentary time was observed among women. The estimates did not appreciably change when participants who died within the first year of follow-up were excluded (highest compared with lowest level of sedentary time, HR 1.19; 95% CI: 0.87-1.62).

Table 10. Baseline characteristics of SCCS participants with diabetes in the "Medicare" group by Physical Activity Quartiles					
	Physical Activity < 5.7 MET-hr/d (n=397)	**Physical Activity 5.7-11.0 MET-hr/d (n=465)**	**Physical Activity 11.1-18.8 MET-hr/d (n=511)**	**Physical Activity ≥ 18.9 MET-hr/d (n=507)**	**p**
Age at Enrollment (years; mean, SD)	68.3 (5.1)	67.0 (4.6)	67.0 (4.4)	66.5 (4.4)	<0.0001
Race (n, %)					
- Black	302 (76.1)	343 (73.8)	378 (74.0)	362 (71.4)	0.14
- White	95 (23.9)	122 (26.2)	133 (26.0)	145 (28.6)	
Age at Diabetes Diagnosis (years; mean, SD)	55.5 (11.2)	55.6 (10.0)	55.4 (10.4)	55.8 (10.1)	0.95
Female (n, %)	242 (61.0)	343 (73.8)	371 (72.6)	377 (74.4)	<0.0001
Education					
- Less than High School	221 (55.7)	217 (46.7)	235 (46.0)	208 (41.0)	<0.0001
- High School Graduate	100 (25.2)	136 (29.3)	130 (25.4)	146 (28.8)	
- Beyond High School	76 (19.1)	112 (24.1)	146 (28.6)	153 (30.2)	
Annual Household Income (n,%)					
- Less than $15K					
- $15-49K	296 (74.6)	325 (69.9)	308 (60.3)	304 (60.0)	<0.0001
- $50K or Greater	94 (23.7)	119 (25.6)	169 (33.1)	174 (34.3)	
	7 (1.8)	21 (4.5)	34 (6.7)	29 (5.7)	
Body Mass Index (n, %; kg/m2)					
- Normal (18.5-24.9)					
- Overweight (25-29.9)	38 (9.7)	35 (7.7)	64 (12.7)	54 (10.7)	0.009
- Obese (30-39.9)	115 (29.4)	128 (28.1)	148 (29.3)	169 (33.6)	
- Severely Obese (40+)	178 (45.5)	220 (48.4)	235 (46.5)	221 (43.9)	
	60 (15.4)	72 (15.8)	58 (11.5)	59 (11.7)	
Time since Diabetes Diagnosis (years)					
- 0-5 years	129 (32.5)	166 (35.7)	192 (37.6)	204 (40.2)	0.014
- 6-10 years	82 (20.7)	106 (22.8)	93 (18.2)	104 (20.5)	
- 11-19 years	87 (21.9)	98 (21.1)	120 (23.5)	101 (19.9)	
- 20+ years	99 (24.9)	95 (20.4)	106 (20.7)	98 (19.3)	
Glucose-Lowering Medication					
- Oral Medication Only	230 (57.9)	294 (63.2)	300 (58.7)	318 (62.7)	0.006
- Insulin Use	127 (32.0)	125 (26.9)	150 (29.4)	120 (23.7)	
- No Medication	40 (10.1)	46 (9.9)	61 (11.9)	69 (13.6)	
Comorbidity History (n, %)					
- Hypertension	345 (86.9)	404 (86.9)	435 (85.1)	424 (83.6)	0.11
- High Cholesterol	209 (52.6)	259 (55.8)	306 (59.9)	304 (60.2)	0.011
Smoking History (n, %)					
- Current	59 (14.9)	82 (17.8)	58 (11.6)	48 (9.6)	0.006
- Former	146 (36.9)	174 (37.7)	192 (38.3)	194 (38.7)	
- Never	191 (48.2)	206 (44.6)	251 (50.1)	260 (51.8)	
Parental History of MI (n, %)	87 (21.9)	116 (25.0)	140 (27.4)	135 (26.6)	0.08

Table 11. Baseline characteristics of SCCS participants with diabetes in the "Medicare" group by Sedentary Time Quartiles					
	Sedentary Time < 5.25 h/d (n=465)	**Sedentary Time 5.25-7.9 h/d (n=485)**	**Sedentary Time 8.0-10.6 h/d (n=485)**	**Sedentary Time ≥ 10.7 h/d (n=445)**	**p**
Age (years; mean, SD)	67.5 (4.8)	67.3 (4.7)	67.0 (4.5)	66.7 (4.5)	0.06
Race (n, %)					
- Black	364 (78.3)	348 (71.8)	352 (72.6)	321 (72.1)	0.06
- White	101 (21.7)	137 (28.3)	133 (27.4)	124 (27.9)	
Age at Diabetes Diagnosis (years; mean, SD)	55.8 (10.4)	55.4 (10.6)	55.9 (10.0)	55.2 (10.5)	0.75
Female (n, %)	335 (72.0)	335 (69.1)	358 (73.8)	305 (68.5)	0.57
Annual Household Income (n,%)					
- Less than $15K					
- $15-49K	341 (73.3)	301 (62.1)	321 (66.2)	270 (60.7)	0.003
- $50K or Greater	108 (23.2)	154 (31.8)	140 (28.9)	154 (34.6)	
	16 (3.4)	30 (6.2)	24 (5.0)	21 (4.7)	
Education					
- Less than High School	267 (57.4)	210 (43.3)	229 (47.2)	175 (39.3)	<0.0001
- High School Graduate	111 (23.9)	151 (31.1)	128 (26.4)	122 (27.4)	
- Beyond High School	87 (18.7)	124 (25.6)	128 (26.4)	148 (33.3)	
Body Mass Index (n, %; kg/m2)					
- Normal (18.5-24.9)	58 (12.7)	49 (10.2)	50 (10.5)	34 (7.7)	**0.03**
- Overweight (25-29.9)	134 (29.3)	163 (34.0)	133 (28.0)	130 (29.5)	
- Obese (30-39.9)	205 (44.8)	206 (42.9)	229 (48.2)	214 (48.5)	
- Severely Obese (40+)	61 (13.3)	62 (12.9)	63 (13.3)	63 (14.3)	
Time since Diabetes Diagnosis (years)					
- 0-5 years	174 (37.4)	172 (35.5)	184 (37.9)	161 (36.2)	0.98
- 6-10 years	87 (18.7)	100 (20.6)	101 (20.8)	97 (21.8)	
- 11-19 years	101 (21.7)	108 (22.3)	99 (20.4)	98 (22.0)	
- 20+ years	103 (22.2)	105 (21.7)	101 (20.8)	89 (20.0)	
Glucose-Lowering Medication					
- Oral Medication Only	294 (63.2)	285 (58.8)	289 (59.6)	274 (61.6)	0.43
- Insulin Use	130 (28.0)	142 (29.3)	132 (27.2)	118 (26.5)	
- No Medication	41 (8.8)	58 (12.0)	64 (13.2)	53 (11.9)	
Comorbidity History (n, %)					
- Hypertension	409 (88.0)	409 (84.3)	412 (85.0)	378 (84.9)	0.39
- High Cholesterol	261 (56.4)	281 (57.9)	257 (53.0)	279 (62.8)	0.02
Smoking History (n, %)					
- Current	47 (10.3)	55 (11.4)	74 (15.3)	71 (16.2)	0.01
- Former	161 (35.2)	182 (37.8)	188 (38.9)	175 (39.9)	
- Never	250 (54.6)	244 (50.7)	221 (45.8)	193 (44.0)	
Parental History of MI (n, %)	103 (22.2)	130 (26.8)	122 (25.2)	123 (27.6)	0.23

Table 12. Hazard Ratios (95% Confidence Intervals) for the association between quartiles of total physical activity and CVD risk among SCCS participants with diabetes in the "Medicare" group				
	Unadjusted	***Minimally Adjusted***	***HR (95% CI) Model A***	***HR (95% CI) Model B***
Total (MET-h/d; n = 1,880)				
- < 5.7	Reference	Reference	Reference	Reference
- 5.8-11.0	0.95 (0.71-1.28)	0.94 (0.69-1.26)	1.01 (0.75-1.37)	1.01 (0.74-1.36)
- 11.1-18.8	0.78 (0.58-1.05)	0.76 (0.56-1.03)	0.79 (0.58-1.09)	0.77 (0.56-1.06)
- ≥ 18.9	0.90 (0.67-1.20)	0.87 (0.64-1.17)	0.95 (0.70-1.29)	0.93 (0.68-1.26)
p-for trend	0.29	0.21	0.44	0.33
Black (MET-h/d; n = 1,385)				
- < 5.7	Reference	Reference	Reference	Reference
- 5.8-11.0	0.98 (0.70-1.38)	0.97 (0.69-1.38)	1.08 (0.76-1.54)	1.08 (0.76-1.54)
- 11.1-18.8	0.83 (0.59-1.18)	0.82 (0.58-1.17)	0.88 (0.61-1.27)	0.88 (0.61-1.27)
- ≥ 18.9	0.93 (0.66-1.31)	0.93 (0.66-1.31)	1.01 (0.71-1.45)	1.01 (0.71-1.45)
p-for trend	0.50	0.49	0.77	0.76
White (MET-h/d; n = 495)				
- < 5.7	Reference	Reference	Reference	Reference
- 5.8-11.0	0.86 (0.47-1.56)	0.88 (0.47-1.63)	0.85 (0.45-1.59)	0.86 (0.46-1.62)
- 11.1-18.8	0.63 (0.34-1.17)	0.65 (0.34-1.21)	0.55 (0.28-1.08)	0.53 (0.26-1.05)
- ≥ 18.9	0.79 (0.44-1.40)	0.71 (0.40-1.29)	0.67 (0.36-1.24)	0.64 (0.34-1.20)
p-for trend	0.32	0.19	0.13	0.10
Males (MET-h/d; n = 547)				
- < 5.7	Reference	Reference	Reference	Reference
- 5.8-11.0	0.93 (0.57-1.50)	0.89 (0.55-1.45)	0.99 (0.60-1.63)	1.00 (0.60-1.65)
- 11.1-18.8	0.66 (0.39-1.10)	0.64 (0.39-1.07)	0.63 (0.36-1.09)	0.64 (0.37-1.11)
- ≥ 18.9	0.70 (0.42-1.17)	0.67 (0.40-1.07)	0.75 (0.43-1.29)	0.76 (0.44-1.31)
p-for trend	0.08	0.06	0.13	0.15
Females (MET-h/d; n = 1,333)				
- < 5.7	Reference	Reference	Reference	Reference
- 5.8-11.0	1.03 (0.70-1.51)	0.98 (0.67-1.44)	1.05 (0.71-1.55)	1.07 (0.72-1.58)
- 11.1-18.8	0.89 (0.61-1.31)	0.85 (0.57-1.25)	0.89 (0.60-1.32)	0.89 (0.60-1.32)
- ≥ 18.9	1.06 (0.73-1.53)	0.98 (0.67-1.43)	1.06 (0.72-1.57)	1.05 (0.71-1.54)
p-for trend	0.92	0.99	0.94	0.96

Table 13. Hazard ratios (95% confidence intervals) for the association between quartiles of total sedentary time and CVD risk among SCCS participants with diabetes in the "Medicare" group				
	Unadjusted	***Minimally Adjusted***	***HR (95% CI) Model A***	***HR (95% CI) Model B***
Total (h/d; n = 1,880)				
- < 5.2	Reference	Reference	Reference	Reference
- 5.2-7.9	1.05 (0.78-1.42)	1.05 (0.78-1.41)	1.05 (0.77-1.43)	1.05 (0.77-1.43)
- 8.0-10.6	1.23 (0.92-1.64)	1.23 (0.92-1.65)	1.21 (0.89-1.63)	1.21 (0.89-1.63)
- ≥ 10.7	1.21 (0.90-1.62)	1.17 (0.87-1.58)	1.20 (0.88-1.63)	1.21 (0.89-1.64)
p-for trend	0.13	0.18	0.17	0.16
Black (h/d; n = 1,385)				
- < 5.2	Reference	Reference	Reference	Reference
- 5.2-7.9	1.00 (0.72-1.39)	1.00 (0.72-1.39)	0.97 (0.69-1.36)	0.97 (0.69-1.36)
- 8.0-10.6	1.05 (0.76-1.46)	1.06 (0.77-1.48)	1.03 (0.74-1.45)	1.03 (0.74-1.45)
- ≥ 10.7	1.02 (0.72-1.42)	1.00 (0.71-1.40)	1.03 (0.73-1.46)	1.04 (0.74-1.48)
p-for trend	0.85	0.92	0.80	0.76
White (h/d; n = 495)				
- < 5.2	Reference	Reference	Reference	Reference
- 5.2-7.9	1.57 (0.73-3.36)	1.53 (0.71-3.28)	1.69 (0.76-3.77)	1.71 (0.77-3.81)
- 8.0-10.6	2.46 (1.20-5.04)	2.24 (1.09-4.62)	2.33 (1.08-5.03)	2.33 (1.08-5.04)
- ≥ 10.7	2.46 (1.20-5.06)	2.22 (1.08-4.57)	2.36 (1.07-5.04)	2.36 (1.09-5.12)
p-for trend	0.005	0.02	0.02	0.02
Males (h/d; n = 547)				
- < 5.2	Reference	Reference	Reference	Reference
- 5.2-7.9	0.81 (0.48-1.37)	0.82 (0.48-1.39)	0.84 (0.48-1.47)	0.84 (0.48-1.47)
- 8.0-10.6	1.25 (0.76-2.07)	1.25 (0.75-2.07)	1.29 (0.76-2.18)	1.29 (0.76-2.18)
- ≥ 10.7	0.83 (0.49-1.40)	0.80 (0.47-1.35)	0.85 (0.78-1.49)	0.85 (0.49-1.50)
p-for trend	0.88	0.76	0.007	0.004
Females (h/d; n = 1,333)				
- < 5.2	Reference	Reference	Reference	Reference
- 5.2-7.9	1.18 (0.82-1.71)	1.18 (0.82-1.71)	1.17 (0.80-1.70)	1.16 (0.80-1.69)
- 8.0-10.6	1.24 (0.86-1.78)	1.23 (0.86-1.76)	1.20 (0.83-1.74)	1.20 (0.83-1.74)
- ≥ 10.7	1.42 (0.99-2.04)	1.40 (0.97-2.00)	1.38 (0.95-2.00)	1.39 (0.96-1.74)
p-for trend	0.06	0.08	0.013	0.008

During follow-up (median follow-up time: 4.2 years, range = 0.01-7.5 years), 188 CVD events or CVD-related deaths occurred in the “TN HDDS” group (37.8%; 38.6% among blacks and 33.7% among whites). The 498 SCCS participants with diabetes in the “TN HDDS” group (83.7% black, 16.3% white, 61.9% female) had an average age at enrollment of 50.1 (6.2) years (**Tables 14 and 15**).

Table 14. Baseline characteristics of SCCS participants with diabetes in the "TN HDDS" group by Physical Activity Quartiles					
	Physical Activity <5.7 MET-hr/d (n = 120)	**Physical Activity 5.7-11.4 MET-hr/d (n = 105)**	**Physical Activity 11.5-19.9 MET-hr/d (n = 100)**	**Physical Activity ≥20.0 MET-hr/d (n = 173)**	**p**
Age at Enrollment (years; mean, SD)	50.8 (6.0)	52.0 (6.3)	49.9 (6.2)	48.6 (6.0)	<0.0001
Race (n, %)					
- Black	93 (77.5)	90 (85.7)	86 (86.0)	143 (82.7)	0.30
- White	27 (22.5)	15 (17.4)	14 (14.0)	30 (17.3)	
Age at Diabetes Diagnosis (years; mean, SD)	42.6 (8.8)	44.5 (8.0)	42.2 (8.2)	42.0 (8.4)	0.25
Female (n, %)	63 (52.5)	70 (66.7)	67 (67.0)	108 (62.4)	0.08
Education					
- Less than High School	36 (30.0)	41 (39.1)	25 (25.0)	42 (24.3)	0.21
- High School Graduate	39 (32.5)	33 (31.4)	35 (34.0)	61 (35.3)	
- Beyond High School	45 (32.5)	31 (29.5)	40 (40.0)	70 (40.5)	
Annual Household Income (n,%)					
- Less than $15K	95 (79.2)	71 (67.6)	52 (52.0)	90 (52.0)	<0.0001
- $15-49K	23 (19.2)	30 (28.6)	40 (40.0)	70 (40.5)	
- $50K or Greater	2 (1.7)	4 (3.8)	8 (8.0)	13 (7.5)	
Body Mass Index (n, %; kg/m2)					
- Normal (18.5-24.9)	17 (14.4)	16 (15.4)	7 (7.0)	19 (11.1)	0.59
- Overweight (25-29.9)	20 (17.0)	19 (18.3)	23 (23.0)	38 (22.1)	
- Obese (30-39.9)	48 (40.7)	46 (44.2)	48 (48.0)	78 (45.4)	
- Severely Obese (40+)	33 (28.0)	23 (22.1)	22 (22.0)	37 (21.5)	
Time since Diabetes Diagnosis (years)					
- 0-5 years	59 (49.2)	50 (47.6)	54 (54.0)	98 (56.7)	0.16
- 6-10 years	28 (23.3)	24 (22.9)	14 (14.0)	40 (23.1)	
- 11-19 years	19 (15.8)	25 (23.8)	22 (22.0)	25 (14.5)	
- 20+ years	14 (11.7)	6 (5.7)	10 (10.0)	10 (5.8)	
Glucose-Lowering Medication					
- Oral Medication Only	63 (52.5)	57 (54.3)	61 (61.0)	89 (51.5)	0.26
- Insulin Use	44 (36.7)	34 (32.4)	24 (24.0)	51 (29.5)	
- No Medication	13 (10.8)	14 (13.3)	15 (15.0)	33 (19.1)	
Comorbidity History (n, %)					
- Hypertension	88 (73.3)	80 (76.2)	74 (74.0)	116 (67.1)	0.35
- High Cholesterol	43 (35.8)	43 (41.0)	36 (36.4)	56 (32.6)	0.57
Smoking History (n, %)					
- Current	61 (51.7)	55 (52.4)	45 (45.0)	74 (42.8)	0.28
- Former	23 (19.5)	25 (23.8)	18 (18.0)	35 (20.2)	
- Never	34 (28.8)	25 (23.8)	37 (37.0)	64 (37.0)	
Parental History of MI (n, %)	49 (40.8)	34 (32.4)	26 (26.0)	61 (35.3)	0.13

Table 15. Baseline characteristics of SCCS participants with diabetes in the "TN HDDS" group by Sedentary Time Quartiles					
	Sedentary Time < 5.5 h/d (n = 91)	**Sedentary Time 5.5-7.9 h/d (n = 99)**	**Sedentary Time 8.0-10.9 h/d (n = 114)**	**Sedentary Time ≥ 11.0 h/d (n = 194)**	**p**
Age at Enrollment (years; mean, SD)	49.7 (6.1)	50.7 (6.6)	49.8 (6.2)	50.2 (6.1)	0.72
Race (n, %)					
- Black	78 (85.7)	82 (82.8)	91 (79.8)	161 (83.0)	0.74
- White	13 (14.3)	17 (17.2)	23 (20.2)	33 (17.0)	
Age at Diabetes Diagnosis (years; mean, SD)	43.0 (8.1)	43.7 (9.0)	41.8 (8.4)	42.6 (8.3)	0.42
Female (n, %)	53 (53.5)	53 (64.9)	74 (64.9)	128 (66.0)	0.15
Education					
- Less than High School	32 (35.2)	33 (33.3)	37 (32.5)	42 (21.7)	0.12
- High School Graduate	32 (35.2)	29 (29.3)	38 (33.3)	58 (35.6)	
- Beyond High School	27 (29.7)	37 (37.4)	39 (34.2)	83 (42.8)	
Annual Household Income (n,%)					
- Less than $15K					
- $15-49K	59 (64.8)	67 (67.7)	78 (68.4)	104 (53.6)	0.06
- $50K or Greater	30 (33.0)	28 (28.3)	31 (27.2)	74 (38.1)	
	2 (2.2)	4 (4.0)	5 (4.4)	16 (8.3)	
Body Mass Index (n, %; kg/m2)					
- Normal (18.5-24.9)					
- Overweight (25-29.9)	12 (13.3)	13 (13.3)	18 (15.9)	16 (8.3)	0.008
- Obese (30-39.9)	24 (26.7)	22 (22.5)	23 (20.4)	31 (16.1)	
- Severely Obese (40+)	31 (34.4)	50 (51.0)	53 (46.9)	86 (44.6)	
	23 (25.6)	13 (13.3)	19 (16.8)	60 (31.1)	
Time since Diabetes Diagnosis (years)					
- 0-5 years	48 (52.8)	57 (57.6)	57 (50.0)	99 (51.0)	0.27
- 6-10 years	22 (24.2)	17 (17.2)	28 (24.6)	39 (20.1)	
- 11-19 years	13 (14.3)	19 (19.2)	15 (13.2)	44 (22.7)	
- 20+ years	8 (8.8)	6 (6.1)	14 (12.3)	12 (6.2)	
Glucose-Lowering Medication					
- Oral Medication Only	52 (57.1)	51 (51.5)	56 (49.1)	111 (57.2)	0.49
- Insulin Use	25 (27.5)	28 (28.3)	40 (35.1)	60 (30.9)	
- No Medication	14 (15.4)	20 (20.2)	18 (15.8)	23 (11.9)	
Comorbidity History (n, %)					
- Hypertension	63 (69.2)	69 (69.7)	87 (76.3)	139 (71.7)	0.64
- High Cholesterol	29 (31.9)	37 (37.4)	42 (36.8)	70 (36.5)	0.85
Smoking History (n, %)					
- Current	53 (58.9)	43 (43.9)	52 (45.6)	87 (44.9)	0.09
- Former	11 (12.2)	28 (28.6)	22 (19.3)	40 (20.6)	
- Never	26 (28.9)	27 (27.6)	40 (35.1)	67 (34.5)	
Parental History of MI (n, %)	32 (35.2)	36 (36.4)	33 (29.0)	69 (35.6)	0.61

Table 14 shows the HRs (95% CI) for CVD risk across quartiles of physical activity in the SCCS cohort participants with diabetes in the “TN HDDS” group, overall and stratified by race. Increased physical activity was not significantly associated with CVD (highest vs. lowest quartile: HR, 0.82; 95% CI: 0.55-0.1.22). The highest level of physical activity corresponds to doing moderate exercise for approximately one hour, five days per week. **Table 15** shows HRs (95% CIs) for the association between quartiles of sedentary time and CVD, overall and stratified by race. Sedentary time in the highest quartile corresponds to spending more than half of the 24-hour day or ¾ of usual waking hours (16 hours) in sedentary behaviors. Among participants with diabetes, those in the highest quartile of sedentary time did not have a significantly different CVD risk than those in the lowest quartile (HR, 0.75; 95% CI 0.50-1.13). For both physical activity and sedentary time, the sample size was not sufficient to conduct race- or sex-specific analyses.

Table 16. Hazard ratios (95% confidence intervals) for the association between quartiles of total physical activity and CVD risk among SCCS participants with diabetes in the "TN HDDS" group				
	Unadjusted Model	***Minimally Adjusted***	***HR (95% CI) Model A***	***HR (95% CI) Model B***
Total (MET-h/d; n = 498)				
- < 5.7	Reference	Reference	Reference	Reference
- 5.8-11.4	1.08 (0.73-1.61)	1.02 (0.69-1.53)	1.07 (0.71-1.62)	1.02 (0.68-1.54)
- 11.5-19.9	0.79 (0.52-1.22)	0.85 (0.55-1.31)	1.00 (0.63-1.58)	0.92 (0.59-1.45)
- ≥ 20.0	0.66 (0.45-0.97)	0.75 (0.51-1.11)	0.90 (0.60-1.34)	0.82 (0.55-1.22)
p-for trend	0.01	0.10	0.53	0.28

Table 17. Hazard ratios (95% confidence intervals) for the association between quartiles of total sedentary time and CVD risk among SCCS participants with diabetes in the "TN HDDS" group				
	Unadjusted	***Minimally adjusted***	***HR (95% CI) Model A***	***HR (95% CI) Model B***
Total (h/d; n = 498)				
- < 5.5	Reference	Reference	Reference	Reference
- 5.5-7.9	0.69 (0.44-1.08)	0.65 (0.41-1.02)	0.67 (0.42-1.07)	0.67 (0.42-1.08)
- 8.0-10.9	0.82 (0.54-1.25)	0.79 (0.52-1.20)	0.69 (0.44-1.07)	0.68 (0.44-1.06)
- ≥ 11.0	0.75 (0.51-1.09)	0.72 (0.49-1.05)	0.75 (0.50-1.13)	0.75 (0.50-1.13)
p-for trend	0.28	0.23	0.31	0.29

Conclusions

The principal findings of this study were that, overall, neither increased levels of physical activity nor increased sedentary time was significantly associated with CVD risk among those with diabetes, both in the younger “TN HDDS” group and the older “Medicare” group. In subgroup analyses, a significant association between increased sedentary time and CVD risk was observed among whites in the “Medicare” group (HR, 2.36; 95% CI: [1.09-5.12]), with a significant dose-response trend. No other race or gender groups exhibited similar associations or trends.

In the SCCS, black and white adults reporting the highest levels of total physical activity and the least sedentary time had a reduced risk of CVD mortality(170). Cohen et al examined physical activity in relation to breast cancer risk in the SCCS female population. The final models showed physical activity had an inverse association and sedentary behavior a positive association with breast cancer risk among white women only(163). The current study adds to the information available from the SCCS population regarding the role of physical activity and sedentary time in the risk of CVD.

Since we do not know the exact mechanisms and lead times associated with the physical activity-CVD relationship studied here, we did not know if participants had enough of an opportunity to experience a physical activity protective event. We do not have information on how long the participants have been as active as they reported at enrollments and we do not know the period of time necessary for physical activity to impact CVD risk. For those enrolled later in the study period, the cumulative likelihood of observing an event (but not necessarily the spontaneous hazard rate) is reduced

because the time in which to observe the event is reduced. Except as noted previously for those enrolled in the SCCS in 2008, all participants had at least a year of follow-up.

For our main exposure variables, total physical activity and total sedentary time, some participants in our analyses reported total hours spent in physical activity or sedentary time in excess of 24 hours (n = 1,547). Since participants were asked about individual activity or sitting times and their responses were not confined to the 24-hour day, we could not reliably determine which individual times were over-reported. Due to our categorization of total physical activity and total sedentary time into quartiles, the participants who over-reported would largely be contained in the highest quartiles of activity or sitting, where they would arguably belong even in the absence of over-reporting.

Additionally, the possibility of reverse causation exists in prospective cohort studies of this kind. Those who are less physically active may be ill in some other way, which may make them more likely to experience a fatal or non-fatal event during the follow-up period. We attempted to control for this potential bias by conducting secondary analyses excluding participants who died within the first year of follow-up. Excluding these participants may leave us with the healthier participants thus biasing our results. However, we do not believe this exclusion are of significant concern because the results of those analyses did not differ significantly from that of the main analyses.

Our studies did not observe a significant, causal relationship between physical activity, sedentary time, and CVD in the two cohorts studied. However, given the small sample size we used in these analyses, we suggest this study be improved among a larger, racially-diverse, and mixed-gender population with diabetes.

CHAPTER 5

Effect Modification of the Association between Physical Activity or Sedentary Time and Cardiovascular Disease by Body Mass Index

Obesity as a Risk Factor for Cardiovascular Complications

Obesity is an epidemic in the United States with the age-adjusted prevalence of overweight and obesity being 68% among both men and women (NHANES 1998-2008)(171). Obesity has been implicated as a risk factor for numerous adverse health conditions from cancer to heart disease to diabetes.

An early study concluded that obesity in type 2 diabetics was not associated with increased risk for incident cardiovascular complications when compared to normal weight (HR: 0.66, 95% CI: 0.56-0.78)(172). This study introduced the idea of an obesity paradox in the relationship to diabetes-related complications - an inverse relationship between BMI and risk, especially among populations with traditional risk factors for CVD. Additional recent studies have also reported the apparent obesity paradox, including a study examining the association between weight status and mortality in diabetics using separate and pooled data from the Atherosclerosis Risk in Communities (ARIC) study, Cardiovascular Health Study (CHS), Coronary Artery Risk Development in Young Adults (CARDIA) study, Framingham Offspring Study (FOS), and Multi-Ethnic Study of Atherosclerosis (MESA)(173). This pooled study included subgroup analysis by race (non-white versus white) and reported that the obesity paradox was more pronounced among non-whites compared to whites, but the difference did not reach significance.

Since the inverse relationship between BMI and mortality is not intuitive, reviews and commentaries have been published attempting to explain the paradox. One paper that focused on the obesity paradox among patients with heart failure suggested that the obese patients used in the studies that reported the paradox may be healthier than their non-obese comparators, the measures of body mass index may not be accurate, cachexia due to other illnesses (wasting syndrome) may be responsible, or the association may be different in the severely obese who have not been studied (174). Another review urged researchers to consider using other indices of body fat distribution (e.g. waist circumference, waist-to-hip ratio) instead of BMI because studies that used BMI reported the obesity paradox, whereas in studies that used other measures of body fatness, obesity was directly and positively associated with higher event rates and total mortality compared to normal weight(175). Though the evidence for and against the existence of the obesity paradox is controversial, the evidence against the paradox has not been reported among those with diabetes and the race-specific pertinence has not been well-established.

Of note, the studies that have identified the obesity paradox may be explained by the methods in regression modeling and the causal pathway. First, obesity is a risk factor for hypertension and hyperlipidemia (high cholesterol). Both of those conditions are risk factors for CVD. The studies examining the relationship between obesity and CVD are often adjusted for these conditions that may be on the causal pathway to CVD. Adjusting for these conditions can remove the effects of the very mechanism that would connect obesity and CVD.

Blacks are more likely to be overweight or obese compared to whites, and obesity may also affect diabetes risk through different mechanisms (176-178). Multivariate analyses have shown that race remains to be an independent risk factor for obesity, even after adjustment for socioeconomic status and other covariates like age and sex[15,182,183]. In the SCCS cohort, 83% of black females were in overweight or obese BMI categories (BMI > 25) compared to 75% of white females(33). The differences observed between women are often hypothesized to be due to the cultural idealization of thinness and the perception of attractiveness related to thinness among whites(179). Sociocultural standards may influence racial differences in obesity, but genetic studies have found evidence that obesity may be hereditary. A recent genetic study discovered three new loci in the human genome distinctly related to BMI in individuals of African ancestry (180). These unique loci may help explain the racial differences observed in BMI between blacks and whites.

The association between physical activity and CVD may differ across BMI levels. High levels of physical activity have been shown to attenuate the risk of obesity at a genetic level through early to late adulthood(181). Additionally, those in the normal BMI category are more likely to attain a higher level of cardiorespiratory fitness compared to obese individuals(182). Several studies have reported an inverse relationship between cardiorespiratory fitness and CVD risk(3, 15, 169). One study performed maximal exercise tests on 2,316 male participants from the ACLS and studied CVD mortality among several BMI strata. This study found that low cardiorespiratory fitness was associated with an increased risk of CVD mortality within all weight categories (normal

weight: HR: 2.7, 95% CI: 1.3-5.7; overweight: HR: 2.7, 95% CI: 1.4-5.1; obese: HR: 2.8, 95% CI: 1.4-5.1)(3).

Methods

Physical activity was assessed using the SCCS physical activity questionnaire as previously described. BMI was calculated from participants' self-reported height and weight values. BMI was modeled in the continuous format for the analysis and categorized for display. Participants were categorized as normal weight (BMI between 18.5 kg/cm^2 and less than 25 kg/cm^2; referent), overweight (BMI between 25 kg/cm^2 and less than 30 kg/cm^2), obese (BMI between 30 kg/cm^2 and less than 40 kg/cm^2), and severely obese (BMI greater or equal to 40 kg/cm^2).

Adjusted Cox proportional hazards models were used to generate hazard ratios and 95% CIs for the association between BMI and CVD risk among the "Medicare" group. The interaction between physical activity and body mass index was assessed by the inclusion of an interaction term to the final adjusted model for the physical activity-CVD association conducted among the "Medicare" group. The interaction was comprised of the categorical physical activity variable and the BMI variable in its continuous form. Models with and without the physical activity and body mass index interaction term were compared using likelihood ratio tests (LRT). Similarly, an interaction term was created for sedentary time and BMI then entered into the final adjusted model for the sedentary time-CVD association conducted among the "Medicare" group. Interactions were considered significant if LRT was significant at the 0.05 level.

All analyses were conducted using SAS software, version 9.3 (SAS Institute Inc, Cary, NC) and all tests were two-sided.

Results

Of the 1,880 participants with diabetes in the “Medicare” group, the majority were considered in the obese or severely obese category (58.7%; **Table 19**). Obese and severely obese participants were significantly younger at enrollment and at the time of diabetes diagnosis. Those who were severely obese were more likely to be female, have prevalent hypertension, be less active, never have smoked, and use insulin as a part of their diabetes treatment regimen. There were no significant differences in racial composition or socioeconomic status between those in each of the BMI categories.

We examined CVD risk in relation to BMI and observe no significantly different risks in the obese categories compared to the normal weight category of those with diabetes (obese: HR: 0.82, 95% CI: 0.57-1.19; severely obese: HR: 0.90, 95% CI: 0.58-1.40). There was not a significant interaction between BMI and physical activity levels (p-for interaction = 0.77). A significant interaction was also not observed between BMI and sedentary time (p-for interaction = 0.33).

Table 18. Baseline characteristics of SCCS participants with diabetes aged 65 years or more (2002-2008) by Body Mass Index Categories					
	BMI Normal (n = 186)	**BMI Overweight (n = 560)**	**BMI Obese (n = 854)**	**BMI Severely Obese (n = 249)**	**p**
Age at Enrollment (years; mean, SD)	68.4 (5.0)	67.6 (4.7)	66.8 (4.5)	66.0 (4.3)	<0.0001
Race (n, %)					
- Black	125 (67.2)	406 (72.5)	648 (75.9)	183 (73.5)	0.10
- White	61 (32.8)	154 (27.5)	206 (24.1)	66 (26.5)	
Age at Diabetes Diagnosis (years; mean, SD)	57.2 (10.3)	56.4 (10.2)	55.4 (10.5)	53.5 (10.1)	0.002
Female (n, %)	115 (61.8)	352 (62.9)	623 (73.0)	217 (87.2)	<0.0001
Education					
- Less than High School	77 (41.4)	261 (46.6)	405 (47.4)	120 (48.2)	0.52
- High School Graduate	59 (31.7)	146 (26.1)	228 (26.7)	72 (28.9)	
- Beyond High School	50 (26.9)	153 (27.3)	221 (25.9)	57 (22.96)	
Household Income (n, %)					
- Less than $15K	119 (64.0)	352 (62.9)	565 (66.2)	172 (69.1)	0.09
- $15K-$49K	57 (30.7)	169 (30.2)	252 (29.5)	72 (28.9)	
- $50K or Greater	10 (5.4)	39 (7.0)	37 (4.3)	5 (2.0)	
Time since Diabetes Diagnosis (years)					
- 0-5 years	72 (38.7)	218 (38.9)	321 (37.6)	72 (28.9)	0.06
- 6-10 years	40 (21.5)	118 (21.1)	164 (19.2)	54 (21.7)	
- 11-19 years	37 (19.9)	99 (17.7)	198 (23.2)	68 (27.3)	
- 20+ years	37 (19.9)	125 (22.3)	171 (20.0)	55 (22.1)	
Comorbidity History (n, %)					
- Hypertension	138 (74.2)	474 (84.6)	741 (86.8)	227 (91.2)	<0.0001
- High Cholesterol	99 (53.2)	337 (60.2)	481 (56.5)	145 (58.5)	0.29
Glucose-Lowering Medication					
- Oral Medication Only	113 (60.8)	360 (64.3)	512 (60.0)	138 (55.4)	0.0009
- Insulin Use	42 (22.6)	133 (23.8)	253 (29.6)	87 (34.9)	
- No Medication	31 (16.7)	67 (31.8)	89 (10.4)	24 (9.6)	
Smoking History (n, %)					
- Current	37 (20.2)	81 (14.7)	103 (12.2)	20 (8.1)	0.0007
- Former	69 (37.7)	217 (39.3)	327 (38.6)	85 (34.4)	
- Never	77 (42.1)	254 (46.0)	418 (49.3)	142 (57.5)	
Parental History of MI (n, %)	46 (24.7)	132 (23.6)	211 (24.7)	76 (30.5)	0.20
Total Physical Activity (MET-hrs/day)					
- < 5.7	37 (19.9)	115 (20.5)	178 (20.8)	60 (24.1)	0.08
- 5.8-11.0	34 (18.3)	128 (22.9)	220 (25.8)	72 (28.9)	
- 11.1-18.8	63 (33.9)	148 (26.4)	235 (27.5)	58 (23.3)	
- ≥ 18.9	52 (28.0)	169 (30.2)	221 (25.9)	59 (23.7)	

Conclusions

Our study did not observe the inverse relationship between BMI and CVD risk as seen in previous studies. The independent associations between physical activity, sedentary time, and CVD risk were not modified by BMI. The results of our study add to the continuing conversation about obesity, physical activity, and CVD. Church et al examined the risk of CVD by BMI and cardiorespiratory fitness levels(3). Obese (BMI > 30 kg/cm^2) individuals with diabetes in the moderate and high fit group were statistically at no higher risk for CVD mortality compared to those of normal weight and similar fitness levels. This finding is consistent with that of our current study. A study of male veterans with diabetes also found similar physical activity-CVD relationships across BMI categories that were specified similar to our study (8).

BMI may not be the correct metric by which to examine this relationship. BMI as a measure of general obesity has been disputed and other metrics, such as waist-to-hip ratio and waist circumference, have often been promoted as measures that better correlate to adverse outcomes(183-185). Future research should explore these analyses with better studied measures like the aforementioned and even investigate other measures or supplements that would better model the obesity-CVD association. Further, the interaction between obesity and physical activity levels can be better studied using more precise and objective measures of activity. Acceleration-based measures may give us a greater understanding of a participant's actual average activity level across a time period rather than relying on reported information.

This study was limited by certain factors. BMI was calculated from self-reported values of height and weight. Poor reporting of weight and height has been consistently reported as being differential between races and genders (186). Studies have noted that severely obese women of lower socioeconomic status tended to underreport their height and weight. Older people tend to over-report their height and more accurately report their weight(187). These differential errors in self-reporting may have caused misclassification of participants and biased our studies.

Additionally, given that BMI was calculated at enrollment and we did not update their height and weight measurements within this study, changes in BMI may have impacted participants' risk of CVD. However, we do not believe this to be as much an issue because BMI is not as sensitive as a weight measurement and fluctuations in weight would need to be quite significant in order to change BMI considerably.

Obesity, while a risk factor for diabetes and CVD, did not impact the relationship between physical activity and CVD.

CHAPTER 6

The Independent Associations between Physical Activity and Sedentary Time with All-Cause Mortality among Low-Income Adults with Diabetes

Methods

The primary outcome was defined as death from any cause. Vital status and date of death were ascertained through linkage of the SCCS cohort with the Social Security Administration (SSA) vital status service for epidemiologic researchers and the National Death Index (NDI) through December 31, 2011(60).

Person-years of follow-up began on the date of enrollment into the SCCS cohort and concluded on the date of death or the end of the study period (December 31, 2011), whichever came first. Descriptive statistics for the study population were calculated, including means and standard deviations for continuous variables as well as counts and percentages for categorical or dichotomous variables. Values for each quartile of physical activity were compared using chi-squared tests and one-way ANOVA tests.

Cox proportional hazards models, using age as the time scale, were constructed to estimate hazards ratios (HR) and 95% confidence intervals (CI) for mortality in relation to total physical activity and total sedentary time, first separately and then mutually adjusted to determine whether the associations were independent of each other. Fully adjusted models included age at enrollment, race (black or white; not included in race-stratified models), sex (not included in sex-stratified models), body mass index (BMI; 18-24.9, 25-29.9, 30-39.9, ≥40 kg/m^2), educational attainment (less than high school,

high school graduate, beyond high school), annual household income (< $15, $15-$50K, ≥$50K), insulin use (yes/no), smoking (current, former, never), hypertension, high cholesterol, or cardiovascular disease (myocardial infarction/bypass and stroke) prevalent at baseline (all yes/no), and duration of diabetes (years). The dose-response trend for total physical activity or total sedentary time was evaluated by entering the ordinal form of the variable into a proportional hazards model with death as the outcome. The p-value for the likelihood ratio test was used to assess the trend for total physical activity or sedentary time.

Sensitivity analyses were conducted to evaluate the potential effect of exposure outliers for physical activity and sedentary time, and to exclude those who died in the first year of follow-up to mitigate the possibility of reverse causation. To test whether outlier values for physical activity and sedentary time impacted estimates, a term ((physical activity outlier: yes or no; sedentary time outlier: yes or no) was added to the models in sensitivity analyses to determine whether adjusting for the distribution of those outliers would appreciably change the estimates. To assess whether those with pre-existing conditions that increased their risk of death outside of physical activity or sedentary time exposure, we conducted another sensitivity analysis where those who died in the first year of follow-up were excluded. To explore whether physical activity and sedentary time jointly influence mortality, we examined the joint effects for these exposures using tertiles. All analyses were conducted using Stata software, version 11 (StataCorp LP, College Station, TX) and all tests were two-sided.

Results

The 15,645 SCCS participants with diabetes (71.2% black, 28.8% white, 65.0% female) had an average age at enrollment of 54.9 (8.9) years (**Table 16**). Approximately two-thirds of the population had a high school education or less, and more than 60% reported an annual household income of less than $15,000. Blacks were slightly younger than whites at both their time of enrollment and time of diabetes diagnosis. Whites were more likely to have obtained a high school education or beyond. A higher proportion of whites than blacks were also in the severely obese (BMI ≥ 40) category and reported prevalent CVD at baseline. Blacks reported slightly but significantly higher total physical activity levels than whites and had higher proportions of individuals in both the highest and lowest categories of sedentary time. Blacks were more likely to never have smoked. Of note, blacks were also significantly more likely to use insulin as a part of their diabetes medication regimen than were whites.

Table 19. Baseline characteristics of SCCS participants with diabetes by race and sex							
	Total (n=15,645)	***Black (n=11,137)***	***White (n=4,508)***	***p***	***Male (n=5,483)***	***Female (n=10,162)***	***p***
Age at Enrollment (mean, SD)	54.9 (8.9)	54.4 (8.8)	56.0 (8.9)	<0.0001	54.6 (8.7)	55.1 (8.9)	<0.001
Age at Diabetes Diagnosis (mean, SD)	46.1 (10.5)	45.4 (10.4)	47.8 (10.8)	<0.0001	46.3 (10.2)	47.3 (10.9)	0.10
Time Since Diabetes Diagnosis (n, %)							
- < 5 years	6,284 (40.2)	4,368 (39.2)	1,916 (42.5)	<0.0001	2,228 (40.6)	4,056 (39.9)	0.06
- 5-10 years	4,407 (28.2)	3,094 (27.8)	1,313 (29.1)		1,638 (29.9)	2,769 (27.3)	
- 11-19 years	3,019 (19.3)	2,214 (19.9)	805 (17.9)		1,056 (19.3)	1,963 (19.3)	
- ≥ 20 years	1,935 (12.4)	1,461 (13.1)	474 (10.5)		561 (10.2)	1,374 (13.5)	
Female (n, %)	10,162 (65.0)	7,290 (65.5)	2,872 (63.7)	0.04	------	-----	
Black Race (n, %)	11,137 (71.2)	------	------		3,847 (70.2)	7,290 (71.7)	
Education (n, %)							
- Less than High School	5,374 (34.4)	4,067 (36.5)	1,307 (29.0)	<0.0001	1,861 (34.0)	3,513 (34.6)	0.68
- High School							
- Beyond High School	5,049 (32.3)	3,535 (31.8)	1,514 (33.6)		1,770 (32.3)	3,279 (32.3)	
	5,219 (33.4)	3,530 (31.7)	1,686 (37.4)		1,849 (33.7)	3,367 (33.1)	
Household Income (n, %)							
- Less than $15K	9,391 (60.8)	6,908 (62.8)	2,483 (55.8)	<0.0001	2,961 (54.7)	6,430 (64.0)	<0.0001
- $15K-$49K	5,124 (33.2)	3,604 (32.8)	1,520 (34.2)		1,950 (36.1)	3,174 (31.6)	
- $50K or Greater	940 (6.1)	492 (4.5)	448 (10.1)		498 (9.2)	442 (4.4)	
Body Mass Index (BMI; n, %)							
- 18.5-24.9	1,662 (10.8)	1,244 (11.3)	418 (9.4)	<0.0001	872 (16.0)	790 (7.9)	<0.0001
- 25-29.9	3,655 (23.6)	2,663 (24.2)	992 (22.2)		1,669 (30.7)	1,986 (19.8)	
- 30-39.9	6,991 (45.2)	4,959 (45.1)	2,032 (45.6)		2,301 (42.3)	4,690 (46.8)	
- ≥ 40	3,155 (20.4)	2,137 (19.4)	1,018 (22.8)		602 (11.1)	2,553 (25.5)	
Prevalent Conditions (n, %)							
- Hypertension	12,432 (79.5)	9,009 (80.9)	3,423 (76.0)	<0.0001	4,287 (78.2)	8,145 (80.2)	0.004
- High Cholesterol	8,644 (55.4)	5,738 (51.6)	2,906 (64.7)	<0.0001	2,930 (53.6)	5,714 (56.3)	0.001
- Heart Attack/Bypass	2,095 (13.4)	1,231 (11.1)	864 (19.2)	<0.0001	948 (17.3)	1,147 (11.3)	<0.0001
- Stroke/TIA	1,722 (11.0)	1,183 (10.6)	539 (12.0)	0.02	633 (11.6)	1,089 (10.7)	0.12
Smoking Status (n, %)							
- Current	4,553 (29.2)	3,267 (29.5)	1,286 (28.7)	<0.0001	2,013 (37.0)	2,540 (25.1)	<0.0001

- Former	4,591 (29.5)	3,050 (27.5)	1,541 (34.4)		1,939 (35.6)	2,652 (26.2)	
- Never	6,418 (41.2)	4,768 (43.0)	1,650 (36.9)		1,490 (27.4)	4,928 (48.7)	
Glucose-Lowering Medication							
- Oral Medication Only	8,769 (56.1)	6,265 (56.3)	2,504 (55.6)	<0.0001	2,975 (54.3)	5,790 (57.0)	
- Insulin Use	4,445 (28.4)	3,351 (30.1)	1,094 (24.3)		1,598 (29.2)	2,847 (28.0)	0.003
- No Medication	2,431 (15.5)	1,521 (13.7)	910 (20.2)		906 (16.5)	1,525 (15.0)	
Physical Activity (MET-h/d; n, %)							
- < 6.9	3,822 (24.4)	2,648 (23.8)	1,174 (26.0)	0.004	1,714 (31.3)	2,108 (20.7)	<0.001
- 6.9-14.1	4,002 (25.6)	2,830 (25.4)	1,172 (26.0)		1,218 (22.2)	2,784 (27.4)	
- 14.2-24.8	3,908 (25.0)	2,811 (25.2)	1,097 (24.3)		1,085 (19.8)	2,823 (27.8)	
- ≥ 24.9	3,913 (25.0)	2,848 (25.6)	1,065 (23.6)		1,466 (26.7)	2,447 (24.1)	
Sedentary Time (h/d; n, %)							
- < 6	3,801 (24.3)	2,784 (25.0)	1,017 (22.6)	0.002	1,289 (23.5)	2,512 (24.7)	0.002
- 6-8.4	3,822 (24.4)	2,656 (23.9)	1,166 (25.9)		1,323 (24.1)	2,499 (24.6)	
- 8.5-11.9	3,647 (23.3)	2,569 (23.1)	1,078 (23.9)		1,236 (22.5)	2,411 (23.7)	
- ≥ 12.0	4,375 (28.0)	3,128 (28.1)	1,247 (27.7)		1,635 (29.8)	2,740 (27.0)	

During follow-up (median follow-up time: 6.2 years, range = 0.01-9.8 years), 2,370 deaths (15.2%, with similar percentages among blacks and whites; 12.3% among females; 20.4% among males) occurred among the study population for a crude annual death rate of 2.44%. **Table 17** shows the HRs (95% CI) for mortality across quartiles of physical activity in the SCCS cohort participants with diabetes, overall and stratified by race and by sex. Increased physical activity was inversely associated with mortality in a dose-response manner (highest vs. lowest quartile: HR, 0.64; 95% CI: 0.56-0.72). The highest level of physical activity corresponds to doing moderate exercise for one hour, five days per week. These associations were not significantly different for blacks and whites (p-for interaction by race = 0.19), or for women and men (p-for interaction by sex = 0.93). The estimates did not appreciably change when participants who died within the first year of follow-up were excluded (results not shown; highest compared with lowest level of physical activity, HR 0.65; 95% CI: 0.57-0.74).

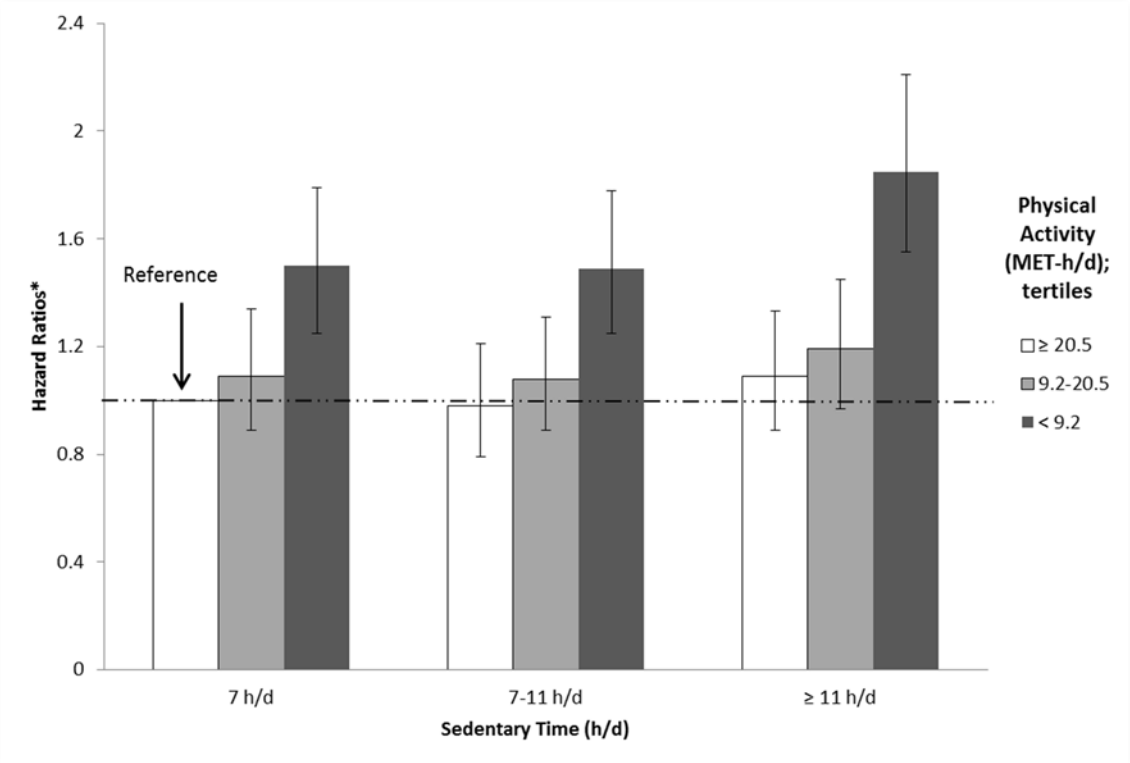
Table 18 shows HRs (95% CIs) for the association between quartiles of sedentary time and mortality, overall and stratified by race and by sex. Sedentary time in the highest quartile corresponds to spending more than half of the 24-hour day or ¾ of usual waking hours (16 hours) in sedentary behaviors. Among participants with diabetes, those in the highest quartile of sedentary time had mortality risk approximately 25% higher than those in the lowest quartile (HR, 1.25; 95% CI 1.11-1.40), with a significant dose-response trend. Race-specific analyses showed that high levels of sedentary time were associated with similarly increased mortality risk among blacks and whites (p-for interaction by race = 0.29). Similarly, sex did not modify the association between sedentary time and mortality (p-for interaction by sex = 0.83).

Analysis of the joint effects of physical activity and sedentary time on mortality (**Figure 4**) showed that individuals who were the most sedentary (≥11 h/d) and the least active (< 9 MET-h/d) were at the greatest risk of death (HR 1.80, 95% CI: 1.50-2.16) compared to other physical activity-sedentary time categories.

Table 20. Hazard Ratios (95% Confidence Intervals) for the association between quartiles of total physical activity and all-cause mortality risk among SCCS participants with diabetes				
	Person-Years	***# Events***	***HR (95% CI)[a]***	***HR (95% CI)[b]***
Total (MET-h/d; n = 15,645)				
- < 6.9	22,004	887	Reference	Reference
- 6.9-14.1	24,050	591	0.76 (0.68 – 0.85)	0.76 (0.68 – 0.84)
- 14.2-24.8	24,275	466	0.65 (0.58 – 0.73)	0.65 (0.57 – 0.73)
- ≥ 24.9	24,245	426	0.65 (0.57 – 0.73)	0.64 (0.56 – 0.72)
p-for trend			< 0.0001	< 0.0001
Black (MET-h/d; n = 11,137)				
- < 6.9	15,780	601	Reference	Reference
- 6.9-14.1	17,578	428	0.81 (0.71 – 0.92)	0.81 (0.71 – 0.92)
- 14.2-24.8	18,067	332	0.68 (0.59 – 0.78)	0.67 (0.58 – 0.77)
- ≥ 24.9	18,368	324	0.70 (0.61 – 0.81)	0.69 (0.60 – 0.79)
p-for trend			< 0.0001	< 0.0001
White (MET-h/d; n = 4,508)				
- < 6.9	6,224	286	Reference	Reference
- 6.9-14.1	6,472	163	0.65 (0.53 – 0.79)	0.65 (0.53 – 0.80)
- 14.2-24.8	6,208	134	0.62 (0.50 – 0.77)	0.62 (0.50 – 0.77)
- ≥ 24.9	5,877	102	0.54 (0.43 – 0.69)	0.54 (0.43 – 0.69)
p-for trend			< 0.0001	< 0.0001
Males (MET-h/d; n = 5,483)				
- < 6.9	9,473	497	Reference	Reference
- 6.9-14.1	7,045	240	0.77 (0.66 – 0.90)	0.77 (0.65 – 0.89)
- 14.2-24.8	6,573	182	0.66 (0.56 – 0.79)	0.66 (0.55 – 0.79)
- ≥ 24.9	8,772	199	0.65 (0.54 – 0.77)	0.64 (0.54 – 0.76)
p-for trend			< 0.0001	< 0.0001
Females (MET-h/d; n = 10,162)				
- < 6.9	12,531	390	Reference	Reference
- 6.9-14.1	17,005	351	0.75 (0.65 – 0.88)	0.75 (0.65 – 0.87)
- 14.2-24.8	17,702	284	0.64 (0.55 – 0.76)	0.64 (0.55 – 0.75)
- ≥ 24.9	15,473	227	0.65 (0.55 – 0.77)	0.64 (0.54 – 0.75)
p-for trend			< 0.0001	< 0.0001

Table 21. Hazard Ratios (95% Confidence Intervals) for the association between quartiles of total sedentary time and all-cause mortality risk among SCCS participants with diabetes				
	Person-Years	***# Events***	***HR (95% CI)[a]***	***HR (95% CI)[b]***
Total (h/d; n = 15,645)				
- < 6	23,162	562	Reference	Reference
- 6 – 8.4	23,263	589	1.03 (0.92 – 1.16)	1.04 (0.92 – 1.17)
- 8.5 – 11.9	22,025	542	1.11 (0.99 – 1.26)	1.13 (1.00 – 1.27)
- ≥ 12	26,124	677	1.23 (1.10 – 1.38)	1.25 (1.11 – 1.40)
p-for trend			<0.0001	<0.0001
Black (h/d; n = 11,137)				
- < 6	17,608	422	Reference	Reference
- 6 – 8.4	16,731	413	1.00 (0.87 – 1.15)	1.01 (0.88 – 1.16)
- 8.5 – 11.9	16,080	386	1.11 (0.97 – 1.28)	1.13 (0.98 – 1.30)
- ≥ 12	19,374	464	1.17 (1.02 – 1.34)	1.19 (1.04 – 1.37)
p-for trend			0.01	0.005
White (h/d; n = 4,508)				
- < 6	5,554	140	Reference	Reference
- 6 – 8.4	6,532	176	1.10 (0.87 – 1.38)	1.09 (0.87 – 1.36)
- 8.5 – 11.9	5,945	156	1.12 (0.89 – 1.42)	1.12 (0.88 – 1.41)
- ≥ 12	6,750	213	1.39 (1.11 – 1.74)	1.38 (1.10 – 1.72)
p-for trend			0.005	0.005
Males (h/d; n = 5,483)				
- < 6	7,491	262	Reference	Reference
- 6 – 8.4	7,923	265	0.97 (0.81 – 1.15)	0.98 (0.82 – 1.17)
- 8.5 – 11.9	7,095	257	1.18 (0.99 – 1.41)	1.20 (1.01 – 1.43)
- ≥ 12	9,354	334	1.20 (1.01 – 1.42)	1.21 (1.02 – 1.44)
p-for trend			0.007	0.004
Females (h/d; n = 10,162)				
- < 6	15,671	300	Reference	Reference
- 6 – 8.4	15,340	324	1.09 (0.93 – 1.28)	1.09 (0.93 – 1.28)
- 8.5 – 11.9	14,930	285	1.06 (0.90 – 1.25)	1.06 (0.90 – 1.26)
- ≥ 12	16,770	343	1.25 (1.07 – 1.48)	1.27 (1.08 – 1.50)
p-for trend			0.013	0.008

Figure 4. Joint effects of total physical activity and total sedentary time on all-cause mortality risk among SCCS participants with diabetes



[a]Adjusted for age, sex, race, BMI, socioeconomic status (education and income), smoking, hypertension, high cholesterol, myocardial infarction, stroke, insulin use, duration of diabetes.

Conclusions

In this prospective analysis of a racially diverse, low-income population with diabetes, we found that higher levels of total physical activity were associated with a nearly 40% reduced risk of mortality after adjusting for sedentary time. Increased total time spent in sedentary behaviors was linked to an approximate 25% increase in mortality risk in this population after adjusting for physical activity. Further, the analysis of the joint effects of both physical activity and sedentary time on mortality risk revealed that across all levels of sedentary time, low levels of physical activity were associated with an increased risk of death. To our knowledge, the current study contributes the first assessment of the independent relationship between total physical activity and sedentary time and mortality in both black and white men and women with diabetes, as well as a comparison of these associations by race and sex. Our study also examined this association in a population from a low socioeconomic status background, populations among whom diabetes prevalence is elevated.

Our findings are generally consistent with prior studies of mortality among those with diabetes, the majority of which were conducted among white men and reported a reduced risk of mortality as activity levels increased (4, 5, 7, 9-15, 188-192). The strengths of the previously reported associations varied, even among relatively similar populations. Studies of males reported risk reductions ranging from 52-78%(4, 9, 11, 13, 15, 188) among those with (variously defined) highest vs. lowest physical activity. The highest quartile in the current study is lower than some studies that were conducted among those with diabetes who were without any other co-morbidities, but higher than studies of general populations that tended to adjust for comorbidities.

Studies that included both males and females had results ranging from 24-60% reductions in risk associated with high physical activity levels (5, 7, 10, 12, 14, 189, 190, 192). It is unclear whether the weaker associations observed in mixed-gender populations was a result of differences in study methodologies or an actual sex-difference in the impact of physical activity on mortality among those with diabetes. The overall reduction in mortality risk (37%) we observed was within the range of other mixed-gender studies, and our sex-specific results demonstrated, for the first time, similar mortality associations in both males and females for both physical activity and sedentary time.

The effect estimates may range between studies in part due to differences in how physical activity was measured for each study, as well as how physical activity levels were categorized and compared for each study. Sluik et al. used quartiles for the assessment of leisure time physical activity and their top quartile was > 113 MET-hr/week (corresponds with approximately > 16.1 MET-hr/day). Mortality risk among their top quartile was reduced by almost 40% compared to the lowest quartile (HR 0.62, 95% CI: [0.46-0.85])(12). Trichopoulou et al. assessed physical activity using quintiles and the highest quintile was ≥ 37 MET-hrs/day. Those in the highest quintile had a decreased mortality risk of more than 20% compared to the lowest quintile (HR 0.76, 95% CI: [0.63-0.92]) (14). Quintiles for physical activity were also the exposure variable used in the study conducted by Tanasecu et al and the highest quintile (≥ 37.2 MET-hr/week) also had a decreased risk of mortality compared to those in the lowest quintile (HR 0.65, 95% CI: [0.45-0.93])(13). Our study showed comparable results with the reduction in risk being approximately 40%. Most studies, like ours, assessed self-

reported total or leisure-time physical activity. However, studies that measured cardiorespiratory fitness as the index of physical activity likewise consistently reported inverse associations with mortality in those with diabetes, with risk reductions of 57-87% when comparing highest level of activity to lowest (9, 11, 15, 188).

sedentary time and mortality risk has been explored previously but not specifically among those with diabetes. Most studies have treated sedentary time as if it were the inverse of physical activity and have not evaluated its independent association with mortality. Our study demonstrated an increased mortality risk of 18% for those who were the most sedentary compared to those who were the least sedentary. These results were after adjustment for physical activity, further highlighting the independence of the relationship. We did however, also explore how physical activity and sedentary time interact and effect mortality risk. Across all levels of sedentary time, those in the lowest category of physical activity with diabetes (< 6.9 MET-hr/day) were at an increased risk of mortality compared to the most active and least sedentary individuals with diabetes. Those who were the least active and most sedentary had the highest risk (HR 1.85, 95% CI: [1.53-2.22]).

Previous investigations also differed regarding covariates used in multivariate models. A number of studies did not adjust for diabetes duration or insulin use or diabetes medication, which have been previously implicated as significant risk factors for mortality among individuals with diabetes(54, 60, 129, 193-195). Our analysis included adjustment for demographic and socioeconomic variables, as well as diabetes duration and treatment variables, which were often not included in multivariate models of other studies.

Currently, the available evidence supporting physical activity as a protective factor against mortality for people with diabetes is derived almost exclusively from white populations. The only study that published race-specific estimates reported a weaker and less graded association among black male veterans than white male veterans (9), similar to our findings of qualitatively weaker trends among blacks than whites. However, our overall findings do not support a differential effect of physical activity or sedentary time on mortality by race, and there would be limited biologic plausibility for such an interaction.

The current study population was racially diverse and by design, black and white SCCS participants were of generally similar socioeconomic status, enabling evaluation of the risk of mortality with minimal confounding by differences in socioeconomic status (with residual confounding adjusted statistically). The findings of the current study suggest that increased physical activity and decreased sedentary time are associated with decreased mortality risk in a mainly low-income population with systematic and standardized follow-up to determine death status.

In summary, the findings suggest that increased physical activity and decreased sedentary time may be viable prevention efforts to reduce mortality burden within a racially diverse, low-income population with diabetes. The study extends to blacks and to women findings that have previously been reported primarily among white men with diabetes, and signals that intervention efforts could be similarly effective across gender and racial groups. Further research exploring objective, repeated measures of physical activity and sedentary time, and examining different types and frequencies of activity

suitable for populations with diabetes may help to clarify intervention strategies aimed at reducing the burden of this increasingly common illness.

CHAPTER 7

Summary Conclusions and Suggestions for Future Research

This research is the first to our knowledge to examine physical activity and sedentary time in association with CVD risk and all-cause mortality in a racially-diverse population of mixed gender with diabetes. Further, this study population is of low socioeconomic status with a high prevalence of CVD risk factors (hypertension, obesity, high cholesterol) compared to previous research. Studies that preceded the current research often reported strong, inverse relationships between physical activity and CVD (**Appendix 3**). Those studies were often conducted among predominantly white males with diabetes and of middle to high socioeconomic status.

Race was not associated with CVD risk among this population of racially-diverse, low-income adults with diabetes, with nearly equal CVD event rates among both blacks and whites. The high rates of CVD observed among this population may be related to the high prevalence of CVD-related risk factors (obesity and hypertension, for example) or low socioeconomic status. Although our study did not find conclusive evidence to suggest that physical activity was significantly inversely associated with CVD risk among diabetics, increased activity did have a strong, inverse relationship with all-cause mortality in this population. Further, low levels of physical activity were significantly associated with mortality in every quartile of sedentary time but especially among those who were the most sedentary. Physical activity may need to be accompanied by other substantial treatment or management changes to impact CVD risk. However, as

observed in other studies, physical activity is a viable intervention for reducing the gap in mortality risk between those with and without diabetes.

Increased levels of physical activity could serve as an intervention to reduce mortality rates among those with diabetes and improve overall, general health. In the SCCS, those with diabetes had almost twice the risk of death compared to those without diabetes (13.9% vs. 8.7% respectively; HR: 1.87, 95% CI: 1.76-2.00). According to the results of our analyses, higher levels of physical activity among those with diabetes may reduce that gap. Sedentary time had a significant, positive relationship with mortality, even after adjustment for physical activity. This suggests that, despite the level of activity, excessive time spent in sedentary behaviors can be equally as dangerous for mortality risk. Patients should be encouraged to minimize sitting time during the waking hours and to meet or exceed the recommended physical activity levels.

The actual average level of physical activity is difficult to ascertain from self-reported information. However, it is inexpensive and does not have the time intensive component of other methods of ascertainment. The nature of the self-reported physical activity exposure may introduce some bias into our study. We hope that future studies will examine these associations using objective measures of activity such as accelerometer data. The SCCS PAQ was validated using accelerometer data and metrics from this tool are often used to determine activity among study subjects. However, it is usually not feasible to get these data on a sample as large as the SCCS. While labor intensive and costly, accelerometer data could provide us with a more accurate picture of physical activity levels as well as possible differences by race and sex.

There is no specific recommendation for those with diabetes and diabetes-related conditions as to how much activity is necessary to provide a benefit for either CVD or mortality. The currently available literature and recommendations are primarily for those without diabetes, or a general population without regard to diabetes. Diabetes-related conditions, such as retinopathy, may prevent those with diabetes from participating in moderate-to-vigorous activity so investigating which activities would provide the greatest benefit to these individuals could prevent advancement of the disease and reduce the incidence of additional comorbidities.

The replication of the analyses exploring the association between physical activity, sedentary time, and CVD as well as mortality would be interesting in a racially-diverse set of adults of higher socioeconomic status. Our follow-up data (event ascertainment) was from separate data sources. Had our sample been adequately powered, we could have conducted several race- and sex-specific analyses in the younger adults with diabetes. The next steps in research would be to investigate the race-specific risk of CVD in association with physical activity and sedentary time among a larger group of middle-aged persons with diabetes with a large, alternate source of follow-up data. Novel interventions based on the results of those studies to increase activity levels among those with diabetes should consider whether race or sex influences the impact of physical activity on CVD or mortality.

It is unclear what role strength training and anaerobic activity plays in the physical activity-CVD or physical activity-mortality relationships. Since the vast majority of studies have explored aerobic activity as the exposure representing physical activity, it could now be important to add other types of activities into the metric in order to

properly assess all activity. For this to happen, new methods of measuring physical activity on a broader, more complete level may need to be developed and validated in a variety of populations. These new methods could be applied widely across health conditions and subpopulations.

Diabetes is a significant global health problem with growing incidence in part due to the expansion of elderly and minority populations that are at an increased risk of developing diabetes(27, 42, 196-200). Reviving strategies and recommendations for increasing physical activity may delay mortality and improve the overall health profile of people with diabetes. However, those strategies and recommendations should be specific and evidence-based in their origin. Tailoring physical activity-related interventions to the patient and ensuring that the healthcare infrastructure supports those interventions may potentially reduce CVD risk and mortality among patients with diabetes.

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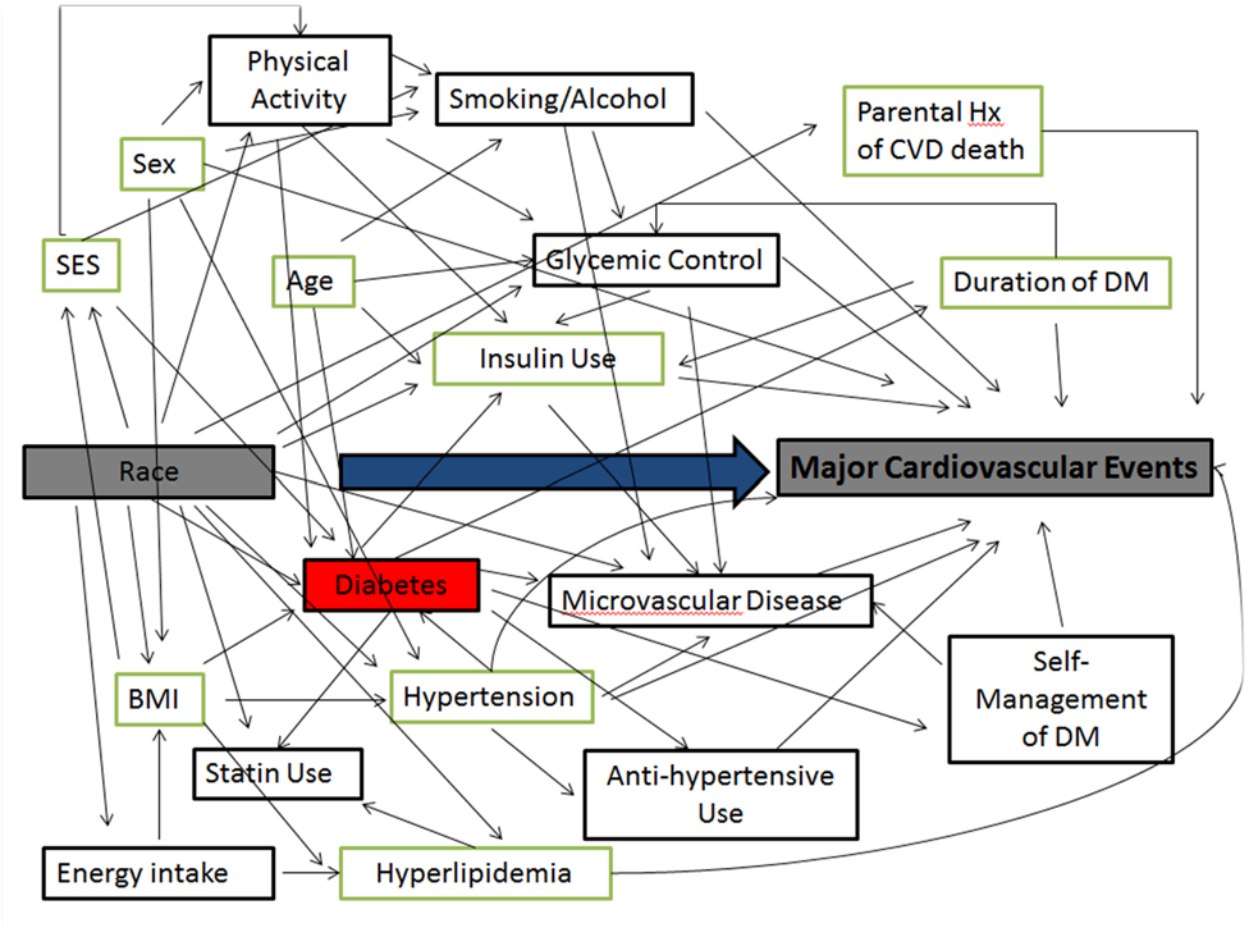
APPENDIX A

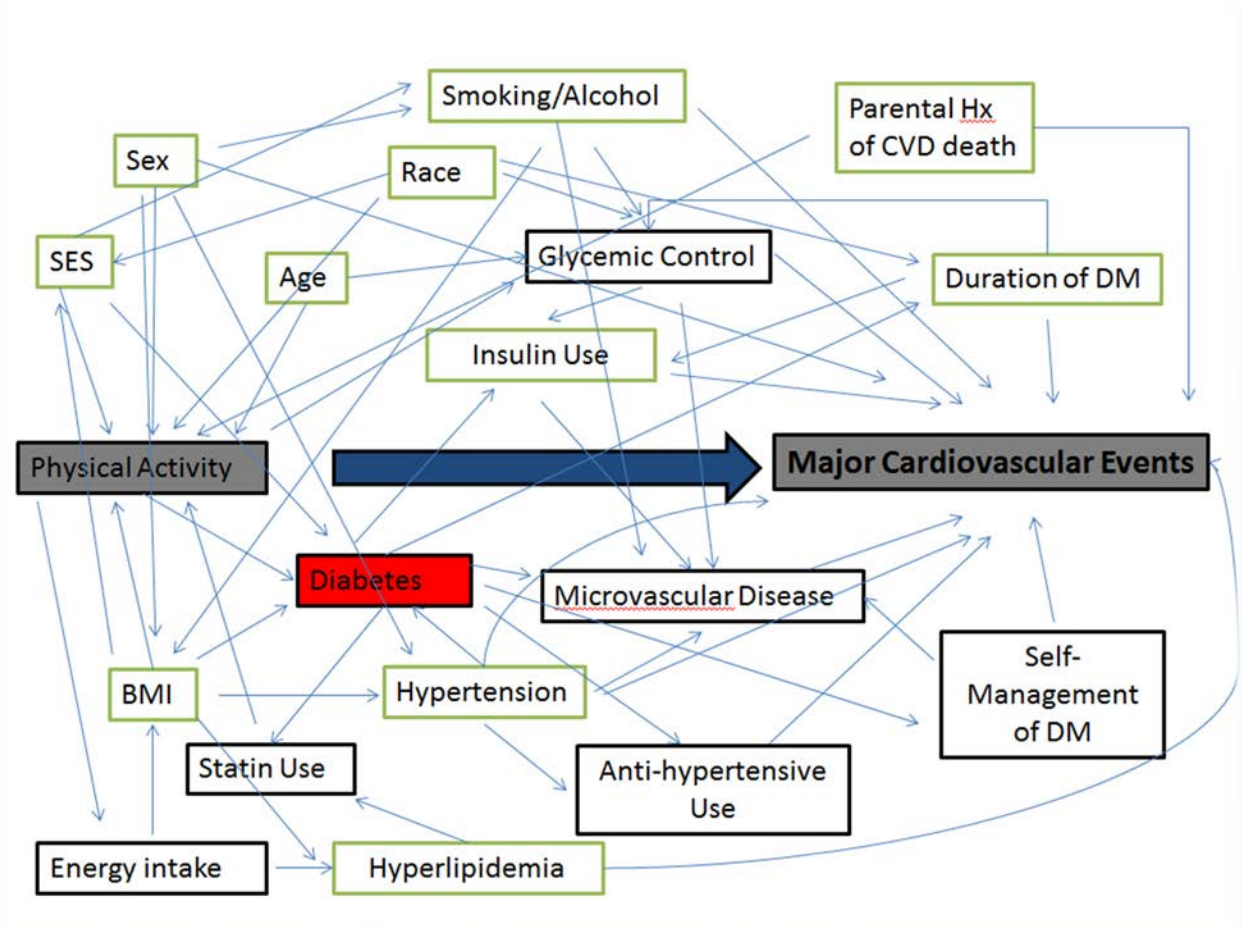
Directed Acyclic Graphs (DAGs)

(1.1) Race-CVD Association



Selected for inclusion in the adjusted models

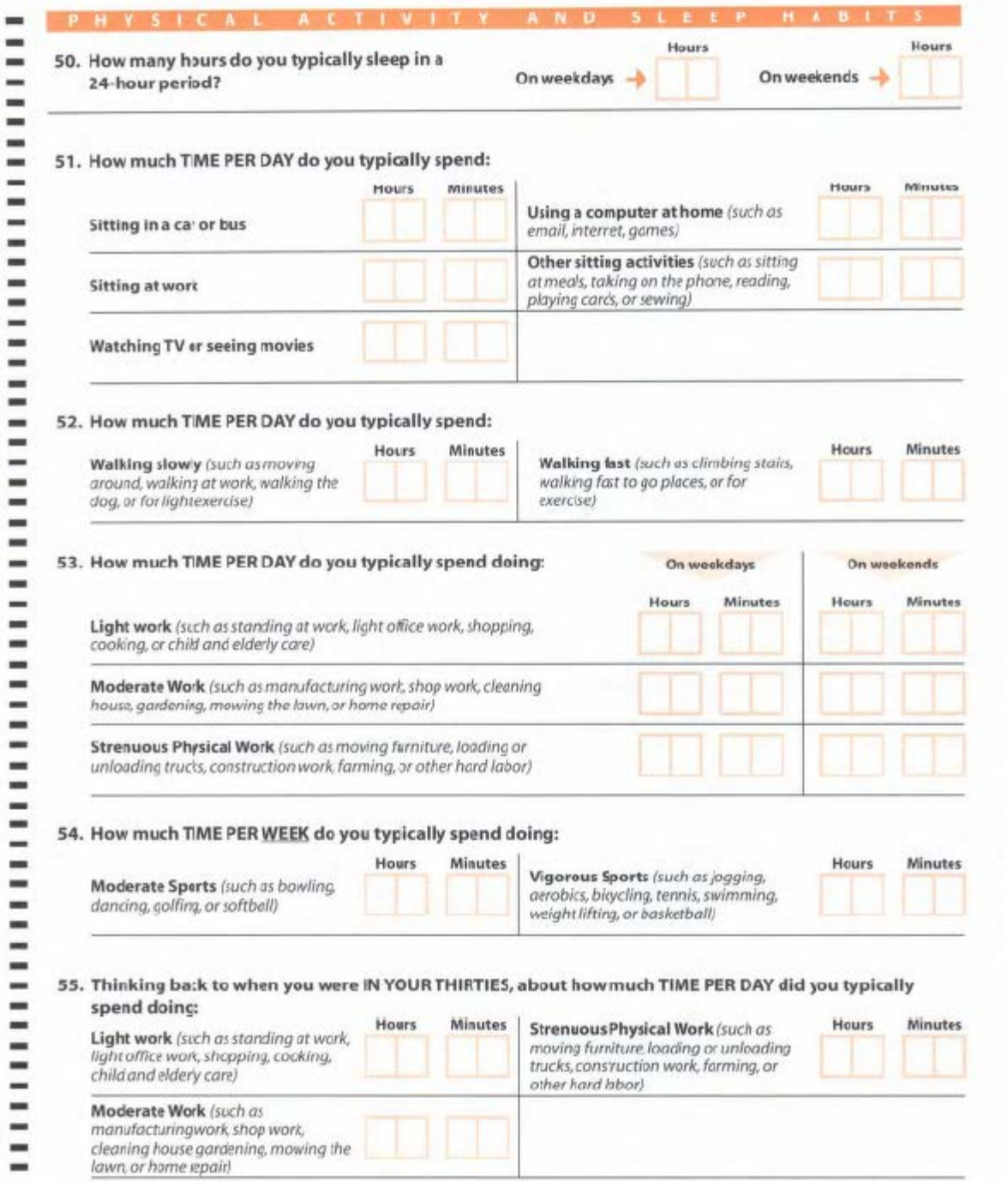
(1.2) Physical Activity and CVD Association



Selected for inclusion in the adjusted models

APPENDIX B

Southern Community Cohort Study Physical Activity Questionnaire (PAQ)



PHYSICAL ACTIVITY AND SLEEP HABITS

50. How many hours do you typically sleep in a 24-hour period? On weekdays → Hours ☐☐ On weekends → Hours ☐☐

51. How much TIME PER DAY do you typically spend:

	Hours	Minutes		Hours	Minutes
Sitting in a car or bus	☐☐	☐☐	Using a computer at home (such as email, interet, games)	☐☐	☐☐
Sitting at work	☐☐	☐☐	Other sitting activities (such as sitting at meals, taking on the phone, reading, playing cards, or sewing)	☐☐	☐☐
Watching TV or seeing movies	☐☐	☐☐			

52. How much TIME PER DAY do you typically spend:

	Hours	Minutes		Hours	Minutes
Walking slowly (such as moving around, walking at work, walking the dog, or for light exercise)	☐☐	☐☐	Walking fast (such as climbing stairs, walking fast to go places, or for exercise)	☐☐	☐☐

53. How much TIME PER DAY do you typically spend doing:

	On weekdays		On weekends	
	Hours	Minutes	Hours	Minutes
Light work (such as standing at work, light office work, shopping, cooking, or child and elderly care)	☐☐	☐☐	☐☐	☐☐
Moderate Work (such as manufacturing work, shop work, cleaning house, gardening, mowing the lawn, or home repair)	☐☐	☐☐	☐☐	☐☐
Strenuous Physical Work (such as moving furniture, loading or unloading trucks, construction work, farming, or other hard labor)	☐☐	☐☐	☐☐	☐☐

54. How much TIME PER WEEK do you typically spend doing:

	Hours	Minutes		Hours	Minutes
Moderate Sports (such as bowling, dancing, golfing, or softball)	☐☐	☐☐	Vigorous Sports (such as jogging, aerobics, bicycling, tennis, swimming, weight lifting, or basketball)	☐☐	☐☐

55. Thinking back to when you were IN YOUR THIRTIES, about how much TIME PER DAY did you typically spend doing:

	Hours	Minutes		Hours	Minutes
Light work (such as standing at work, light office work, shopping, cooking, child and elderly care)	☐☐	☐☐	Strenuous Physical Work (such as moving furniture, loading or unloading trucks, construction work, farming, or other hard labor)	☐☐	☐☐
Moderate Work (such as manufacturing work, shop work, cleaning house gardening, mowing the lawn, or home repair)	☐☐	☐☐			

APPENDIX C

Previous Literature Related to Physical Activity, CVD, CVD Mortality, and All-Cause Mortality among Subjects with Diabetes

Author(s), Year	Outcomes Measure(s)	Physical Activity Measure	Cohort	Sample Size	Major Findings/Comments**
Church, 2005	CVD mortality	CR Fitness	Aerobics Center Longitudinal Study (ACLS)	2,316	Low fitness level was associated with increased risk of CVD mortality within normal weight, overweight, and obese weight categories.
Church, 2004	ACM	CR Fitness	Aerobics Center Longitudinal Study (ACLS)	2,196	There was a steep inverse gradient between fitness and mortality in this cohort of men with documented diabetes, and this association was independent of BMI.
de Fine Olivarius, 2010	ACM; CVD mortality	Self-reported Leisure Time Physical Activity	Diabetes Care in General Practice Study	1,323	Sedentary people were 60% more likely to die than active persons with diabetes. Approximately the same HRs for CVD mortality.
Ford, 1991	ACM; CVD mortality	Self-reported leisure-time physical inactivity	NHANES I	602	Non-leisure-time physical inactivity was associated with all-cause mortality. The strength of the associations between risk factors and all-cause and coronary heart disease mortality did not differ significantly among persons with and without diabetes.

Gaziano, 2005	ACM	Self-reported Frequency of Vigorous Exercise	Physicians' Health Study	2,838	Exercise is associated with a significant reduction in overall mortality among male diabetic physicians without a history of MI, stroke, or cancer. The association is linear with increasing relative risk reduction through to the highest exercise category.
Hu, 2004	ACM; CVD mortality	Self-reported total physical activity	Finnish Population	3,316	Moderate or high levels of physical activity reduce total and CVD mortality among patients with type 2 diabetes. Not only leisure-time physical activity but also occupational and commuting physical activities are important components of a healthy lifestyle among patients with diabetes.
Hu, 2001	CVD events; CVD mortality	Self-reported total physical activity (including walking)	Nurses' Health Study	5,125	Among diabetic women, increased physical activity, including regular walking, is associated with substantially reduced risk for cardiovascular events.
Iijima, 2012	CVD events	Self-reported physical activity	Japanese Elderly Diabetic Intervention Trial (J-EDIT)	938	Lower physical activity is a strong and independent predictor of all CVD events in the elderly with type 2 diabetes beyond traditional risk factors.
Janevic, 2013	CVD events	Self-reported physical activity	US Health and Retirement Study	1,811	Adults with diabetes with complications of the eyes, kidneys, or nerves and those with heart disease are less likely to meet physical activity guidelines compared to those without these complications.
Kokkinos, 2009	ACM	CR Fitness	Veterans Exercise Testing Study (VETS)	3,148	Exercise capacity is a strong predictor of all-cause mortality in African American and Caucasian men with type 2 diabetes. The exercise capacity-related

					reduction in mortality appears to be stronger and more graded for Caucasians than for African Americans.
Nothlings, 2010	ACM	Self-reported physical activity	European Prospective Investigation into Cancer and Nutrition (EPIC) – Potsdam Study	1,263	No significant difference in mortality risk in active compared to inactive persons
Nylen, 2013	ACM	CR Fitness	Veterans Exercise Testing Study (VETS)	2,867	Augmented exercise capacity is associated with lower risk of mortality in people with type 2 diabetes aged 50 to 65 as well as in those older than 65.
Sluik, 2012	ACM; CVD mortality	Self-reported physical activity	European Prospective Investigation into Cancer and Nutrition (EPIC)	5,859	Higher levels of physical activity were associated with lower mortality risk in individuals with diabetes. Even those undertaking moderate amounts of activity were at appreciably lower risk for early death compared with inactive persons. Compared with physically inactive persons, the lowest mortality risk was observed in moderately active persons
Sone, 2013	ACM; CVD events	Self-reported physical activity	Japan Diabetes Complications Study (JDCS)	1,702	In Japanese persons with type 2 diabetes, LTPA of 15.4 MET h/week or more was associated with a significantly lower risk of stroke partly through ameliorating combinations of cardiovascular risk factors.
Spencer, 2008	CVD events	Self-reported physical activity	Million Women Study – UK	25, 915	Incidence of CVD in women with diabetes 4.5 (active) and 5 (inactive) per 100 women aged 50-69 over 5 years.
Tanasescu,	ACM; CVD	Self-reported	Health Professionals'	3,058	Physical activity was associated with reduced risk of

2003	events	physical activity	Follow-up Study (HPFS)		CVD, cardiovascular death, and total mortality in men with type 2 diabetes. Walking and walking pace were associated with reduced total mortality.
Trichopoulou, 2006	ACM	Self-reported physical activity	European Prospective Investigation into Cancer and Nutrition (EPIC) – Greek study	1,013	Physical activity was strongly inversely associated with mortality.
Wei, 2000	ACM	CR Fitness	Aerobics Center Longitudinal Study (ACLS)	1,263	Low cardiorespiratory fitness and physical inactivity are independent predictors of all-cause mortality in men with type 2 diabetes.

*ACM = all-cause mortality, CR = cardiorespiratory, CVD = cardiovascular disease