SPECIFIC AIMS

US Hispanics are the largest US minority group, constituting over 15% of the US population and growing to one-third of the US by 2050. Hispanics match or exceed any other race-ethnicity group in having a high burden of diabetes and pre-diabetes. Especially given the relatively young age of US Hispanics, nondiabetics and the group with prediabetes (e.g.,fasting plasma glucose 100-125 mg/dl) are of immense public health importance because 15-30% of people with prediabetes will develop diabetes within five years[1]. Physical activity (PA) is an effective preventive behavior in the battle to prevent diabetes as suggested by the DPP, Da Qing and Finland diabetes prevention program trials[2-4]. In this context, the Hispanic/Latino population presents a paradox. Particularly among low SES men, Hispanics have high workplace moderate-to-vigorous PA (MVPA). Light intensity PA (LPA) is higher and time spent sedentary is lower among Hispanics than other race-ethnic groups. These facts have come to light only recently through accelerometry studies, which capture movement such as transportation and work-related activity as well as sedentary behavior (SB) which are not usually recorded in traditional self-reported PA assessments. Our four-center NIH Hispanic Community Health Study-Study of Latinos (HCHS-SOL, n=16,415) has also revealed substantial variation in PA levels across Hispanic groups such as Mexicans, Puerto Ricans and Dominicans. There is also an apparent contradiction between a high risk of prediabetes/diabetes among Hispanics, while at the same time Hispanics have favorable mortality rates vs. others and may also have lower incidence of cardiovascular disease (CVD).

The present application will leverage the HCHS-SOL and the Framingham Heart Study (FHS) Third Generation and Omni Gen 2 (FHS Gen3/Omni2) cohorts. We seek to understand the relationship among PA, SB, diabetes, and CVD in a large, representative population study of nondiabetics while comparing predictors of physical activity in **Hispanics and non-Hispanics**. An important goal is to ascertain detailed information regarding the intensity and type of PA over time that can prevent diabetes and its complications (e.g., CVD) in non-diabetics. Shifting time from prolonged SB to LPA might prevent diabetes and CVD, which is of particular importance in the high diabetes risk population who may have difficulties performing MVPA. As shown by HCHS-SOL and other studies, high SB is associated with unfavorable cardiometabolic risk, even among those meeting national guidelines for MVPA levels[5]. Our findings can be applied toward future guidelines to recommend target levels of MVPA, LPA and SB in this vulnerable target group of prediabetics, who have not been well studied. Specifically, we will define what amount of SB should be replaced with LPA or MVPA to maximize benefits, and examine the health outcomes associated with PA and SB of different bout lengths. We will also fill a gap in our understanding of the groups at highest risk of having worsening PA habits over time (as is typically seen across young adulthood to middle age), by focusing on a population across the entire adult age range in multiple ethnic groups.

Our multi-site approach not only increases generalizability of our findings to the total US population, but also helps us understand what is unique about Hispanics. In all, 5500 Hispanic and non-Hispanic individuals nondiabetics will be studied, all of whom had 7-day Actical accelerometry measurements (2008-2011) which will be repeated during 2017-2020. Fasting and post-OGTT measures of glycemia, HOMA-IR, additional cardiometabolic risk factors such as lipids and incident CVD events and mortality are measured by the parent HCHS-SOL and FHS cohorts. This will capture ~780 participants who will convert to diabetes and ~527 who sustain incident CVD events. Specific aims are:

1. Among 5500nondiabetics, to identify PA and SB patterns associated with conversion to diabetes up to 12 years aged 18 to 80 years old by adding a second accelerometry measure to HCHS-SOL. We will examine influence of bout length and intensity of PA to define the dose-response relationships affecting diabetes risk.

2. Amongnondiabetics, to identify the relationship between MVPA, LPA and SB with incident CVD events and mortality, in order to define the magnitude of risks and dose-response for duration, intensity and bout length.

3. To investigate demographic and psychosocial correlates associated with 6+ year changes in patterns of PA and SB in Hispanics/Latinos and non-Hispanics/Latinos without a diagnosis of diabetes. .

Our hypothesized predictors of PA/SB include age, sex and race/ethnic and national background – comparing a mostly (80+%) immigrant HCHS-SOL Hispanic/Latino population versus US born Hispanics/Latinos and non-Hispanics/Latinos. We hypothesize that younger, non-Hispanic/Latino white adults and women will have high risk of decreasing MVPA and increasing SB over time. Using the rich characterization of the cohorts, additional analyses will examine mental and physical well-being, employment and economic indicators, acculturation, diet, comorbidities and health care use in relation to changes in MVPA, LPA and SB. Thus we will not only identify the patterns of PA and SB that predict disease **(Aims 1+2)**, but also the barriers and

facilitators of these patterns as well as the groups in greatest need of intervention **(Aim 3)**.

B. Background and Significance

B1. Gaps in knowledge about physical activity Americans have become increasingly sedentary over the past decades [6,7] yet becoming physically active is "one of the most important steps that Americans of all ages can take to improve their health"[8]. Guidelines for PA typically focus on promoting MVPA, or moderate-to-vigorous intensity aerobic (endurance) activity. Current guidelines are incomplete regarding specific behavior patterns that should be either adopted or avoided. For instance, since 1995, Americans have been advised to accumulate MVPA in bouts of 8-10 minutes.[9] New evidence suggests that exercise bursts of even shorter duration may be beneficial[10], but few studies have examined the health effects of short exercise bouts. Most existing PA data comes from self-report, which lacks the ability to define detailed patterns, and is often limited to recall of "leisure time" activities and relatively long bouts of high intensity PA. The 2008 US Guidelines for Americans recommend a level of aerobic exercise equivalent to 75+ weekly minutes of vigorous PA, or 150+ weekly minutes of moderate PA, or a combination thereof, in order to forestall disease and lengthen lifespan[11]. However, specific recommendations for individuals with high cardiometabolic risks remain incomplete. For example, what should be recommended to non-diabetics or individuals with pre-diabetes or diabetes? Given that not all such individuals are able to perform MVPA, what combination of LPA and MVPA can prevent or postpone the conversion of nondiabetics to pre-diabetes and diabetes? SB or prolonged sitting and reclining, may itself raise cardiometabolic risks, due to effects of skeletal muscle contraction on metabolic function. Among all outcomes studied, diabetes has the strongest association with SB levels[12]. Even light activity such as walking to interrupt SB time may be beneficial[13-16], and brief breaks from sitting may be sufficient to avert the adverse health consequences of being sedentary[42a]. Only a few national guidelines set targets for SB (Australia, UK)[17-20], but this situation may change with additional data describing the dose-response patterns linking SB levels with adverse health outcomes, independent of MVPA. Reduction of SB may be a particularly useful complementary strategy beyond promotion of MVPA. Public health strategies that will empower people to reduce SB (e.g., increased walking, standing at work, taking breaks from sitting) are different than those that promote MVPA.

Notably, these issues are particularly salient among Hispanics/Latinos, who have among the highest prevalences of diabetes of any group (e.g., 17.7% in individuals of Central American, 18.0% of Dominican, 18% of Puerto Rican, and 18.3% of Mexican background). Our HCHS-SOL group has also showed higher risks of diabetes with greater years of living in the US, lower education and household income among the predominantly immigrant HCHS-SOL cohort[21]. On the other hand, total PA is higher in Hispanics/ Latinos relative to other ethnic groups, especially for men with high levels of MVPA at the workplace, which may explain their favorable health outcome (the "Hispanic Paradox"). Given the particular demographic characteristics of US Hispanics, including a high proportion being foreign-born, lack of acculturation to the US mainstream, low status occupations, large families and young age distribution, it is important to understand the leading influences across the life course that enable or discourage favorable PA and SB patterns over time. Yet, due to their exclusion from most prior large cohort follow-up studies, Hispanics have not been well characterized for longitudinal changes in PA.

B2. Accelerometer assessment of PA and SB PA is a complex process and includes all body movement resulting in energy expenditure. Metrics of PA are intensity, frequency, duration, and type of PA. Strengths and weaknesses are associated with all PA measurement approaches including direct and indirect calorimetry along with doubly labeled water, behavioral observation, motion sensors such as accelerometers, and self-report[22]. Most large studies use self-report to estimate PA levels, with all of the inaccuracies associated with a complex recall task[23-26]. Many self-report approaches are limited to leisure-time PA activity obtained in longer bouts (e.g., ≥10 min), which despite being easier to recall, provides an incomplete profile that excludes work-related or transportation-related PA. With the benefits of MVPA now well accepted, the most pressing challenge is to refine our knowledge about the dose and mode of behaviors required to reduce cardiometabolic risk. Accelerometry avoids the problem of recall error and records the incidental and intermittent body movements that may be most subject to recall error in a survey[27]. Estimates of SB time are very difficult to derive from self-report, and prior approaches have been mainly limited to reports of TV watching[12]. Self-report rather than accelerometry may underestimate the magnitude of the relationships between SB and cardiometabolic risk factors (**sec. D1d, Prelim. Data, Figure 2**)[28].

B3. Determinants of PA and SB An important feature of this proposal is the plan to study a population sample of adults aged 18 to 80 from different race-ethnic groups. Older adults are the least active of any age group[6], yet they may nonetheless have better stability or even improvement in MVPA habits over time and may respond better to PA interventions as compared with younger persons[29,30]. Higher SB time is associated both with poverty and with higher education levels[31]. Hispanics/Latinos and foreign born adults are less sedentary[31]. Hispanics/Latinos are now ~15% of the US population, have the youngest average age of any major group, and are mostly foreign born. Longitudinal studies are needed to understand whether adoption of unfavorable PA habits with greater time of living in the US contributes to Hispanics/Latinos' high risk of obesity and diabetes.[21,32] With some Hispanics/Latinos having high PA levels, especially those working in unskilled labor occupations (e.g., construction), this may also explain the "Hispanic paradox" of low CVD incidence despite high CVD risk factor burden,[33] poor health care access and low SES.[33] The low-sedentary, low-intensity PA pattern is often found among people who work in service jobs or who have small children (both of these characteristics are common among low SES Hispanics/Latinos) [34]. **Overall, contributors to known gender, age or ethnic differences in PA may be stress,[35] work and retirement, comorbidity (CVD, asthma), social support and depression (Figure 1)[36-38]**. Knowing what drives PA behavior will inform public health initiatives tailored to specific groups, especially Latino immigrants who are a focus of our application.

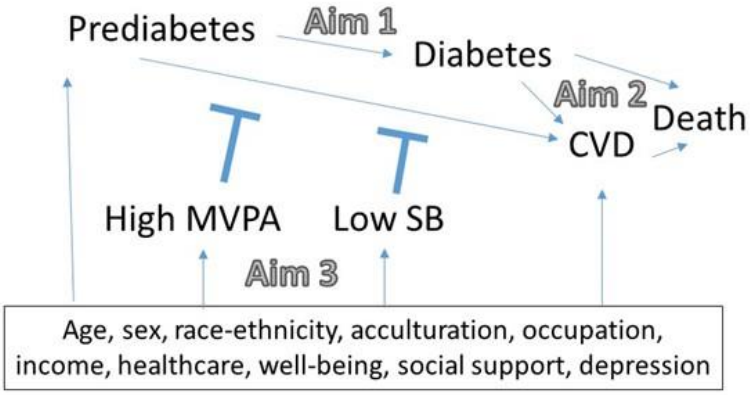
B4. Biological mechanisms MVPA improves glucose metabolism, lipids, muscle, skeletal health, balance and mood. Vigorous PA confers improved cardiorespiratory fitness and weight control[39,40]. Several studies have shown MVPA to be associated with metabolic benefits[41-43]. There are insufficient data comparing benefits of long exercise bouts versus multiple short exercise bouts[44]. SB is becoming recognized as a health risk in itself distinct from PA. Low-intensity exercise increases mRNA expression of mitochondrial and metabolic genes in skeletal muscle,[45-48] which may explain the health risks of excessive SB time.

Figure 1. Overview of Specific Aims

Aim 1 examines PA and SB patterns related to conversion from being non-diabetic to being diabetic.

Aim 2 examines the relationship between PA and SB with incident CVD and mortality**.**

Aim3 examines the demographic and psychosocial correlates associated with changes in PA and SB among Hispanics & non-



C. INNOVATION

1) Knowing the level and impact of shift in LPA or MPA and SB that may reduce diabetes and CVD risk will provide a powerful low-cost strategy to enhance the health of society. This information can rapidly be incorporated into national and worldwide guidelines to refine existing PA recommendations for individualswho are nondiabetic. We examine the benefits of exercise sessions of shorter duration than the standard 8-10 min bout. We also examine specific dose response patterns relating changes in SB time to conversion from being non-diabetic to diabetes. Current guidelines lack specific advice about these issues.
2) Most prior studies relied upon self-report, often assessed only at a single occasion. We obtain longitudinal accelerometry data over 6+ years to define groups with changing or persistent PA and SB habits.
3) Modern accelerometry devices provide extraordinarily rich data, allowing us to vary assumptions and definitions concerning bout length, counts to distinguish SB and PA intensity levels, and other aspects.
4) Self-reported data on SB levels are woefully inadequate. Here the accelerometry protocol is of unique value to discern **dose-response** relationships relating sitting or reclining with diabetes risk.
5) Nearly identical data come from two demographically distinct cohorts covering the entire adult age range.
6) HCHS-SOL is uniquely suited to study Latinos and the influence of acculturation on change in PA. Among this group, one-fifth lived in the US for 10 years or less at enrollment, capturing an important US demographic. By inclusion of the FHS we test the correlates and outcomes of behaviors between ethnic and SES groups.

7) Analytical innovation includes combining individual participant level data from two cohorts. This overcomes the challenges of comparing across studies of disparate designs. Cross-cohort comparisons can draw suitable inferences about ethnic differences in dose-response relations for PA and SB with the outcomes evaluated.

D. APPROACH

D1. Preliminary Studies

D1a. Relationship between proposed and existing studies HCHS-SOL and FHS Gen3/Omni2 are both NHLBI-sponsored longitudinal cohort studies. Prior grants and contracts have funded participant recruitment, multiple in person clinic examinations, assessment of incident and prevalent major health outcomes, expert medical records adjudication, and mortality surveillance. Physical activity assessment including accelerometry and questionnaires was included in the Visit 1 (baseline) of HCHS-SOL, but has not been included in the HCHS-SOL follow-up phase. Collection of repeat PA/SB data in non-diabetic HCHS-SOL participants is a major operational task to be completed through this application. We will recruit approximately 4760 SOL participants or 1190 at each of four centers identified as being nondiabetic at visit 1 or visit 2 (from base of about 6600 estimated with 72% recruitment rate which approximates prior SOL ancillary study recruitment rate of 80+% for a study of comparable size and complexity.**) In FHS, longitudinal collection of accelerometry and physical activity questionnaire data are already being supported by existing funding (**1R01 HL131029, Joint PI, Ramachandran, NHLBI, data collection 2016-2018). Across the two cohorts, joint analysis and harmonization of longitudinal changes in PA and SB will be accomplished by this application. The present proposal does not duplicate scientific or logistical aims of other FHS grants and contracts.

D1b. Design of HCHS-SOL N=16,415 HCHS-SOL participants were recruited in 2008-2011 with a two-stage random sample of the 18 to 74 year old Hispanic/Latino residents of the four HCHS-SOL Field Centers located in the Bronx NY (Albert Einstein College of Medicine), Chicago IL (University of Illinois, Chicago), Miami FL (University of Miami), and San Diego CA (San Diego State University)[49,50]. The Cycle 1 in-person clinic visit included medical history and symptoms, medication use, socio-demographic information, both self-reported and objective measures of PA, sleep duration and quality, sleep apnea, and pulmonary disease, cognitive and hearing tests, two 24 hour diet recalls and food propensity questionnaire (FPQ), anthropometry, seated BP, ankle brachial BP index (ABI), resting ECG, laboratory measures from urine and blood drawn fasting and 2-hours after a 75g glucose load. The coordinating center (CC) and specialized reading centers performed central training, QC, questionnaire translation and repeatability studies[51]. At each annual follow-up wave up to and beyond year 6, 80% to 85% completed their scheduled phone contact (many who miss while out of country return for a subsequent wave). A second in-person examination (Cycle 2) is being conducted between October 2014 – September 2017 (6 years) to repeat key measurements.

D1c. Design of FHS Recruitment of FHS Gen 3 (N=4,095), the grandchildren of the 1948 Original Cohort[52], was from 2002 to 2005.[53] In 2002-2005 we also recruited a minority cohort from the Framingham area, the Omni Gen 2 cohort (N=410). Annual contacts obtain health history updates and maintain contact information. Of the 4505 participants in the combined Gen3/Omni2 cohorts, 3800 participated in Cycle 2 exams after a mean interval of 6.5 years (2008-2011) and a similar number are expected to participate in Cycle 3 exams (2016-2018). The core FHS visit includes consent, fasting phlebotomy, a CVD-targeted physician medical history and physical examination[54], medication use, standardized anthropometry, resting ECG, BP, ABI, diet/FFQ and PA questionnaires, and laboratory measurements. This sample is expected to be 6.3% minority, reflecting the overall composition of the combined Gen3/Omni2 (details in **Human Subjects section**). In the overall FHS Gen3/Omni2, diabetes prevalence is 4%, and educational attainment is high (14% ≤ high school education, 65% college, 21% graduate degree)[55].

D1d. Cohort data collection During 2008-2011, core exams were conducted by both HCHS-SOL (Cycle 1) and FHS Gen3/Omni2 cohorts (Cycle 2). The content and methods of core exams were largely overlapping and included blood chemistry (fasting and 2 hour OGTT), medical history, sociodemographics, health behaviors, etc (**Table 1**). Staff training, data collection, follow-up methods and ongoing quality control (QC) are highly standardized in both cohort studies. Annual questionnaires in all years capture incident diagnoses (including diabetes), medications, and key health outcomes. Incident major health outcomes including CVD

(myocardial infarction, stroke, heart failure) and deaths are collected in both cohorts and adjudicated using similar methods. Retention over time has been high and similar across cohorts (~85%).

Table 1. Data collection timeline for HCHS-SOL and FHS core visits

Timeline	Calendar years	2008-2011	2014-2020	2008-2020
	Follow-up time in years	0 (baseline)	6	up to 12
Data collection episode		Exam 1	Exam 2	Annual (non-Exam yrs)
Schedule of key variables	7-day Actical, PA questionnaire	X	⌘SOL	
	Blood/urine laboratory tests*	X	X	
	BP, anthropometry	X	X	
	Socioeconomic, demographic	X	X	
	Medical history, symptoms, Rx	X	X	X
	Smoking, alcohol	X	X	X
	Dietary patterns	X	XFHS	
	Emotions, social support	X	X	
	Echocardiography		X	
	Spirometry, sleep	X		
	Ankle brachial BP index/ABI	X	XFHS	
	Hospitalization, CVD, death	X	X	X

X, XFHS Both or only one cohort already has the measurement

⌘ New measurement added by this R01 grant

* fasting and 2-hour post-load glucose, insulin, HOMA-IR, HgbA1c, lipid profile, renal function markers

D1e. Preliminary data on accelerometry: HCHS-SOL and FHS

Completeness and repeated measures pilot study From 2008 to 2011, 16,415 HCHS-SOL participants were instructed in use of an Actical accelerometer for 1 week.[56] Overall, 86% had 3+ days of wear time, and 80% had 4+ days of wear time.[56] From 2008 to 2011, 3,800 adults attended the FHS Gen3/Omni2 cohort Cycle 2 visit and were asked to wear an Actical accelerometer following this visit for 8 days. Overall 84% wore the accelerometer for 5+ adherent days with at least 1 weekend day.[55] We repeated the HCHS-SOL accelerometry protocol after (median) 387 days, which produced *r*=0.70 for SB and *r*=0.63 for total MVPA (n=63). Substantial numbers of individuals in the one-year repeated measures pilot study were either concordant or discordant for meeting MVPA targets per 2008 US PA Guidelines for Americans, at the repeated accelerometry visits; 27% met MVPA targets at both measurements, 46% were persistently less active than recommended, and the remainder only met MVPA targets at the first (14%) or second (13%) measurement.

Table 2. Accelerometry based PA and SB among FHS and HCHS-SOL cohorts

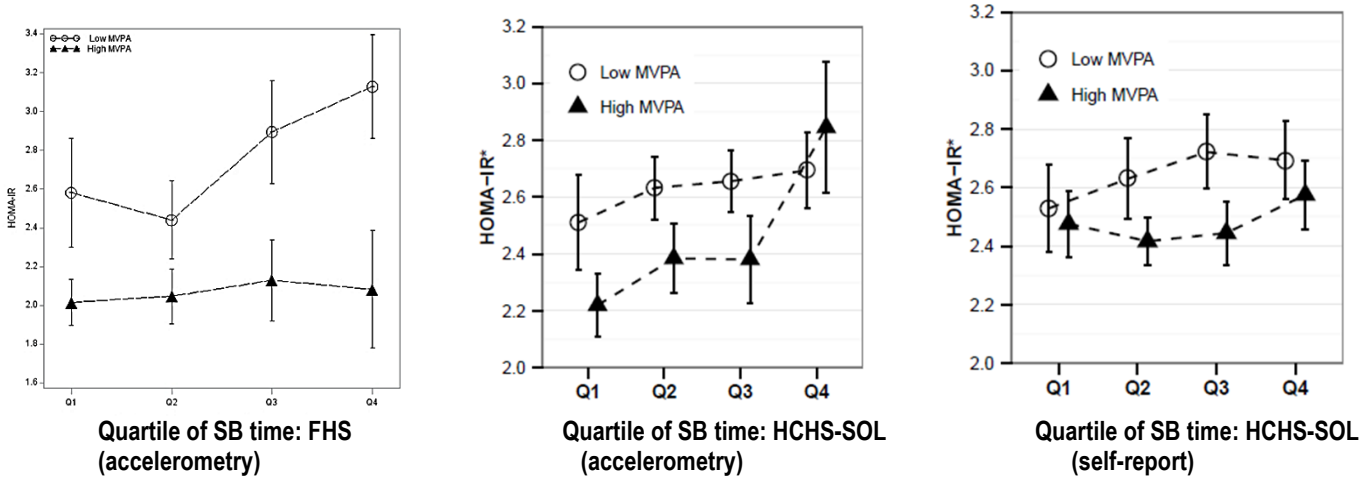
	MVPA Min/day, mean	Meets US MVPA guidelines, %	SB, Min/day, mean
FHS, Women	25	43	788
FHS, Men	29	53	776
HCHS-SOL, Women	19	33	718
HCHS-SOL, Men	31	53	695

MVPA, SB, and predictors by cohort Achievement of 2008 US Guidelines for Americans MVPA targets, including all MVPA time, was 51% in FHS and 42% in HCHS-SOL (achievement of target MVPA time when including only time in 10+ min bouts was 13% and 14%, respectively). Among men, MVPA levels were comparable between the cohorts (**Table 2**). HCHS-SOL women had lower likelihood of meeting MVPA targets than FHS women (33% vs 43%). Despite having less intensive-activity than other groups, Latino women had relatively low SB time. SB levels tended to differ more by cohort than by gender, being lower in HCHS-SOL than in FHS. Latino men under 50 years old have a very high contribution of workplace MVPA, averaging >2 hrs/day MVPA at work (estimated from HCHS-SOL self-report data). Other predictors and confounders of relevance to this application have been the focus of published studies. HCHS-SOL participants who had higher burden of chronic stressors had significantly higher SB levels[35] as well as higher risk of obesity[57] and poorer diabetic glycemic control[58]. Shorter sleep duration and insomnia are associated with diabetes, being non-US born, having high depression symptoms, and with employment, income and education[57a, 57b].

Association of MVPA and SB with cardiometabolic outcomes FHS[55] and HCHS-SOL[59] have shown that SB, $MVPA_{\geq 10min}$ and $MVPA_{<10min}$ each is associated with levels of HDL-c, triglycerides, glucose, and HOMA-IR cross-sectionally. The correlation between MVPA in 10+ min bouts versus shorter duration MVPA was modest, *r*=0.25[55]. FHS showed an association of high MVPA with decreased arterial stiffness and increased left ventricular mass.[60] In both FHS & HCHS-SOL, HOMA-IR levels are higher at higher quartiles of SB time (Q1 through Q4) (**Figure 2**), and high MVPA is associated with lower HOMA-IR levels more so for FHS participants than HCHS-SOL participants especially for SB at Q4. **Figure 2** also illustrates the enhanced

robustness of accelerometry data over self-report in elucidating associations -- the trend in outcomes across SB categories was much clearer in accelerometry (middle panel) as compared with self-reported PA data (right panel, based upon GPAQ[61-63]). Associations of SB with outcomes were seen both among those meeting recommended MVPA targets (closed triangles) and those who did not meet MVPA targets (open circles). Of those meeting MVPA targets, 31% had SB time above median levels. HCHS-SOL participants with diabetes who spent less SB time were more likely to achieve goals for CVD risk factor control, particularly glycemic and triglyceride control. This association was observed regardless of MVPA levels. Additionally, substituting 60-minute/day of SB time with 60-minutes/day of LPA was associated with better glycemic, low HDL-cholesterol and high triglyceride control.[5]

Figure 2. Association of objective and subjective MVPA and SB with glycemic traits. Both low levels of MVPA (counts>1535/min) and higher SB time (counts<100/min) predict glycemic/insulin resistance and lipid traits.[59] LEFT, FHS, accelerometer data. CENTER, HCHS-SOL accelerometer data. RIGHT, HCHS-SOL questionnaire (GPAQ) data are presented to illustrate weaker associations with self-reported versus accelerometer measures. Low MVPA levels (circles) or high MVPA levels (triangles) were defined according to 2008 US guidelines. (From Qi Q et al.) [59]



D1e. Feasibility of meeting recruitment goals Of the 4505 participants in the combined Gen3/Omni2 FHS cohorts, 3800 participated in Cycle 2 exams and a similar number are expected to participate in Cycle 3 exams. In HCHS-SOL, >80% of the 16,415 participants recruited in Cycle 1 are expected to attend Cycle 2 exams. Consecutive recruitment will be attempted until the target sample size is reached. Prior add-on HCHS-SOL ancillary studies of comparable complexity have had 80+% participation.

D2. Research Design & Methods

D2a. Overview The "Cardiometabolic Outcomes in multi-ethnic physical activity and sedentary behavior study" (COMPASS) will enroll 5500 non-diabetic participants aged 23 to 80 years old across two major NHLBI/NIDDK funded studies: HCHS-SOL and FHS Generation 3/Omni 2 . All participants will be free of diagnosed diabetes mellitus according to in person SOL visit data. All had baseline 7-day accelerometry and questionnaires to capture PA habits at anexamination in 2008-2011. Accelerometry along with exercise questionnaires (GPAQ) will be repeated in both cohorts after a 6+ year interval during 2016-2020. **Figure 3** displays the relationship between exposure and outcome variables in the longitudinal study framework, which will make use of the complete accelerometry data, cardiometabolic outcomes, and predictors of PA levels and trajectories.

D2b. Study team Please refer to **MPI Leadership Plan** for a more detailed description. Team leaders are: *Mossavar-Rahmani (MPI, Einstein):* expert in measurement of nutrition and PA in diverse US populations; led indirect calorimetry studies in the Women's Health Initiative and HCHS-SOL through R01 grants. *Kaplan (MPI, Einstein):* PI of the New York HCHS-SOL Center, chairs the HCHS-SOL Steering Committee. *Vasan Ramachandran (MPI, Boston U):* cardiologist, epidemiologist, overall PI for the FHS and Chair of Preventive Medicine. *Diaz (consultant, Columbia U):* PhD exercise physiologist at the New York HCHS-SOL Field Center. *Sotres-Alvarez (Co-I, UNC-CH):* Biostatistics and data archiving at HCHS-SOL Coordinating Center and leads the PA working group for HCHS-SOL. *Evenson (Co-I, UNC-CH):* expert in PA assessment

at the HCHS-SOL Coordinating Center**.** *Larson (Co-I, Boston U):* Senior statistician at the Framingham Heart Study.

D2c. Definitions

Terminology: We refer to the initial baseline data collection point during 2008-2011 as "Exam 1" (HCHS-SOL Cycle 1 and FHS Cycle 2). The repeated 6+ year accelerometry data collection, along with concurrent core exam data on outcomes, predictors and covariates, we refer to as "Exam 2" (2014-2020).

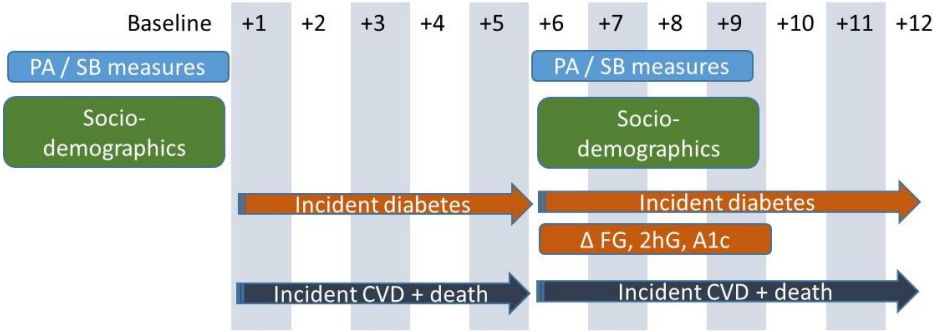


Figure 3. Approach to address aims

Aim 1: Relate PA and SB related patterns with conversion from being nondiabetic to diabetic over up to 12-year follow up among 18-80 year old Hispanic and non-Hispanic adults. *Hypothesis: high levels of MVPA and LPA and low levels of SB will delay conversion to diabetes.*

Aim 2: Assess the relationship of vigorous, moderate, and combined MVPA, and SB levels with CVD events. *Hypotheses: Both MVPA and SB will have independent contributions to prediction of CVD outcomes. Trajectories of decreasing MVPA and increasing SB levels will be associated with worsening glycemic outcomes over time.*

Aim 3: Investigate demographic and psychosocial correlates associated with PA changes in Hispanics and non-Hispanics. Hypotheses: *favorable levels and trajectories in MVPA and SB will be observed among younger Latino men, whereas younger women (both Latina and non-Hispanic) will have decreasing MVPA and increasing SB levels over time. Recent Latino immigrants to the US will have unfavorable trajectories in MVPA and SB with increasing time in the US and rising acculturation. Specific barriers and facilitators may partially explain differences across these demographic groups (e.g., occupation, depression, comorbidity).*

i) Accelerometry based measures. SB defined as accelerometry-based estimates of min/day sedentary time (counts/min < 100), standardized to 16 hours of wear time. Accelerometry-based estimates of PA include min/week of average counts per minute of light, moderate and vigorous intensity PA[64,65].

ii) Incident diabetes (Aim 1): Among individuals defined as nondiabetic at baseline by levels of FPG, 2hrPG, and hemoglobin A1c, the follow-up period will be define incident diabetes, as either: 1) reported use of diabetes medication with physician diabetes diagnosis during up to 12 annual follow-up interviews; or 2) measured FPG≥126 mg/dL, 2hrPG≥200 mg/dL, or HgbA1c>6.5% at follow-up examinations. While not identical to clinical criteria for diabetes, we have evidence of the validity of diabetes data in our study. Among those who reported that they did not have diabetes, study measurements of FPG were in the non-diabetic range for 97.6% of these individuals. Moreover, of those that were determined to be diabetic by FPG, 2hrPG or A1c, only 2.3% had a self-reported diagnosis that could not be confirmed with laboratory tests (glucose and A1c levels) or use of diabetes medication.

iii) CVD events (Aim 2): CVD events to be examined include: myocardial infarction, angina, heart failure, stroke, peripheral artery disease, hospitalization for CVD event or procedure.

iv) Barriers/facilitators of PA and SB (Aim 3): (Measures that are likely to substantially change between Exam 1 and Exam 2 are indicated in **bold**.) **Age**, sex, race/ethnicity, birthplace, **time in US**, age at migration, **language and social acculturation (modified SASH) score**[66], **income**, education, **occupation/work hours**, smoking history, alcohol use, AHEI-2010 diet score[67], **medical diagnoses and treatments** (arthritis, asthma, COPD, pulmonary symptoms, sleep apnea), sleep quality and duration, spirometry, ankle brachial BP index (ABI), **self-rated health/SF-12**, **depression/CES-D**[68], **stress scale**[35]**, social support/ISEL**[51] (in HCHS-SOL only)**, number of social contacts**, **children in home**, dog ownership, month of data collection, local temperature/weather.

v) Other key covariates and confounders: BP/hypertension, Tc, LDL-c, lipid and BP medications, CRP, kidney function (serum creatinine, Cys-C, UACR), BMI, WC, echocardiographic measures such as LV mass.

vi) Accelerometry data: Collection and processing We will begin immediately to re-analyze existing accelerometry data to harmonize definitions, processing of data including determining non-wear, across HCHS-SOL and FHS. For collection of the repeat accelerometry during years 1 to 3 of the grant, we will use

the same approaches that achieved excellent compliance previously, with most of the same staff members still involved at the field centers.

vii) Coding of accelerometry data All raw accelerometry data from Exam 1 and Exam 2 will be analyzed according to a standardized protocol. The data for PA and SB used in main analysis will be computed from 1 min recording epochs which was the epoch length used in Exam 1 recordings. Non-wear time will be defined according to the validated Choi algorithm[69] as consecutive zero counts for at least a 90 min, allowing for short time intervals with nonzero counts lasting up to 2 min if no counts were detected during both 30 min before and 30 min after the nonzero intervals. An adherent day will be defined as at least 10 hrs of wear time, with 4+ days required for inclusion in main analyses. To define PA intensity (moderate, vigorous), count thresholds will follow published standards[64,65] (vigorous ≥3962 counts/min, moderate 1535-3961 counts/min, light 100-1534 counts/min). Minimum bout length for MVPA will be 10 min allowing 1-2 min below the count threshold as per guidelines[70]. SB has no accepted standard for bout length and will be examined as total minutes. As described below (**section D5v)**, in secondary analyses we will vary parameters including cutpoints to define PA intensity, inclusion of all MVPA minutes vs MVPA from bouts of varying length, and accounting for breaks in SB time. This will reveal the outcomes (Aim 1 and Aim 2) and predictors (Aim 3) associated with specific patterns of behavior.

Actical devices: Existing devices are supported by the manufacturer (Actical B-1 version model 198-0200-00/03)[71]. Based on past experience, these devices can be lost or can malfunction, and a constant supply is to be maintained in the clinic so that at any time about 40 or more devices may be 'out' with participants awaiting their wearing of their device and mailing back. Every year the devices are subjected to recalibration and a shake test to ensure high quality data acquisition through an arrangement with Dr. Dale Esliger, PhD, University of Loughsborough, UK for FHS. Philips/Respironics support for calibration ends in early 2018 after which we may consider using a shake test locally if needed to calibrate acticals.

Eligibility: FHS will offer accelerometry to all participants attending core exams. In HCHS-SOL, participants who have completed visit 2 and are nondiabetic will be invited by mail/phone in the Bronx, Chicago and Miami and by in-clinic visit in San Diego to enroll and will be provided with a monetary incentive. Exclusions will be made for non-ambulatory participants.

Data collection protocol: Participants will complete informed consent and receive brief refresher training on how to complete the 7 day accelerometry protocol. Participants wear the accelerometer above the iliac crest on the right side, the location most sensitive to vertical movements consistent with ambulation. They will be told to undertake usual activities, removing the device only for swimming, showering and sleeping. The accelerometry devices will be returned by mail using a prepaid mailer. Halfway through the 7 day accelerometry period, study staff will call participants to encourage adherence and answer any questions that participants may have. For HCHS-SOL sites using mail/ telephone to recruit participants, instructions for the actical will be conducted over the phone (see Protection of Human Subjects) and acticals will be mailed to participants and mailed back to the clinic. Quality control and monitoring: In ongoing fashion, we will examine noncompletion of accelerometry, daily wear time, and missing days, aiming for 7 days with 10+ hrs of recording. Sustained non-zero counts of >10 min will be examined for possible device malfunction. In case of device errors, the chance to obtain a repeated study will be offered. The cohorts will be monitored and compared on these metrics and we will also identify characteristics that are associated with missing or incomplete data (age, sex, employment status, etc).

Overall Design: Approximately 3,900 nondiabetic participants who are eligible for the study from HCHS/SOL & FHS Exam 1 and a total of 1,615 nondiabetic participants from Exam 2 will be enrolled. Assuming not more than 4% attrition rate due to loss to follow-up, competing risks, etc, we expect to obtain complete follow-up for at least 3,700 nondiabetics enrolled at Exam 1, among them 3,100 are from SOL and 600 are from FHS; at Exam 2, about 1500 nondiabetics, among them ~1400 are from SOL and about 100 are from FHS. Combining enrollment of nondiabetics at visits 1 & 2, we will have a total of over 5,200 eligible participants with complete follow-up (~4,500 from SOL and ~700 from FHS). Among them, we expect about ~800 will develop diabetes and ~500 will develop cardiovascular disease during the study.

viii) Preliminary analyses All data will be examined for needed transformations, outlier or implausible values. We will examine distributions of PA and SB by day of week, month of year, average local temperature, etc. to see if these temporal variables differ by age, sex, and cohort/site. We will confirm our expectation that data distributions and missingness are not systematically different across the field centers. If any field center is an outlier in completeness of accelerometry, we will explore the impact by excluding this site in sensitivity analyses. We derive ways to classify variables in comparable fashion across FHS and HCHS-SOL.

Missing data: Because we exclude participants with <4 days of accelerometry data, we use inverse probability weighting (IPW) to correct for the bias of the estimates obtained by our complete-case analyses. IPW can be implemented for complex survey designs such as was used in HCHS-SOL[49] and has been applied to our Actical data.[56,72] Specifically, the complete cases (i.e., 4 or more adherent days) are weighted by the inverse of their probability of being a complete case. We prorate accelerometry readings of <7 days duration to the entire week, assuming that non-wear days and hours were the same as the wear period. For other covariates, we will examine for patterns in the missingness mechanism, and characteristics of participants that are lost to follow up will be compared to those that remain in the study. If the missingness mechanism is not a function of underlying unobserved data, then either no adjustment is necessary or multiple imputations can be used and sensitivity analyses will be performed to evaluate robustness of results to different imputation models.

Statistical software: All analyses will be conducted using SAS 9.3 (SAS Institute Inc, Cary, NC 2014) or SUDAAN (Research Triangle Institute, NC 2005). All power calculations were conducted using PASS11 (Hintze J. PASS NCSS LLC. Kaysville, Utah. 2011), and for specific models which are not available in PASS11 we either used simulations or R (version 2.15.2, The R Foundation for Statistical Computing, 2012).

D.3. Analyses to Address Aim 1: Association of MVPA and SB levels with risk of diabetes

i) Rationale Increasing physical activity, mainly quantified in prior studies as MVPA, is known to favorably influence the risk of developing diabetes. SB levels have some evidence of association with diabetes and glycemic measures, but this needs confirmation, especially regarding the shape of the dose-response curve, the importance of SB bout length and breaks in SB, and whether this is independent of MVPA.

ii) Hypotheses **a)** High MVPA and low SB levels are associated with lower risk of diabetes. **b)** SB levels are directly associated with adverse diabetes risk irrespective of the level of MVPA. **c)** The dose-response curve relating SB levels with outcomes may not be linear across the range of SB time values. **d)** Controlling for total time spent in MVPA or SB, shorter (<10 min) bouts of MVPA are at least as beneficial as longer MVPA bouts.

iii) Primary Analyses The primary outcome for Aim 1 is incident diabetes. The primary exposure variables are (1) total MVPA in min/wk, (2) MVPA accumulated in bouts of length greater or less than 10 min ($MVPA_{<10}$ and $MVPA_{\geq 10}$), (3) SB levels in min/wk. We expect that definition (2) for MVPA will be the most the informative; for instance, we previously showed that $MVPA_{<10}$ was independently associated with metabolic risk factors, even after controlling for MVPA in 10+ min bouts[55]. Then, joint adjustment for MVPA and SB will be done to establish whether each aspect has an independent association with outcomes, using either approaches (1) or (2) to capture MVPA. We also test interactions between MVPA and SB exposures. Both continuous levels of MVPA/SB and categorical levels categorized by quantiles or tertiles will be considered. We will also compare two extreme groups which are low MVPA & high SB vs high MVPA and low SB.

We expect that Aim 1 results will be similar between HCHS-SOL and FHS so we will emphasize pooled analyses, although we will confirm this within cohorts. Base models include age, sex, cohort, accelerometer wear time and field site as adjustment variables. Potential confounders will be selected according to our experience with these types of analyses[55,59] and evaluated by the change-in-estimate approach: education, income, self-reported health, employment status, smoking status, sleep, alcohol consumption, diet quality, health insurance status, healthcare utilization. Use of CVD medications (antihypertensives, lipid-lowering drugs) will also be considered as confounders. We also will conduct stratified analysis by age decade, sex and site.

A Cox proportional hazards model stratified by cohort (i.e., HCHS-SOL and FHS) will be used to model time to the development of diabetes with MVPA and SB as the primary exposure variables while adjusting for other potential confounding variables described above. We stratify baseline hazards on cohort because the incidence rate of diabetes differs between these two cohorts. Within the stratum, the proportional hazards assumption will be examined using graphical approaches including the Log-log plots and observed versus expected plots[73] and the goodness of fit test based on Schoenfeld residuals[74,75]. If violation of proportionality is

indicated for a particular variable, two approaches will be applied to address non-proportionality: one approach is to stratify on this variable. If this variable is continuous, we will categorize it first; however, if this variable is of primary interest, such as MVPA and SB, we will apply the second approach: a time-dependent covariate such as follow up time (t) or log (t) or a Heaviside function of time will be included in the Cox model as an effect modifier for that variable. Dose response analysis: We will examine categorical (quartile or tertile) variables and spline analyses to examine the threshold effects among the range of MVPA and SB to allow a non-linear association between MVPA/SB and outcomes evaluated. We will also examine alternate bout lengths and count thresholds to define MVPA and SB time. To account for uncertainty about count thresholds, we also will examine average counts/min, thereby avoiding the need to decide upon thresholds to define the PA intensity level, as well as age-varying thresholds. Holding total SB time constant, we will examine whether more frequent breaks in SB time is associated with better outcomes. Most intervention studies of SB levels use sedentary bouts ~30 min[76,77] and this will be a sensitivity analysis approach in addition to total SB time. To understand the relative benefits of vigorous intensity versus moderate intensity PA, among individuals reporting any MVPA, we will examine risk of outcomes by the proportion of time spent in vigorous versus moderate PA (controlling for total volume). To determine whether there is an ideal cutoff for MVPA and SB variables, we will follow the approach used in Gebel, et al.[78] Specifically, we will plot the association of MVPA and SB levels with development of diabetes using a segmented (i.e., piecewise) regression model in order to identify if there is cut-off at which the magnitude of association changes substantially.

iv) Statistical Power For power calculations we assumed a two-sided type I error rate < 5%, and R^2 = 0.2 between the primary exposure variables and the other adjusting variables. We present minimum detectable effect sizes (MDE) for 80% power. With a total of 5276 nondiabetics and about 15% event rate of diabetes over the 6+ year follow-up, we will be able to detect a hazard ratio (HR) of 1.11 associated with per SD increase of the primary exposure variable, or HR of 1.35 between the highest and lowest quartiles of the primary exposure variable. Therefore, our study has sufficient power to detect a small or moderate effect size associated with the exposure variable.

v) Pitfalls/alternate approaches, Aim 1 Interpretation of associations between SB level and outcome will consider the potential high correlation between light PA and SB time. Penalty models-such as ridge estimator and the LASSO estimate have been used commonly in regular regression models to deal with collinearity in regression models by shrinking estimators towards 0 to achieve better estimation and prediction (Xue, 2007). Further, for a subset of patient who were enrolled in EXAM 1 and did not develop diabetes before EXAM2, we will use an updated MVPA/SB for them. Longitudinal analyses are subject to retention biases, although cohort follow-up and completeness is excellent, while accelerometry adherence ≥ 80% exceeds other studies like NHANES. While HCHS-SOL and FHS used household/family-based sampling designs, analyses will address family correlation and complex survey sampling design in HCHS-SOL by incorporating sampling weights appropriately[49,79]. Secondary analyses will consider change in continuous glycemic measures as the outcome (e.g., fasting glucose, 2hr glucose, fasting insulin, HOMA-IR, hemoglobin A1c). These may provide additional insights beyond quantifying the risk of new onset diabetes.

D.4. Analyses to Address Aim 2: Association of MVPA and SB levels with CVD risk

i) Hypotheses **a)** High MVPA and low SB levels are associated with lower risk of CVD. **b)** Higher SB levels are associated with CVD outcomes irrespective of the level of MVPA. **c)** The dose-response curve relating SB levels with outcomes may not be linear across the range of SB time values. **d)** Controlling for total time spent in MVPA or SB, shorter (<10 min) bouts of MVPA are at least as beneficial as longer MVPA bouts.

ii) Primary Analyses **We expect that Aim 2 results will be similar between HCHS-SOL and FHS so we will emphasize pooled analyses, although we will confirm this in separate analyses within cohorts**. The primary outcome is CVD, inclusive of myocardial infarction, stroke, heart failure, cardiac revascularizations, and other death due to CVD. Both HCHS-SOL and FHS have adjudicated, confirmed events using similar methods. The same primary exposure variables and potential confounders as those described in Aim 1 will be used here. Similarly, a Cox proportional hazards model will be used to model time to the development of CVD with MVPA and SB as the primary exposure variables while adjusting for other confounding variables described above. Dose response analysis will also be conducted. All- cause mortality will be a secondary outcome.

iii) Statistical Power For power calculations we assumed a two-sided type I error rate < 5%, and R^2 = 0.2 between the primary exposure variable and the other adjusting variables. We present minimum detectable

effect sizes (MDE) for 80% power. With a total of 5276 individuals with nondiabetics and about 10% event rate of CVD, we will be able to detect a hazard ratio (HR) of 1.15 associated with per SD increase of the primary exposure variable, or HR of 1.44 between the highest and lowest quartiles of the primary exposure variable.

iv) Pitfalls/alternate approaches, Aim 2 Diagnosis of diabetes may change health behavior as well as the underlying risk of CVD and therefore will be addressed by including the development of diabetes as a time-dependent covariate in the model. Collinearity and household/family-based sampling design will also be addressed as described above.

D.5. Analyses to address Aim 3: Factors influencing change in PA and SB levels over time

i) Rationale Identification of groups at risk of decreasing MVPA and increasing SB over 6+ yrs will identify opportunities and needs for health promotion through lifestyle. Unfavorable trends in PA behaviors within age, sex and ethnicity groups may be explained by barriers (low SES, sedentary occupation, depression, stress, comorbidity). Other characteristics may promote favorable MVPA and SB patterns (working as unskilled laborer, having high social support and SES).

ii) Hypotheses **a)** Young non-Hispanic adults and women are most at risk of unfavorable trajectories in MVPA and SB. **b)** Young Latino men will have the most sustained, favorable MVPA as compared with other groups who will have worsening habits over time. **c)** Among Hispanic/Latino immigrants, having longer time living in the US and increasing acculturation (SASH score)[66] will produce unfavorable changes in MVPA and SB over time (increasing time in the US is a diabetes risk factor in HCHS-SOL)[21]. **d)** Barriers and facilitating factors partially explain MVPA and SB differences across these demographic groups (e.g., high workplace MVPA among young Latino men, high depressive symptoms among women)[68]. **e)** Changes in barriers and facilitators (e.g., employment, comorbidity) will mirror changes in MVPA and SB levels. **f)** Some barriers to MVPA (such as asthma, CVD) might still permit light intensity PA such as walking so as to reduce overall SB time.

iii) Primary Analyses Because sufficient data are available for each cohort and we expect differences between cohorts, analyses will first be conducted separately by cohort and then pooled together while allowing differential association between exposure and outcome association between cohorts. Total MVPA, $MVPA_{\geq 10min}$ (accumulated time in bouts of ≥10min) and SB will first be treated as continuous. Total MVPA will also be dichotomized into putative "healthy" or "non-healthy" categories such as meet or fail to meet MVPA guidelines (150 min/wk moderate PA, 75 min/wk vigorous PA, or a combination thereof, with 1 min vigorous PA = 2 min moderate PA). In the absence of guideline targets for SB time, the lowest tertile will define healthful SB levels. Alternatively we will analyze MVPA and SB time as quartile level variables.

Within each cohort, first, we examine cross-sectional associations between potential barriers and facilitators of PA habits (independent variables) with MVPA and SB (outcome variables). Each participant will contribute two observations. For continuous outcomes, the linear mixed effects model will be used to account for repeated observations per participant. Proper transformation such as log transformation will be used to improve normality if necessary. For binary outcomes (MVPA/SB healthy or non-healthy levels), a logistic regression implemented using the generalized estimating equation (GEE) will be used. For ordinal outcomes (quartile level of SB), an ordinal scale model such as the proportional odds model implemented using GEE will be used. Proportionality assumptions of the proportional odds model will be examined[80]. If not satisfied, adjacent categories logit model implemented with GEE will be used instead[81].

Second, we examine characteristics that influence 6+ year trajectories in MVPA and SB. For continuous MVPA/SB, we use linear regression while adjusting for the MVPA/SB level at visit 1. If a log transformation is used, change in log-scale reflects the log of the ratio in the original scale therefore representing relative change. We will also categorize the participants into four groups: consistently having healthful levels (e.g., at Exam 1 and Exam 2), changing from healthy to non-healthy, changing from non-healthy to healthy, and consistently having non-healthy levels. These outcomes will be analyzed using an appropriate ordinal scale model as described above. We will also examine the likelihood of adopting healthy levels among those who begin with non-healthy levels, and the risk of becoming non-healthy among those who begin at healthy levels. We use both exposure measures from Exam 1 as well as change in exposures at Exam 2 to predict change in MVPA/SB. This describes how within-person change in exposure affects the individual's change in behavior. Independent variables that are likely to change include employment (job class, retirement), CES-D depression score, comorbidity and SASH acculturation score.

After completing cohort-specific Aim 3 analyses, we then will pool HCHS-SOL and FHS data. This provides an external non-Hispanic comparison group to contrast *vs* US-born and foreign-born Latinos. For predictors of PA and SB that are shared between the two cohorts, pooling the cohorts will refine estimates of association with narrow confidence intervals. For key variables showed differential effect across cohorts, effect modification will be examined by cohort using interaction terms. Age and sex interactions will also be examined. *Confounder selection:* The analyses will proceed stepwise with a base model to include age, sex, race/ethnicity, HCHS-SOL site and accelerometer wear time as independent variables. Next, among the HCHS-SOL group we add independent variables related to birthplace and acculturation such as language preference, time in the US and SASH acculturation scores (~80% of HCHS-SOL born outside of US). Then we will identify other independent variables that are associated with PA or SB when added individually to the base model (e.g., comorbidity, occupation, income, psychosocial variables).This may reveal specific characteristics of demographic groups that account for the demographic group differences in behaviors observed the base model (e.g., unskilled labor occupations in Hispanic/Latino men). Final multivariable analyses will identify the strongest associated variables for the MVPA and SB outcomes while controlling for confounders.

iv) Exploratory Analysis After completing Aims 1 & 2, we may identify patterns of MVPA and SB that are of particular importance for diabetes and incident CVD outcomes (e.g., short discontinuous bouts of MVPA; vigorous PA episodes; etc). We will then use Aim 3 to examine the longitudinal patterns and predictors of these behavior patterns of interest. To identify subgroups in whom employment or transportation contribute to high MVPA levels, we will compare demographic groups and MVPA/SB level groups by self-reported PA information (GPAQ, Physical Activity Index), which capture the sources and context of PA.

v) Sensitivity Analysis **1)** MVPA guidelines are based mainly upon self-reported data (leisure-time PA only)[82-84] which are generally overestimated. Accelerometry is more accurate and captures non-leisure time, usually showing a lower percentage of people meeting guideline targets[85-88]. Thus we will use moderate PA>100 min and vigorous PA>50 min as alternative criteria for "healthy" MVPA levels**.** Similarly, we will alternatively include all MVPA minutes or only 10+ min bouts of MVPA in definitions. **2)** Recognizing that cutpoints for intensity of PA are possibly inaccurate and lead to potential loss of information, we will also examine average counts per minute. Given the wide study age range, in sensitivity analyses older adult-specific counts/min thresholds will also be examined for those >65 yrs old[36]. **3)** At Exam 1, HCHS-SOL recorded accelerometry data in 1 minute epochs while FHS recorded data in 30 second epochs. Exam 2 will be recorded in 15 second epochs but all Exam 1 and Exam 2 will be aggregated into 1 minute epochs for consistency over time; secondary analyses can be performed that de-aggregate 1 minute epochs into briefer episodes (15s, 30s) to examine whether this changes the results. **4)** The accelerometry measurement may not consistently cover weekdays, weekends, work days and non-work days for all participants. Additional analyses will examine patterns and confounding by day of week.[89]

vi) Statistical Power For participants enrolled in Exam 1 (N=3,742), we will examine factors associated with change in MVPA/SB. For all participants (N=5,276), we will examine factors associated with level of MVPA/SB. To estimate statistical power, we consider binary exposure variables with 10% to 50% being exposed, as well as continuous exposure variables. For instance, HCHS-SOL and FHS have 40-46% men; high school education or lower is 14% in FHS and 65% in HCHS-SOL; prevalence of CES-D>10 (depression) in HCHS-SOL is 27%.[68] Among HCHS-SOL, 20% were US born. We assumed a correlation of 0.5 to 0.7 between repeated MVPA and SB measures at the two exams. We estimated minimum detectable effect sizes (MDE) for 80% power and a two-sided type I error rate of not more than 5%. R^2 of 0.2 was assumed between the primary exposure variable and the other adjusting variables in the model, taking into account repeated observations per subject[90]. Because each hypothesized predictor is specified *a priori* and represents an independent potential influence on behavior, no multiple tests are adjusted in terms of type I error rate although the results will be interpreted cautiously. *Cross-sectional analysis:* MDE was calculated as a minimum odds ratio (OR) associated with being in the healthful category of MVPA/SB levels. For binary exposures, MDE ranges from OR=1.4 (50% exposed) to 1.6 (10% exposed). For per SD increase in a continuous exposure variable, our study has 80% power to detect an OR of 1.2-1.3. For effect modification, we used the example of a gender effect that varies across cohorts. Our study has 80% power to detect a ratio of 1.7 in ORs for healthful behavior associated with gender between HCHS-SOL (n=4,535) and FHS (N=741). As compared with the binary outcome approach, we have better power when defining continuous outcomes, as minimum difference in mean of MVPA/SB (original scale or on log scale). *Change from Exams 1 to 2:* For categorical MVPA and SB outcomes (i.e., healthy levels), assuming a proportional odds ratio model, we used simulations

to examine the statistical power associated with a binary exposure. Our results showed MDE of OR = 1.2 to 1.4 for having more healthy MVPA/SB levels if the proportion of exposure varies from 10 to 50%. Among people who had healthful levels at Exam 1, our study can detect an OR of 1.4-1.6 for the risk of changing to non-healthy levels at Exam 2, and similarly for those who change in the opposite direction. For continuous MVPA/SB outcomes, our study has 80% power to detect 0.1 to 0.2 SD in difference in change (or relative change on a log scale) between exposed and un-exposed groups, and 0.05 SD in the combined sample. For comparison between participants who changed from inactive jobs or not employed at Exam 1 to an active job at Exam 2 (assuming 10-20% among the total), vs. those who remained at inactive jobs or nonworking over time (assuming 30-50% among total), we will have 80% power to detect a difference of 0.4 SD in change of MVPA/SB; and the detectable OR for having more healthy MVPA/SB levels over time = 1.5-1.6. For interactions by cohort, power is >80% to detect a difference of 0.25 SD in the gender effect on change in continuous level of MVPA/SB between HCHS-SOL and FHS, a moderate effect size of interaction.

vii) Pitfalls/alternate approaches While HCHS-SOL foreign born vary on time in the US (conditional on age), to avoid faulty conclusions we will consider models adding decade of migration and national background. Complex patterns of confounding may make conclusions difficult, although in general our large sample permits models with many predictor variables. Place of residence is a potential confounder and we will examine for confounding by region, season of data collection, average local temperature and precipitation. Place will also be examined as an effect modifier. We examine the effect of incomplete accelerometry by repeating analyses with both more stringent and more lenient exclusion criteria (e.g., require 3+ days or 5+ days rather than 4+ days of accelerometry). The use of cutpoints to define MVPA above or below recommended ("healthy") levels is widely accepted although this may cause a loss of information. We also analyze data as continuous, with the caveat that small statistically significant changes may not be clinically meaningful. We will keep abreast of methodological advances in the definition of non-wear time to improve accuracy of SB time assessment; we opted for the Choi wear time algorithm although it was originally developed for the ActiGraph[69]. Analyses will account for sampling weights and correlation between family and household members. Finally, to avoid reverse causation we plan to repeat analyses after excluding individuals with activity-limiting comorbidity (CVD, stroke, diabetes, cancer, PAD, ABI<0.9, arthritis, self-reported mobility limitation, etc).

D6. Limitations, Challenges and Solutions

1) Differences between cohorts. While the large and diverse combined sample will be powerful, nonetheless, differences between HCHS-SOL and FHS include not only ethnicity but also average SES, geography, etc. On the other hand, replication of findings across the two cohorts will be a strength.

2) Between-individual differences in exercise response. We acknowledge that optimal doses and benefits of exercise may differ according to genetics, exercise capacity or other factors. Stratification by age, gender, and ethnicity may provide some clues to the individual level factors that influence response to MVPA and SB.

3) Representativeness. HCHS-SOL represents well the majority (~90%) of US Latinos that reside in urban areas. After 3 generations, the FHSGen3 cohort has diversified geographically and socio-economically, while Omni2 provides some diversity (8% of FHS are non-Caucasian). We acknowledge that PA measurement over one week period may not be representative of the entire year; however this is the standard of measurement and in allows us to understand longitudinal changes particularly in weight stable individuals.

4) Coordination. We will coordinate protocols, QC of Actical devices using a shake test, and data measures to ensure data comparability. We will analyze outcome data within each cohort before combining, so that there is no need to assume *a priori* that values are harmonized across the study platforms. Fortunately, prior accelerometry protocols and equipment as well as other procedures were all very similar. HCHS-SOL sites have been collaborating together for nearly a decade. Dr. Vasan Ramachandran's FHS team has collaborated extensively with other NHLBI cohort studies. Both cohorts are part of the CHARGE and Cross-Cohort Collaboration groups.

5) Limitations of accelerometry. Limitations depend on where the accelerometer is worn. Our centrally placed accelerometers (waist) are not worn during water-related activities (swimming), and sitting activities such as bicycling are not captured well. Measurements of SB time cannot distinguish position (standing still, lying down, sitting). Added context will comes from questionnaires (e.g., transit PA). We are aware of the sensitivity range of Actical devices, which will be addressed by altering bout lengths for SB[91].

6) Mismeasurement. Validation studies (doubly labeled water and indirect calorimetry) have been collected in HCHS-SOL, which allows for a detailed understanding of mismeasurement with our PA assessments with

respect to total energy expenditure[92]. Our experience comparing across the HCHS-SOL sites and subgroups (e.g., Mexican, Cuban) will help us to interpret any differences that emerge across the sites.
7) Observational design. While observational in design, the main strength of this study lies in extensive data on behavioral factors, diabetes and CVD events among the high risk group of nondiabetics over up to 12 years. Findings from this study can inform an intervention study in the future.

D7. Timeline
Year 1: Train staff, HCHS-SOL and FHS data collection;
Year 2: HCHS-SOL and FHS data collection, analyses;
Year 3: HCHS-SOL and FHS data collection, continue analyses;
Years 4: Complete recruitment; data and analyses; manuscript preparation
Year 5: Manuscript preparation & publications.

REFERENCES

1. Prediabetes. http://www.cdc.gov/diabetes/pubs/statsreport14/prediabetes-infographic.pdf.
2. Neamah HH, Kuhlmann AK, Tabak RG. Effectiveness of Program Modification Strategies of the Diabetes Prevention Program: A Systematic Review. *The Diabetes educator.* 2016.
3. Chen Y, Wang J, An Y, et al. [Effect of lifestyle interventions on reduction of cardiovascular disease events and its mortality in pre-diabetic patients:long-term follow-up of Da Qing Diabetes Prevention Study]. *Zhonghua nei ke za zhi.* 2015;54(1):13-17.
4. Rautio N, Jokelainen J, Polonen A, et al. Changes in lifestyle modestly reduce the estimated cardiovascular disease risk in one-year follow-up of the Finnish diabetes prevention program (FIN-D2D). *European journal of cardiovascular nursing : journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology.* 2015;14(2):145-152.
5. Wang X, Jung M, Mossavar-Rahmani Y, et al. Macronutrient intake, diagnosis status and glycemic control among U.S. Hispanics/Latinos with diabetes. *The Journal of clinical endocrinology and metabolism.* 2016:jc20153237.
6. Matthews CE, Chen KY, Freedson PS, et al. Amount of time spent in sedentary behaviors in the United States, 2003-2004. *American journal of epidemiology.* 2008;167(7):875-881.
7. Owen N. Sedentary behavior: understanding and influencing adults' prolonged sitting time. *Preventive medicine.* 2012;55(6):535-539.
8. Elmadfa I, Meyer AL. Developing suitable methods of nutritional status assessment: a continuous challenge. *Adv Nutr.* 2014;5(5):590s-598s.
9. Pate RR, Pratt M, Blair SN, et al. Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *Jama.* 1995;273(5):402-407.
10. Macfarlane DJ, Taylor LH, Cuddihy TF. Very short intermittent vs continuous bouts of activity in sedentary adults. *Preventive medicine.* 2006;43(4):332-336.
11. 2008 physical activity guidelines for Americans. US Department of Health and Human Services; http://www.health.gov/PAGuidelines. Accessed June 2, 2015.
12. Biswas A, Oh PI, Faulkner GE, et al. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. *Annals of internal medicine.* 2015;162(2):123-132.
13. Manson JE, Hu FB, Rich-Edwards JW, et al. A prospective study of walking as compared with vigorous exercise in the prevention of coronary heart disease in women. *The New England journal of medicine.* 1999;341(9):650-658.
14. Kim J, Tanabe K, Yokoyama N, Zempo H, Kuno S. Objectively measured light-intensity lifestyle activity and sedentary time are independently associated with metabolic syndrome: a cross-sectional study of Japanese adults. *The international journal of behavioral nutrition and physical activity.* 2013;10:30.
15. DiPietro L, Gribok A, Stevens MS, Hamm LF, Rumpler W. Three 15-min bouts of moderate postmeal walking significantly improves 24-h glycemic control in older people at risk for impaired glucose tolerance. *Diabetes care.* 2013;36(10):3262-3268.
16. Beddhu S, Wei G, Marcus RL, Chonchol M, Greene T. Light-Intensity Physical Activities and Mortality in the United States General Population and CKD Subpopulation. *Clinical journal of the American Society of Nephrology : CJASN.* 2015.
17. Centers for Disease Control and Prevention. Physical Activity for Everyone. http://www.cdc.gov/physicalactivity/basics/children/index.htm. Accessed July 6th, 2014.
18. *World Health Organization. Global recommendations on physical activity for health.* Geneva, Switzerland: WHO Press; 2010.
19. Mossavar-Rahmani Y, Jung M, Patel SR, et al. Eating behavior by sleep duration in the Hispanic Community Health Study/Study of Latinos. *Appetite.* 2015;95:275-284.
20. Patel SR, Sotres-Alvarez D, Castaneda SF, et al. Social and Health Correlates of Sleep Duration in a US Hispanic Population: Results from the Hispanic Community Health Study/Study of Latinos. *Sleep.* 2015;38(10):1515-1522.
21. Schneiderman N, Llabre M, Cowie CC, et al. Prevalence of diabetes among Hispanics/Latinos from diverse backgrounds: the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Diabetes care.* 2014;37(8):2233-2239.

22. Ainsworth BE, Haskell WL, Leon AS, et al. Compendium of physical activities: classification of energy costs of human physical activities. *Medicine and science in sports and exercise.* 1993;25(1):71-80.
23. Fung TT, Hu FB, Yu J, et al. Leisure-time physical activity, television watching, and plasma biomarkers of obesity and cardiovascular disease risk. *American journal of epidemiology.* 2000;152(12):1171-1178.
24. Hu FB, Li TY, Colditz GA, Willett WC, Manson JE. Television watching and other sedentary behaviors in relation to risk of obesity and type 2 diabetes mellitus in women. *Jama.* 2003;289(14):1785-1791.
25. Evenson KR, McGinn AP. Test-retest reliability of a questionnaire to assess physical environmental factors pertaining to physical activity. *The international journal of behavioral nutrition and physical activity.* 2005;2:7.
26. Evenson KR, McGinn AP. Test-retest reliability of adult surveillance measures for physical activity and inactivity. *American journal of preventive medicine.* 2005;28(5):470-478.
27. Sloane R, Snyder DC, Demark-Wahnefried W, Lobach D, Kraus WE. Comparing the 7-day physical activity recall with a triaxial accelerometer for measuring time in exercise. *Medicine and science in sports and exercise.* 2009;41(6):1334-1340.
28. Celis-Morales CA, Perez-Bravo F, Ibanez L, Salas C, Bailey ME, Gill JM. Objective vs. self-reported physical activity and sedentary time: effects of measurement method on relationships with risk biomarkers. *PloS one.* 2012;7(5):e36345.
29. Djousse L, Petrone AB, Blackshear C, et al. Prevalence and changes over time of ideal cardiovascular health metrics among African-Americans: the Jackson Heart Study. *Preventive medicine.* 2015;74:111-116.
30. Izquierdo-Porrera AM, Powell CC, Reiner J, Fontaine KR. Correlates of exercise adherence in an African American church community. *Cultural diversity & ethnic minority psychology.* 2002;8(4):389-394.
31. Yi SS, Bartley KF, Firestone MJ, Lee KK, Eisenhower DL. Self-reported sitting time in New York City adults, the Physical Activity and Transit Survey, 2010-2011. *Preventing chronic disease.* 2015;12:E85.
32. Isasi CR, Ayala GX, Sotres-Alvarez D, et al. Is acculturation related to obesity in Hispanic/Latino adults? Results from the Hispanic community health study/study of Latinos. *Journal of obesity.* 2015;2015:186276.
33. Rodriguez CJ, Allison M, Daviglus ML, et al. Status of cardiovascular disease and stroke in Hispanics/Latinos in the United States: a science advisory from the American Heart Association. *Circulation.* 2014;130(7):593-625.
34. Hamilton M, Owen N. Sedentary behavior and inactivity physiology (Chapter 4). *Physical Activity and Health*. Second ed. Champaign IL: Human Kinetics 2012.
35. Vasquez E, Strizich G, Gellman MD, et al. The role of stress in understanding differences in sedentary behavior in Hispanic/Latino adults: Results from the Hispanic Community Health Study/ Study of Latinos Socio-cultural Ancillary Study. *Journal of Physical Activity and Health* In Press 2015.
36. Jefferis BJ, Sartini C, Lee IM, et al. Adherence to physical activity guidelines in older adults, using objectively measured physical activity in a population-based study. *BMC public health.* 2014;14:382.
37. Chinn DJ, White M, Harland J, Drinkwater C, Raybould S. Barriers to physical activity and socioeconomic position: implications for health promotion. *Journal of epidemiology and community health.* 1999;53(3):191-192.
38. Macintyre S. The social patterning of exercise behaviours: the role of personal and local resources. *British journal of sports medicine.* 2000;34(1):6.
39. Rennie KL, McCarthy N, Yazdgerdi S, Marmot M, Brunner E. Association of the metabolic syndrome with both vigorous and moderate physical activity. *International journal of epidemiology.* 2003;32(4):600-606.
40. Panagiotakos DB, Pitsavos C, Chrysohoou C, et al. Impact of lifestyle habits on the prevalence of the metabolic syndrome among Greek adults from the ATTICA study. *American heart journal.* 2004;147(1):106-112.
41. Atienza AA, Moser RP, Perna F, et al. Self-reported and objectively measured activity related to biomarkers using NHANES. *Medicine and science in sports and exercise.* 2011;43(5):815-821.
42. Metzger JS, Catellier DJ, Evenson KR, Treuth MS, Rosamond WD, Siega-Riz AM. Associations between patterns of objectively measured physical activity and risk factors for the metabolic syndrome. *American journal of health promotion : AJHP.* 2010;24(3):161-169.

43. Sisson SB, Camhi SM, Church TS, Tudor-Locke C, Johnson WD, Katzmarzyk PT. Accelerometer-determined steps/day and metabolic syndrome. *American journal of preventive medicine.* 2010;38(6):575-582.
44. Murphy MH, Blair SN, Murtagh EM. Accumulated versus continuous exercise for health benefit: a review of empirical studies. *Sports medicine.* 2009;39(1):29-43.
45. Tremblay MS, Colley RC, Saunders TJ, Healy GN, Owen N. Physiological and health implications of a sedentary lifestyle. *Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme.* 2010;35(6):725-740.
46. Yanagibori R, Kondo K, Suzuki Y, et al. Effect of 20 days' bed rest on the reverse cholesterol transport system in healthy young subjects. *Journal of internal medicine.* 1998;243(4):307-312.
47. Hamburg NM, McMackin CJ, Huang AL, et al. Physical inactivity rapidly induces insulin resistance and microvascular dysfunction in healthy volunteers. *Arteriosclerosis, thrombosis, and vascular biology.* 2007;27(12):2650-2656.
48. Osler ME, Fritz T, Caidahl K, Krook A, Zierath JR, Wallberg-Henriksson H. Changes in gene expression in responders and nonresponders to a low-intensity walking intervention. *Diabetes care.* 2015;38(6):1154-1160.
49. Lavange LM, Kalsbeek WD, Sorlie PD, et al. Sample design and cohort selection in the Hispanic Community Health Study/Study of Latinos. *Annals of epidemiology.* 2010;20(8):642-649.
50. Sorlie PD, Aviles-Santa LM, Wassertheil-Smoller S, et al. Design and implementation of the Hispanic Community Health Study/Study of Latinos. *Ann Epidemiol.* 2010;20(8):629-641.
51. Merz EL, Roesch SC, Malcarne VL, et al. Validation of interpersonal support evaluation list-12 (ISEL-12) scores among English- and Spanish-speaking Hispanics/Latinos from the HCHS/SOL Sociocultural Ancillary Study. *Psychological assessment.* 2014;26(2):384-394.
52. Dawber TR, Meadors GF, Moore FE, Jr. Epidemiological approaches to heart disease: the Framingham Study. *American journal of public health and the nation's health.* 1951;41(3):279-281.
53. Splansky GL, Corey D, Yang Q, et al. The Third Generation Cohort of the National Heart, Lung, and Blood Institute's Framingham Heart Study: design, recruitment, and initial examination. *American journal of epidemiology.* 2007;165(11):1328-1335.
54. Lewis GD, Gona P, Larson MG, et al. Exercise blood pressure and the risk of incident cardiovascular disease (from the Framingham Heart Study). *The American journal of cardiology.* 2008;101(11):1614-1620.
55. Glazer NL, Lyass A, Esliger DW, et al. Sustained and shorter bouts of physical activity are related to cardiovascular health. *Medicine and science in sports and exercise.* 2013;45(1):109-115.
56. Evenson KR, Sotres-Alvarez D, Deng YU, et al. Accelerometer adherence and performance in a cohort study of US Hispanic adults. *Medicine and science in sports and exercise.* 2015;47(4):725-734.
57. Isasi CR, Parrinello CM, Jung MM, et al. Psychosocial stress is associated with obesity and diet quality in Hispanic/Latino adults. *Annals of epidemiology.* 2015;25(2):84-89.
58. McCurley JL, Mills PJ, Roesch SC, et al. Chronic stress, inflammation, and glucose regulation in U.S. Hispanics from the HCHS/SOL Sociocultural Ancillary Study. *Psychophysiology.* 2015.
59. Qi Q, Strizich G, Merchant G, et al. Objectively-measured sedentary time and cardiometabolic biomarkers in U.S. Hispanic/Latino adults: The Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Circulation.* Under Review.
60. Andersson C, Lyass A, Larson MG, et al. Physical activity measured by accelerometry and its associations with cardiac structure and vascular function in young and middle-aged adults. *Journal of the American Heart Association.* 2015;4(3):e001528.
61. Bull FC, Maslin TS, Armstrong T. Global physical activity questionnaire (GPAQ): nine country reliability and validity study. *Journal of physical activity & health.* 2009;6(6):790-804.
62. Hoos T, Espinoza N, Marshall S, Arredondo EM. Validity of the Global Physical Activity Questionnaire (GPAQ) in adult Latinas. *J Phys Act Health.* 2012;9(5):698-705.
63. Kabat GC, Heo M, Ochs-Balcom HM, et al. Longitudinal association of measures of adiposity with serum antioxidant concentrations in postmenopausal women. *Eur J Clin Nutr.* 2015.
64. Colley RC, Tremblay MS. Moderate and vigorous physical activity intensity cut-points for the Actical accelerometer. *Journal of sports sciences.* 2011;29(8):783-789.
65. Wong SL, Colley R, Connor Gorber S, Tremblay M. Actical accelerometer sedentary activity thresholds for adults. *Journal of physical activity & health.* 2011;8(4):587-591.

66. Marin G, Sabogal F, Marin BV, Oterosabogal R, Perezstable EJ. Development of a Short Acculturation Scale for Hispanics. *Hispanic J Behav Sci.* 1987;9(2):183-205.
67. Schwingshackl L, Hoffmann G. Diet quality as assessed by the Healthy Eating Index, the Alternate Healthy Eating Index, the Dietary Approaches to Stop Hypertension score, and health outcomes: a systematic review and meta-analysis of cohort studies. *Journal of the Academy of Nutrition and Dietetics.* 2015;115(5):780-800 e785.
68. Wassertheil-Smoller S, Arredondo EM, Cai J, et al. Depression, anxiety, antidepressant use, and cardiovascular disease among Hispanic men and women of different national backgrounds: results from the Hispanic Community Health Study/Study of Latinos. *Annals of epidemiology.* 2014;24(11):822-830.
69. Choi L, Liu Z, Matthews CE, Buchowski MS. Validation of accelerometer wear and nonwear time classification algorithm. *Medicine and science in sports and exercise.* 2011;43(2):357-364.
70. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. *Medicine and science in sports and exercise.* 2008;40(1):181-188.
71. John D, Freedson P. ActiGraph and Actical physical activity monitors: a peek under the hood. *Medicine and science in sports and exercise.* 2012;44(1 Suppl 1):S86-89.
72. Seaman SR, White IR. Review of inverse probability weighting for dealing with missing data. *Statistical methods in medical research.* 2013;22(3):278-295.
73. Kleinbaum DG, Klein M. *Statistics for Biology and Health: Survival Analysis, A Self-learning Text. Chapter 5* Second ed. New York, USA: Springer; 2005.
74. Harrel F, Lee K. *Proceedings of the Eleventh Annual SAS User's Group International.* 1986.
75. Schoenfeld D. Partial residuals for the proportional hazards model. *Biometrika.* 1982;69:51-55.
76. Peddie MC, Bone JL, Rehrer NJ, Skeaff CM, Gray AR, Perry TL. Breaking prolonged sitting reduces postprandial glycemia in healthy, normal-weight adults: a randomized crossover trial. *The American journal of clinical nutrition.* 2013;98(2):358-366.
77. Altenburg TM, Rotteveel J, Dunstan DW, Salmon J, Chinapaw MJ. The effect of interrupting prolonged sitting time with short, hourly, moderate-intensity cycling bouts on cardiometabolic risk factors in healthy, young adults. *Journal of applied physiology.* 2013;115(12):1751-1756.
78. Gebel K, Ding D, Chey T, Stamatakis E, Brown WJ, Bauman AE. Effect of Moderate to Vigorous Physical Activity on All-Cause Mortality in Middle-aged and Older Australians. *JAMA internal medicine.* 2015;175(6):970-977.
79. Xue X, Kim MY, Shore RE. Cox regression analysis in presence of collinearity: an application to assessment of health risks associated with occupational radiation exposure. *Lifetime data analysis.* 2007;13(3):333-350.
80. Stiger TR, Barnhart HX, Williamson JM. Testing proportionality in the proportional odds model fitted with GEE. *Statistics in medicine.* 1999;18(11):1419-1433.
81. Touloumis A, Agresti A, Kateri M. GEE for multinomial responses using a local odds ratios parameterization. *Biometrics.* 2013;69(3):633-640.
82. U.S. Department of Health and Human Services. Physical Activity Guidelines Advisory Committee Report, 2008. http://www.health.gov/paguidelines/report/pdf/committeereport.pdf.
83. Lee IM, Skerrett PJ. Physical activity and all-cause mortality: what is the dose-response relation? *Medicine and science in sports and exercise.* 2001;33(6 Suppl):S459-471; discussion S493-454.
84. Oguma Y, Sesso HD, Paffenbarger RS, Jr., Lee IM. Physical activity and all cause mortality in women: a review of the evidence. *British journal of sports medicine.* 2002;36(3):162-172.
85. Hagstromer M, Oja P, Sjostrom M. Physical activity and inactivity in an adult population assessed by accelerometry. *Medicine and science in sports and exercise.* 2007;39(9):1502-1508.
86. Sims J, Smith F, Duffy A, Hilton S. The vagaries of self-reports of physical activity: a problem revisited and addressed in a study of exercise promotion in the over 65s in general practice. *Family practice.* 1999;16(2):152-157.
87. Watkinson C, van Sluijs EM, Sutton S, Hardeman W, Corder K, Griffin SJ. Overestimation of physical activity level is associated with lower BMI: a cross-sectional analysis. *The international journal of behavioral nutrition and physical activity.* 2010;7:68.
88. Dyrstad SM, Hansen BH, Holme IM, Anderssen SA. Comparison of self-reported versus accelerometer-measured physical activity. *Medicine and science in sports and exercise.* 2014;46(1):99-106.

89. Evenson KR, Wen F, Metzger JS, Herring AH. Physical activity and sedentary behavior patterns using accelerometry from a national sample of United States adults. *The international journal of behavioral nutrition and physical activity.* 2015;12:20.
90. Xue X, Hoover DR. Statistical methods in cancer epidemiological studies. *Methods in molecular biology.* 2009;471:239-272.
91. Evenson KR, Wen F. Performance of the ActiGraph accelerometer using a national population-based sample of youth and adults. *BMC research notes.* 2015;8:7.
92. Mossavar-Rahmani Y, Shaw PA, Wong WW, et al. Applying Recovery Biomarkers to Calibrate Self-Report Measures of Energy and Protein in the Hispanic Community Health Study/Study of Latinos. *American journal of epidemiology.* 2015;181(12):996-1007.

PROTECTION OF HUMAN SUBJECTS

Risks to Subjects

Human Subjects Involvement and Characteristics*:* Five sites (four from the HCHS-SOL and one from FHS Gen3 & Omni2) are participating in the study with total sample size of 5500 nondiabetic participants defined based on HgbA1c, fasting and 2-hour post-OGTT levels of glucose at visits 1 & 2 for HCHS-SOL and exam 2 for FHS (Gen3 & Omni 2) and on HgbA1c and fasting glucose for FHS exam 3 as 2-hour post OGTT levels are not available at exam 3. Distributions of HCHS-SOL by age and sex appear in Table 1. FHS Gen 3 and Omni age and sex distribution shown in Table 2.

.

Table 1.	Projected Participants, HCHS-SOL, Visit 2		
Age group	**Women**	**Men**	**Total**
<40	205	252	457
40-49	390	337	727
50-59	962	650	1612
60-69	902	515	1417
70-85	332	215	547
All ages	2791	1969	4760

Table 2.	Projected Participants Gen 3 & Omni 2, Exam 3		
Age group	**Women**	**Men**	**Total**
<40	10	15	26
40-49	60	94	154
50-59	134	200	334
60-69	97	105	202
70-85	15	10	25
All ages	316	425	740

Note that in FHS, longitudinal collection of accelerometry and physical activity questionnaire data are already being supported by existing funding *(*1R01 HL131029, Joint PI, Ramachandran, NHLBI, data collection 2016-2018),and that this application is to request funding for collection of accelerometry and physical activity questionnaire data at HCHS-SOL and harmonization of data and data analysis of HCHS-SOL with FHS.

Exclusion Criteria: Noncompliance or incomplete adherence to the accelerometry protocol at the HCHS-SOL visit 1 and 2 and FHS Exam 2 and 3 is a basis for exclusion. HCHS-SOL study staff will obtain a monthly list of potentially eligible participants from the University of North Carolina HCHS-SOL Coordinating Center for the HCHS-SOL sites. Participants who are unable to ambulate will be excluded. We will also exclude participants with a proxy (participants who are unable to complete forms on their own, etc.). All data collection, informed consent, and other activities will be conducted by the staff of the HCHS-SOL and FHS core centers.

Recruitment will be done at by mail or in clinic at HCHS-SOL sites. FHS is collecting accelerometry data on all participants (see section D2c under data collection protocol). In clinic approach): At recruitment contacts, each participant will receive the informed consent form and have time to discuss the study and have questions answered. Once questions are answered, the participant will be given time to consider and sign the consent form. A model consent form will be circulated to the sites before it undergoes review by respective IRBs. Activities at this visit consist of reviewing the informed consent (10 minutes); reviewing the use of the accelerometer (5 minutes); completing a physical activity questionnaire the HCHS-SOL Physical Activity Questionnaire (PAQ): https://www2.cscc.unc.edu/hchs/system/files/forms/UNLICOMMPhysicalActivityPAE02182008.pdf (15 minutes). Participants are to wear the accelerometer for a period of a week and will remove when sleeping or performing water-related activities (showering, swimming). Participants will mail back the accelerometer once they have completed study activities after the week period.

Via mail/telephone approach: Informed consent and study information will be mailed to participants. Discussion of the informed consent will occur by telephone and informed consent will be obtained. Activities by phone are same as described above for in-clinic approach.

Physical Activity Questionnaire: All HCHS-SOL sites will administer the HCHS-SOL PAQ and FHS will administer the FHS Physical Activity Questionnaires which consist of: Physical activity index (Kannel 1979, similar to IPAQ) Physical activity questionnaire (modified Minnesota Questionnaire, Taylor 1978) Physical Activity Scale for the Elderly (Washburn 1993.) Questionnaires will be administered by phone for all HCHS-SOL sites except the SOL San Diego site and participants will be provided with a mailer and postage to mail back the accelerometer. FHS is administering the questionnaire as part of its in-clinic examination that is already funded as mentioned earlier.

Potential Risks: We do not expect there to be any medical problems as a result of participation in the study.

Adequacy of Protection against Risks
The relevant Observational Study Monitoring Board (OSMB) members organized by NIH for the parent cohorts will monitor this study. The protocol will be independently reviewed by the Albert Einstein Institutional Review Board (IRB) (lead institution) and IRB of respective sites associated with FHS (Boston University) as well as other HCHS-SOL field centers and coordinating center. A model informed consent form will be developed that will undergo IRB review before circulation to participants. All participants will sign written informed consent form as appropriate. The consent form follows standard Institutional Review Board guidelines and will describe the study, why it is being done, number of participants, what is involved in the study, all activities that form the study protocol, length of the study, risks, benefits, options, mechanisms for protecting confidentiality, costs, participants rights and information about whom to call should questions arise. The consent form will be signed by the participant and by the site Principal Investigator or Designated Study Staff.

Confidentiality: All efforts will be made to keep participant information confidential. We cannot guarantee absolute confidentiality. Personal information may be disclosed if required by law. The Office of Human Research Protection and the Institutional Review Board may have access to participant research records to ensure that the participant rights are being met. Within HCHS-SOL and FHS confidentiality is highly guarded whereby only pertinent staff at the field centers have access to linkages identifying participants' information with the participant member ID. Participant charts will be kept in locked areas. All staff and investigators will have completed an approved Human Subjects Training and an approved HIPAA training. The web-based data collection and storage system encrypts all data transfer with firewall protection.

Participant data will be kept in locked areas. The study web-based data collection and storage system encrypts all data transfer with firewall protection. Data analyses will occur at Einstein, the HCHS-SOL Coordinating Center at University of North Carolina and at Boston University. No data will be released or published in a manner in which individuals can be identified. Participants may end their participation in the study at any time, for any reason, with no consequence to their participation in the parent study. We do not expect any adverse effects to occur. If medical problems do occur, we will refer the participant to his/her personal physician or other appropriate care. The participant or his/her health insurance will be responsible for the costs of any such care.

Sources of Materials*:* The sources of data for this study will come from participants in the study. Records will be limited to data collected during participants' enrollment and follow-up. Examples include demographic data at baseline and physical measures such as weight, and questionnaire data such as acculturation that were collected in the parent study. During the project, data recorded on the human subjects will include reported physical activity levels (from a physical activity questionnaire) and accelerometer. We will not request any personal health information from other sources, such as hospitals or the participant's physician. All data will be entered into the DMS web-based database which is protected by encrypted data transfer and institutional fire walls.

Data to be collected: Accelerometer data (Actical) and the respective physical activity questionnaires (HCHS-SOL & FHS) will be included in the data collection protocol. The project also makes use of *previous data collected as part as prior and ongoing NIH-funded core examinations and follow-up of the HCHS-SOL and FHS: Socio-demographic information (age at enrollment in parent study, sex, economic status, Hispanic ethnicity, acculturation, years in mainland US, etc.), SOL & FHS Gen 3/Omni 2 physical activity questionnaires; accelerometry data (at prior visit);* fasting and 2-hour post-OGTT levels of glucose, HgbA1, incident diabetes, *cardiovascular events: myocardial infarction, angina, heart failure, stroke, peripheral artery disease in all sites and venous embolism and pulmonary embolism at HCHS-SOL sites only.*

Data Management: The Data Management System (DMS) for HCHS-SOL and this study is web-based and allows immediate update of the central database (located at the University of North Carolina-UNC-CC) upon data entry; ease of integration of laboratory and reading center data with field center data for generating results reports, alert reports to participants and their providers for medical care. The UNC-CC will integrate the data

from COMPASS with HCHS-SOL and send the data set to the Bronx site; data from FHS Gen3 will be integrated with that of COMPASS at the Bronx site for analyses related to both studies. Features of the DMS include a menu-driven graphical user interface, data validation upon entry, transaction auditing, database updating, database closure, reports, data archiving, and data retrieval. Reading center and field site data are uploaded to the study server over the web and automatically loaded into the centralized data management system files. Participant result reports are assembled within 24 hours of receipt at the UNC-CC and are available to be downloaded by field centers at the beginning of each work day. COMPASS data from the field centers will be integrated to the UNC-CC centralized data management system files. Data collected at the Field Center are transmitted to the UNC-CC weekly at a minimum for editing and processing. Most data are directly entered over the internet on the server in the UNC-CC.

Data confidentiality and security are applied at all levels of data acquisition, transfer and storage for all study agencies from field centers to the study sites. The password controlled access to the study equipment and the DMS is the initial level of security. All data collected at the field centers and in hospital record rooms are encrypted by the system and can only be decrypted for display on-screen by authorized study personnel. Personal identifiers are collected on separate forms (and transferred as separate, encrypted records).

Potential Benefits of the Proposed Research to the Subjects

Participants will not directly benefit from this project. The knowledge gained from this study will help scientists better understand relationships between physical activity, particularly sedentary behavior, moderate and vigorous activity and cardio-metabolic disease risk in both a mainstream and a diverse US Hispanic population. This study provides a unique contribution to the field by characterizing the relationship between physical activity and cardio-metabolic risk in an understudied and growing population in the US. The proposed study is both efficient and cost effective. By incorporating the ancillary study into the main study efforts for recruiting, tracking, the collection of data such as acculturation, anthropometry and health outcomes are not duplicated. The ancillary study only adds ta total of 30 minutes for the informed consent, questionnaire and instructions for wearing the accelerometer. The accelerometer is worn over a period of a week and returned via mail. Thus respondent burden is minimized.

Importance of Knowledge to be Gained

Knowledge from this study will help scientists determine the relationship between cardio-metabolic disease and physical activity over a six year period in both a mainstream and an under-studied, but rapidly growing population in the US. This information can help guide the physical activity guidelines for Americans not just for moderate and vigorous physical activity, but also for sedentary behavior.

Data Safety Monitoring Plan Adverse Event Monitoring

Process: Data and safety monitoring will be overseen by the Observational Safety Monitoring Board of the parent studies HCHS-SOL and FHS. Locally it will be performed by the principal investigators in conjunction with the respective medical professionals affiliated at each site. All abnormal and incidental findings during the physical encounters from the study visits will be documented on a case report form and reviewed by study health personnel within 24 hours of receipt.

Reporting: All adverse events will be compiled and reported in summary form on an annual basis to the local CCI/IRB and at the conclusion of the study. Unanticipated (non-serious) adverse events will be reported to the local CCI/IRB within 30 days via submission of the local CCI/IRB Adverse Event Report or per requirements of local IRBs. Serious adverse events will be reported to the local CCI/IRB by phone, email or fax; a completed local CCI/IRB Adverse Event Report will be submitted within 10 days of initial local CCI/IRB notification. All deaths will be reported to the local CCI/IRB upon 48 hr of discovery.

Recruitment Monitoring

Process: The investigator group will assess the recruitment and retention of study subjects on an ongoing basis and determine whether adjustments need to be made in recruitment rate. The recruitment goal is 5,500 participants, whereas power calculations have assumed that 5,276 individuals with completed data will be used to address the study aims with adequate statistical power. Reporting: Summary statistics regarding recruitment and retention of study subjects will be reported to the local CCI/IRB on an annual basis, and at the conclusion of the study.

References

Kannel WB, Sorlie PD. Some health benefits of physical activity: The Framingham Study. Arch Intern Med. 1979 Aug;139(8):857-61

Taylor HL, Jacobs DR Jr, Schucker B, Knudsen J, Leon AS, Debacker G. A questionnaire for the assessment of leisure time physical activities. J Chronic Dis. 1978;31(12):741-55.

Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. J Clin Epidemiol 1993;46(2):153-62

Washburn RA, McAuley E, Katula J, Mihalko SL, Boileau RA. The physical activity scale for the elderly (PASE): evidence for validity. J Clin Epidemiol 1999;52(7):643-51