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Sedentary Time and Peripheral Artery Disease: The Hispanic Community Health Study/Study of Latinos

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Abstract

Background: Experimental evidence suggests sedentary time (ST) may contribute to cardiovascular disease by eliciting detrimental hemodynamic changes in the lower limbs. However, little is known about objectively-measured ST and lower extremity peripheral artery disease (PAD).

Methods: We included 7,609 Hispanic/Latinos (ages 45–74) from the Hispanic Community Health Study/Study of Latinos. PAD was measured using the ankle brachial index (ABI≤0.9). ST was measured using accelerometry. We used multivariable logistic regression to assess

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associations of quartiles of ST and PAD then used the same logistic models with restricted cubic splines (RCS) to investigate continuous non-linear associations of ST and PAD. Models were sequentially adjusted for traditional PAD risk factors, leg pain, and moderate-vigorous intensity physical activity (MVPA).

Results: Median ST was 12.2 hours/day and 5.4% of individuals had PAD. Fully adjusted RCS models accounting for traditional PAD risk factors, leg pain, and MVPA, ST had a significant overall (p= 0.048) and non-linear (p= 0.024) association with PAD. A threshold effect was seen such that time spent above median ST was associated with higher odds of PAD. That is, compared to median ST, 1, 2 and 3 hours above median ST was associated with a PAD OR of 1.16 (95% CI: 1.02–1.31), 1.44 (1.06–1.94) and 1.80 (1.11–2.90), respectively.

Conclusions: Among Hispanic/Latino adults, ST was associated with higher odds of PAD, independent of leg pain, MVPA, and traditional PAD risk factors. Notably, we observed a threshold effect such that these associations were only observed at the highest levels of ST.

Introduction

Recent technological changes and trends in occupational, transportation and home-life has allowed for increases in daily sedentariness.[1] This is concerning, as higher daily sedentary time has been shown in numerous studies to be associated with increased risk for cardiovascular events, cardiovascular mortality and all-cause mortality.[2–5] Given the rising trend in daily sedentariness and its association with poor cardiovascular outcomes, it is critical to further understand the mechanisms through which sedentary behaviors influence cardiovascular disease.

Peripheral artery disease (PAD) is an important clinical and public health endpoint because it is associated with reduced quality of life and with increased risk for cardiovascular events and mortality.[6, 7] Previous research has shown that the development of extra coronary atherosclerosis tends to occur in the arteries in the lower versus upper extremities.[8] Prolonged exposure to sitting may promote endothelial dysfunction.[9] Given that endothelial dysfunction is the hallmark feature for the initiation of the atherosclerotic process,[10] sitting may promote the development of lower extremity PAD. Two previous studies have demonstrated a possible association between sedentary time and PAD, but the results were inconsistent and neither study had any representation of Hispanic/Latinos, a growing and aging population within the United States.[11, 12]

Given that cardiovascular death is one of two major leading causes of death among US Hispanics/Latinos,[13] we investigated cross-sectional associations between objectively-measured sedentary time and prevalent PAD in a large, diverse Hispanic/Latino population. We hypothesized that higher daily sedentary time was associated with higher odds of PAD, independent of traditional PAD risk factors, leg pain, and moderate-vigorous physical activity (MVPA).

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Methods

Study Population

The design, implementation and recruitment strategies for the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) have been published in detail.[14, 15] In brief, between March 2008 and June 2011, this population-based cohort recruited 16,415 self-identified Hispanic/Latino men and women 18–74 years of age from randomly selected households in four United States communities (San Diego, CA; Bronx, NY, Chicago, IL; Miami, FL). Households were selected using a stratified two-stage area probability sample design. Census block groups were randomly selected in the defined community areas of each field center, and households were randomly selected in each sampled block group. Oversampling occurred at each stage, with block groups in areas of Hispanic/Latino concentration, households associated with a Hispanic/Latino surname, and persons aged 45–74 years selected at higher rates than their counterparts. Sampling weights were generated to reflect the probabilities of selection at each stage. As a result, the HCHS/SOL included participants from Cuban, Dominican, Mexican, Puerto Rican, Central American, and South American backgrounds. Institutional review boards at each participating institution approved the study and written informed consent was obtained from all participants.

By design, individuals younger than 45 years of age (n=6,701) did not undergo measurements used to compute the ABI and were thus excluded from this study. From the 9,714 participants 45–74 years old, we excluded 67 individuals >45 years of age who did not complete the ABI procedure, 1,748 who were non-adherent to the Actical accelerometer, 68 who had > 23 hours of daily average accelerometer wear time, 39 who had prior surgical intervention for PAD revascularization and 183 with an ABI >1.4, to avoid PAD masked by stiff arteries. These exclusions resulted in an analytic sample of 7,609 individuals.

Data Collection

Ankle Brachial Index (ABI)—After the participant rested quietly for 5 minutes in the supine position, a Doppler probe (Elite 100r) was used to measure systolic blood pressures, starting in the right arm and moving counter-clockwise to obtain the right brachial, dorsalis pedis (DP), posterior tibial (PT) arteries and left PT, DP and brachial arteries. Trained personnel were instructed to identify each artery with the doppler prior to cuff inflation to 20 mm Hg above the level at which the pulse sound disappeared. If the pulse could still not be obliterated, the cuff pressure was increased to a maximum of 300 mm Hg. If staff personnel could not locate the artery (i.e. detect a signal) after 3 minutes of systematic searching, they were instructed to record that the pressure was not obtainable for that artery. For arteries that could not be assessed because of lesions or amputation, the pressure was recorded as missing.

Leg-specific ABIs were calculated by taking the higher of the DP/PT artery ankle pressure and dividing by the higher of the two brachial artery pressures according to guideline recommendations.[16] The analysis used the lower of the left and right leg ABI.

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The presence of PAD was defined as having an ABI value ≤ 0.9. Those with an ABI 0.91.4 were considered the normal “referent group”. In a sensitivity analyses, an ABI value of ≤ 0.8 was used as a cutoff with an ABI 0.8–1.4 as the “referent group”, to increase specificity.[17]

Objectively Measured Sedentary Time and Physical Activity—HCHS/SOL used the Actical accelerometer (version B-1, model 198-0200-03, Philips-Respironics Co. Inc., Bend, OR, USA) to measure physical activity. A more in-depth description on accelerometer adherence and performance characteristics in this cohort has been described elsewhere.[18] In brief, participants were fitted with a belt and departed the clinic wearing the accelerometer above the right iliac crest. They were told to perform their usual activities while wearing the accelerometer, and to remove it for swimming, sleeping or showering for one week. We adhered to data processing with the most common metric of total sedentary time accumulation to represent weekly behavior.[19] Previous work has shown that a minimum of 3 days[20] provides a sufficient estimate of physical activity for the week and this is a reliable measure of activity over 2–3 years.[21, 22] The Actical was programmed to measure accelerations in “counts” in 1-minute epochs (cpm). Non-wear time was determined using the Choi algorithm[23], defined as > 90 minutes of zero counts, with allowance of 1 or 2 minutes of nonzero counts if no counts were detected in a 30-minute window upstream and downstream of the 90-minute period. Accelerometer data were summarized as the number of minutes per day spent sedentary (< 100 cpm), and moderate (≥ 1,535 cpm) or vigorous (≥ 3,962 cpm) physical activity according to established cut-points.[24] Accelerometer adherence was defined as greater than 10 hours of wear time per day for at least three days. As clinic visit appointments ended at different times of day, the coordinating center decided to standardize the accelerometer data start time for 5:00am the day after the clinic visit. This resulted in total possibility of a maximum of 6 accelerometer wear days.

Assessment of Covariates—Sociodemographic variables included age, sex, self-identified Hispanic/Latino background (Dominican, Central American, Cuban, Mexican, Puerto-Rican, South American, mixed/other), education (<high school (HS) diploma, HS diploma/General Education Diploma (GED only), > HS diploma/GED), and marital status (single, married or living with a partner, separated/divorced/widower). Both alcohol use and smoking were self-reported (current, former, and never). Height was measured to nearest centimeter and weight measured to nearest 0.1 kilogram. Body mass index (BMI) was computed as weight in kilograms divided by height in meters-squared. After a 5-minute rest period, 3 seated blood pressure measurements were obtained with an automatic sphygmomanometer. Hypertension was defined as an average of 3 blood pressure readings ≥140/90 mm Hg or a medication review revealing use of an antihypertensive medication.

Blood samples, including plasma glucose (fasting and after a 2-hour oral glucose load) were collected in all participants according to standardized protocols. Total serum cholesterol was measured using a cholesterol oxidase enzymatic method and high-density lipoprotein (HDL) cholesterol with a direct magnesium/dextran sulfate method. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation.[25] Dyslipidemia was defined as LDL > 160 mg/dL, HDL < 40 mg/dL, total cholesterol >240 mg/dL or use of cholesterol/ lipid lowering medication. Plasma glucose was measured using a hexokinase enzymatic

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method (Roche Diagnostics). Hemoglobin A1c was measured using a Tosoh G7 Automated HPLC Analyzer (Tosoh Bioscience). Diabetes was defined as a fasting glucose ≥126 mg/dL, 2-hour post-oral glucose tolerance test ≥200 mg/ml, or hemoglobin A1C ≥6.5%. We also included in the definition of diabetes any use of prescription drugs for diabetes or self-report of diabetes. Impaired glucose tolerance was defined as fasting glucose ≥100 mg/ml, but less than 126 mg/ml, 2-hour post-oral glucose tolerance test 140–199 mg/ml or hemoglobin A1C 5.7–6.5%.[26] Creatinine was measured in serum and urine on a Roche Modular P Chemistry Analyzer (Roche Diagnostics Corporation) using a creatinase enzymatic method (Roche Diagnostics, Indianapolis, IN 46250). Serum creatinine measurements were isotope dilution mass spectrometry (IDMS) traceable. Estimated glomerular filtration rate (eGFR) was estimated using the equation developed by the Chronic Kidney Disease Epidemiology Collaboration working group, which includes serum creatinine, age, sex and race components.[27]

Prevalent coronary heart disease was ascertained with EKG reports of possible prior myocardial infarction as well as self-report of angina, heart attack or procedure (angioplasty, stent, bypass). History of stroke was assessed by self-report using the question: “Has a doctor ever said that you had a stroke?” Diet quality was assessed with the Alternative Healthy Eating Index (AHEI)-2010,[28] which was calculated based on two-24 hour dietary recalls using the National Cancer Institute methodology.[29] The AHEI-2010, scored 0–110, is a measure of diet quality with higher scores indicating healthier eating habits.[28]

Leg Symptoms/Physical function—The San Diego Claudication Questionnaire was used to assess leg symptoms with activity. As a minority with PAD have classic intermittent claudication,[30, 31] we used “do you get pain or discomfort in either leg on walking?” to maximize sensitivity for assessing leg pain that may influence activity. Additionally, patients were asked about activity limiting arthritis with the question, “do you have painful inflammation or swelling of your joints that limits your activities?” Physical function was assessed with the short form-12 aggregate physical health[32] scored according to population norms developed by Ware and colleagues.[33]

Statistical Analysis

All results were estimated with sampling weights, clustering, and stratification to account for nonresponse and oversampling of specific population segments using SAS 9.4 (SAS Institute Inc., Cary, NC). Weights were trimmed to reduce the variability of the weights as well as the impact of extremely large sampling weights, and then calibrated to 2010 US Census characteristics by age, sex and Hispanic/Latino background in the target population at each field center.[14, 18] As previously described, results were additionally adjusted for missing or incomplete accelerometer data with inverse probability weighting (IPW).[34] IPW was used to correct for the bias of estimates obtained by using complete-case analyses (i.e., adherent participants). An IPW weight was created from a logistic regression model predicting Actical compliance based on age, gender, income level, marital status, education, employment status, language preference, immigrant generation, self-reported physical activity, BMI, physical health score, field center by background cross-classification, sampling stratum, and sampling weight.

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Due to the high correlation between sedentary time and accelerometer wear time (r= 0.82), we standardized sedentary time to 16 hours/day of wear time (approximate average wear/awake time in study) using the residuals from regressing sedentary time on wear time as done previously in the HCHS/SOL and other studies.[34–37] First, using complex survey procedures we regressed measured sedentary time against accelerometer wear time, field center, and the wear time by field center interaction. We used this to calculate residuals to represent the observed minus predicted sedentary time. Given a mean wear time of 16 hours/day, we summed individual residual sedentary time values with the field center-specific mean predicted sedentary time.

Descriptive characteristics across quartiles of sedentary time were calculated as predicted marginals of the mean using complex survey linear regression for continuous variables, and as predicted marginals of the prevalence for categorical variables. We used progressively adjusted logistic regression models to study PAD (ABI ≤ 0.9) as the dependent variable and quartiles of sedentary time as the key independent variable. Quartiles of sedentary time were modeled to avoid assumption of a linear association and better portray the nature of the relationship. Model 1 included age, sex, field center, education, marital status, Hispanic/Latino background and health behaviors including diet quality, alcohol use and smoking history as we believed these to be important sociodemographic and behavioral confounders of the sedentary time and PAD relationship. To control for disease confounders, model 2 added to model 1: hypertension, diabetes, stroke, coronary heart disease, dyslipidemia, BMI, and kidney function. These medical conditions may be potential mediators of the sedentary time and PAD relationship leading to potentially attenuated effect estimates of the sedentary time and PAD relationship. To account for leg pain and physical function in an attempt to address the potential for reverse causality, model 3 added the following covariates to model 2: symptoms of leg pain/discomfort in either leg on walking, activity limiting arthritis, and physical function. Model 4 added accelerometer-measured MVPA to model 3 covariates to test whether a direct association between sedentary time and PAD was present after accounting for MVPA. Tests for linear trend across quartiles were conducted by treating sedentary time as a continuous linear variable in the regression models. To assess for effect modification, the fully adjusted model (Model 4) included multiplicative interaction terms for sedentary quartile and age, sex and MVPA. We modeled restricted cubic splines (RCS) with 3 knots placed at the 10^{th}, 50^{th} and 90^{th} percentile of sedentary time to assess the non-linear relationship between sedentary time and PAD, using the SAS macro by Desquilbet[38] with modifications to account for the complex survey design.

Sensitivity Analyses

For sensitivity analyses, we used an ABI cutoff of ≤ 0.8 to define PAD. This represents a more conservative and “specific” threshold for detecting PAD.[17, 39] Then, to limit the possibility of reverse causality of PAD increasing sedentary time, we repeated the analyses in asymptomatic individuals by excluding individuals with symptomatic leg pain with walking or activity limiting arthritis. To determine if the association was present in non-smoking Hispanic/Latinos, we repeated the analyses excluding individuals who self-report current or former smoking. Furthermore, we ran sensitivity analyses adding employment and income variables to assess if the sedentary time and PAD association was different with the

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addition of other potential sociodemographic confounders. Finally, to account for potential misclassification of sleep time for sedentary time, we repeated analysis in individuals with less than 20 hours and separately less than 16 hours of accelerometer wear time.

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Results

Of the 7,609 participants, 2 (0.03%), 3 (0.04%) , 30 (0.39%) and 7,574 (99.54%) wore the accelerometer for 3, 4, 5 and 6 days, respectively. After standardizing wear time to a 16-hour waking day, the median sedentary time was 12.2 [IQR, 11.1–13.3] hours/day among adults aged 45–74 years old. The prevalence of PAD (ABI ≤ 0.9) was 5.4% (95% CI: 4.6–6.2). Population characteristics according to quartile of sedentary time are reported in Table 1. Those in higher quartiles of sedentary time were older, female, had higher BMI, and had worse kidney function, physical function and diet quality. Additionally, those with higher sedentary time were more likely to reside in the Bronx, have Dominican or Puerto Rican background and higher prevalence of diabetes, stroke, hypertension, coronary heart disease, arthritis and leg pain with movement. Current cigarette and alcohol use were more prevalent at lower levels of sedentary time. Consistent with a previous publication,[18] those with missing or incomplete (non-adherent) accelerometer data were slightly younger, but had a slightly higher burden of cigarette smoking, hypertension, diabetes, prevalent coronary heart disease, and stroke (data not shown).

Table 2 presents results from sequentially adjusted logistic regression models of sedentary quartiles regressed on PAD. In model 1, adjusting for demographics and health behaviors, Hispanic/Latinos with the highest sedentary time (quartile 4) had 1.49 (OR=1.49; 95% CI=1.02–2.18; p-trend=0.004) times higher odds of PAD than Hispanic/Latinos with the lowest sedentary time (quartile 1). The association was attenuated after additional adjustment for disease confounders/potential mediators (OR=1.33; 95% CI=0.91–1.93; p-trend=0.026) and leg symptoms and physical function (OR=1.28, 95% CI=0.87–1.89; p-trend=0.040), and was further attenuated after adjustment for MVPA (OR=1.09, 95% CI: 0.71–1.67; p-trend=0.130). Notably, in all regression models, quartile 2 had lower ORs than quartiles 1 and 3, indicating a potential non-linear association. To assess this, we modeled sedentary time using restricted cubic splines; and results are presented in in Table 3.

Results from restricted cubic spline modeling indicate that sedentary time is related to prevalent PAD in a non-linear fashion with (p-overall=0.048, p-non-linear=0.024) and without (p-overall=0.012, p-non-linear=0.049) additional adjustment for MVPA (Figure 1). For example, in fully adjusted models, the odds of PAD (compared to Hispanic/Latinos who are sedentary for 12.2 h/day) were 1.16 (95% CI=1.02–1.31) for adults that were sedentary for 13.2 h/day, 1.44 (95% CI=1.06–1.94) for Hispanic/Latinos who were sedentary for 14.2 h/day, and 1.80 (95% CI=1.11–2.90) for Hispanic/Latinos who were sedentary for 15.2 h/

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day. Notably, the odds ratio of PAD for Hispanic/Latinos that were sedentary for less than 12.2 h/day were not significantly different from those that were sedentary for 12.2 h/day.

There were no significant statistical interactions observed between sedentary time quartiles and age, sex or MVPA (p-interaction > 0.10 | all).

Sensitivity Analyses

Using an ABI ≤ 0.8 threshold, the prevalence of PAD was 1.8% (95% CI=1.3–2.4). When using this more specific ABI cutoff value, we observed a strong linear association across quartiles of sedentary time (Table 4). More specifically, and after adjustment for confounders/mediators, leg symptoms and physical function, Hispanic/Latinos with higher sedentary time had higher odds of having PAD than those with lower sedentary time. Comparing Hispanic/Latinos with the highest vs lowest quartiles of sedentary time, those who were sedentary for ≥13.3 h/day had 6.61-times the odds (OR=6.61; 95% CI=2.84–15.40; p-trend<0.001) of PAD than Hispanic/Latinos who were sedentary for ≤11.1 h/day. Further adjustment for MVPA (model 4) attenuated the ORs, but the overall pattern (quartile 4 vs. quartile 1 OR=5.08; 95%CI=2.05–12.57; p-trend= 0.002) persisted. Using model 4 covariates and sedentary time as a continuous variable, each one hour increase in sedentary time was associated with a 1.43 (95% CI=1.14–1.79) higher odds of PAD. See Figure 2 for a plot of the continuous associations of sedentary time and ABI ≤ 0.8.

Further sensitivity analyses among individuals without leg symptoms, never smokers and individuals who wore accelerometer < 20 hours or < 16 hours per day showed similar pattern of results (data not shown). The addition of employment and income covariates did not change the effect estimates of the sedentary time and PAD relationship (data not shown). The shape and effect sizes of the non-linear continuous dose-response in individuals without leg pain was similar to that depicted in Figure 1. For example, in fully adjusted models, the odds of PAD (compared to Hispanic/Latinos who are sedentary for 12.2 h/day) were 1.17 (95% CI=0.95–1.43) for adults that were sedentary for 13.2 h/day, 1.43 (95% CI=0.91–2.25) for Hispanic/Latinos who were sedentary for 14.2 h/day, and 1.75 (95% CI=0.86–3.59) for Hispanic/Latinos who were sedentary for 15.2 h/day in those without leg pain.

Discussion

In this large, population-based sample of Hispanic/Latinos from diverse backgrounds, higher objectively-measured sedentary time was associated with higher odds of having PAD, which persisted after adjusting for physical function, leg pain and traditional PAD risk factors that included potential disease mediators such as hypertension, diabetes, and dyslipidemia. The use of restricted cubic splines allowed us to evaluate the entire distribution of sedentary time, which demonstrated a continuous dose-response relationship that was non-linear and indicated that higher odds of PAD were associated with higher sedentary time for those above median sedentary time (≥12.2 h/d), a result that persisted after adjustment for MVPA. These results suggest that high amounts of sedentary time may play an important role in the development of atherosclerosis in the lower extremities, independent of known PAD risk factors[40] that include elevated blood pressure and the dysfunction of glucose metabolism, which are also related to sedentary behavior.[41–43]

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Our study expands upon two previous and smaller studies assessing objectively-measured sedentary time and PAD. A study in National Health and Nutrition Examination Survey (NHANES) found greater sedentary time was associated with higher odds of an ABI <1.0 in 1,443 asymptomatic black and white Americans.[11] While their results showed independent associations of sedentary time and MVPA, they did not assess the association in Hispanics/Latinos or in individuals with any physical impairments that may affect their activities. In 945 British males, Parsons et al. demonstrated that higher sedentary time was associated with a greater odds of an ABI < 0.9. However, adjusting for MVPA attenuated the effect size and p-value towards the null.[12] The difference in results could be attributed to the small sample size that lacked sex and racial/ethnic diversity.

The non-linear dose-response association observed in our primary analysis was consistent with results from a recent meta-analysis by Pandey et al. that found a non-linear association between sedentary time and incident cardiovascular disease with significant associations appearing at >10 hours of self-reported sedentary time.[5] In both studies, a higher disease burden was observed at the highest levels of sedentary time. However, in the only other sedentary time and cardiovascular disease dose-response association tested with accelerometer-measured sedentary time that we are aware of, the association was found to be linear.[44] Furthermore, results from our sensitivity analysis, using an ABI ≤0.8 cutoff, also demonstrated a linear pattern. A central theme among all dose-response analyses to date is that very high levels of sedentary time are detrimentally associated with cardiovascular disease. In our analysis, the use of restricted cubic splines allowed us to evaluate the associations of sedentary time and PAD across the entire distribution of sedentary time and not be restricted to data in quartiles. The differences seen across studies could be due to the different groups under study, the specific outcome, or the method of measurement of sedentary time. Further work is needed to fully assess the shape of the dose-response trajectory to determine if a “threshold effect” exists for associations between sedentary time and cardiovascular disease.

While the amount of available experimental evidence is limited, studies suggest that sitting may adversely affect the vasculature by altering blood pressure and glucose metabolism.[43, 45–47] However, adjustment for hypertension and diabetes (model 2) in our analyses only minimally attenuated the association, suggesting blood pressure and glucose regulation do not fully mediate the association. Thus, sitting may exert other independent detrimental effects on the vascular endothelium. Consistent evidence shows that when sitting, leg blood flow is reduced[9, 48] and this reduction may lead to endothelial dysfunction.[9] Restaino and colleagues showed this mechanism, in part, is mediated through a reduction in antegrade shear stress,[49] a phenomenon seen in the superficial femoral artery after one hour of sitting.[50] Furthermore, Morishma et al. showed that reproducing the sitting position while lying down with hips/knees bent at 90 degrees markedly reduced popliteal artery blood flow and shear rate by 45% compared with the body positioned straight while lying down.[51] The authors suggested that reduced leg artery blood flow while sitting may, in part, be related to “arterial angulations”.[51] Antegrade shear stress preserves endothelial function by activating nitric oxide production, while low and turbulent shear stress can promote atherosclerosis, inflammation and oxidative stress.[52] While future “real-world” and longer follow up studies are needed, laboratory studies demonstrate that acute exposures to sitting promote

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endothelial dysfunction, which is a hallmark feature for the initiation of the atherosclerotic process.[10] However, given the prolonged and increasing nature of our modern sitting habits, chronic exposures may have more detrimental effects.

Our results may have important therapeutic implications. There are no consistent interventions that prevent incident PAD. For those with symptomatic PAD, the only proven non-medication or surgical intervention is supervised exercise training. While supervised exercise training has been shown to improve walking distance and quality of life, the mortality benefit is inconclusive based on data from clinical trials.[53] Given that sedentary time is associated with PAD and mortality, future research and trials are needed to explore methods for decreasing sedentary time in individuals at higher risk for PAD or in those with PAD. For example, a recent pilot, laboratory-based trial in overweight postmenopausal women demonstrated improvements in superficial femoral artery flow-mediated dilation, a measure of endothelial function, with interruption of sitting with 10 minutes of standing every hour.[54] A similar trial in patients with PAD or at high-risk for PAD may show improvements in endothelial function and the possibility of decreased disease-related morbidity and mortality.

Strengths and Limitations

Our study had notable strengths and differences from previous work. In addition to objectively-measured sedentary time and MVPA, our ABIs were obtained in a standardized method by trained technicians.[16, 17] Furthermore, our sample size was threefold greater than the other two studies combined, which allowed us to control for important confounders and perform a variety of sensitivity analyses in the first study using a diverse Hispanic/Latino population.

Our study also has limitations. First, the cross-sectional nature of the analysis limits the inference into the cause and effect nature of the association. Reverse causality is a possibility as low ABI may lead to higher sedentary behavior, in part due to the leg pain associated with clinical PAD. To rule this out, we controlled for leg pain, including claudication, in our primary analyses, and in a sensitivity analysis, we demonstrated similar relationships between sedentary time and PAD in individuals with and without any leg pain. Second, key behavioral and health confounders (e.g., tobacco/alcohol use and prevalent coronary disease) were self-reported and are therefore subject to reporting and recall bias. Third, the Actical accelerometer does not distinguish between postures (e.g., sitting/standing). Thus, we relied on an intensity-only definition of sedentary time and this may result in biased estimates of sedentary time. As a result, standing still could be misclassified as sedentary time. The extent to which the measurement error is related to PAD and/or its risk factors and how the physiological changes differ between standing still and sitting conditions should be the subject of future investigations. Sedentary time was measured during a one week period, which has been shown to be a reliable measure of two to three year behavior patterns, but may not fully capture typical sedentary time in all Hispanic/Latino adults.[21] If feasible, future investigations should consider longer measurement periods. However, assuming this potential misclassification is unrelated to our outcome, we would expect our effect estimates to be biased towards the null. We are also aware that accelerometers could have been worn

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to bed despite the protocol indicating they be taken off before entering bed and put on in the morning. To address this, we standardized our measures of sedentary time to 16 h/d as has been done in several previous studies, and results from our sensitivity analyses demonstrated results were unchanged in Hispanic/Latinos with accelerometer wear time below 20 h/d and 16 h/d (results not shown). Lastly, the HCHS/SOL has a significant amount of missing accelerometer data (missing or non-adherent). While we used IPW to account for this missingness, this adjustment may not fully account for significant differences in the adherent versus non-adherent sample. However, the non-adherent group had a higher burden of medical comorbidities and we hypothesize the sedentary time and PAD relationship would be similar or slightly stronger in this group. To advance the field and help inform sedentary behavior-related guidelines, future prospective studies with hard clinical endpoints, such as incident PAD or decline in ABI, are needed to corroborate the associations observed in the present study and to help clarify the possible causal relationship.

Conclusions

In conclusion, high amounts of objectively-measured sedentary time, particularly in excess of 13 hours per day, were associated with higher odds of PAD in a large, diverse cohort of Hispanic/Latinos in the United States. This association was independent of traditional PAD risk factors, leg pain and MVPA. Our findings, supported by previous laboratory investigations, suggest sitting may be a risk factor for the development of lower extremity atherosclerosis, independent of blood pressure, glucose dysregulation and other known PAD risk factors.

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Highlights

- Hispanic/Latino adults have a high prevalence of peripheral artery disease.
- Sedentary time is associated with peripheral artery disease in the legs.
- In asymptomatic individuals, sedentary time is associated with peripheral artery disease.
- The association is independent of moderate-vigorous physical activity.

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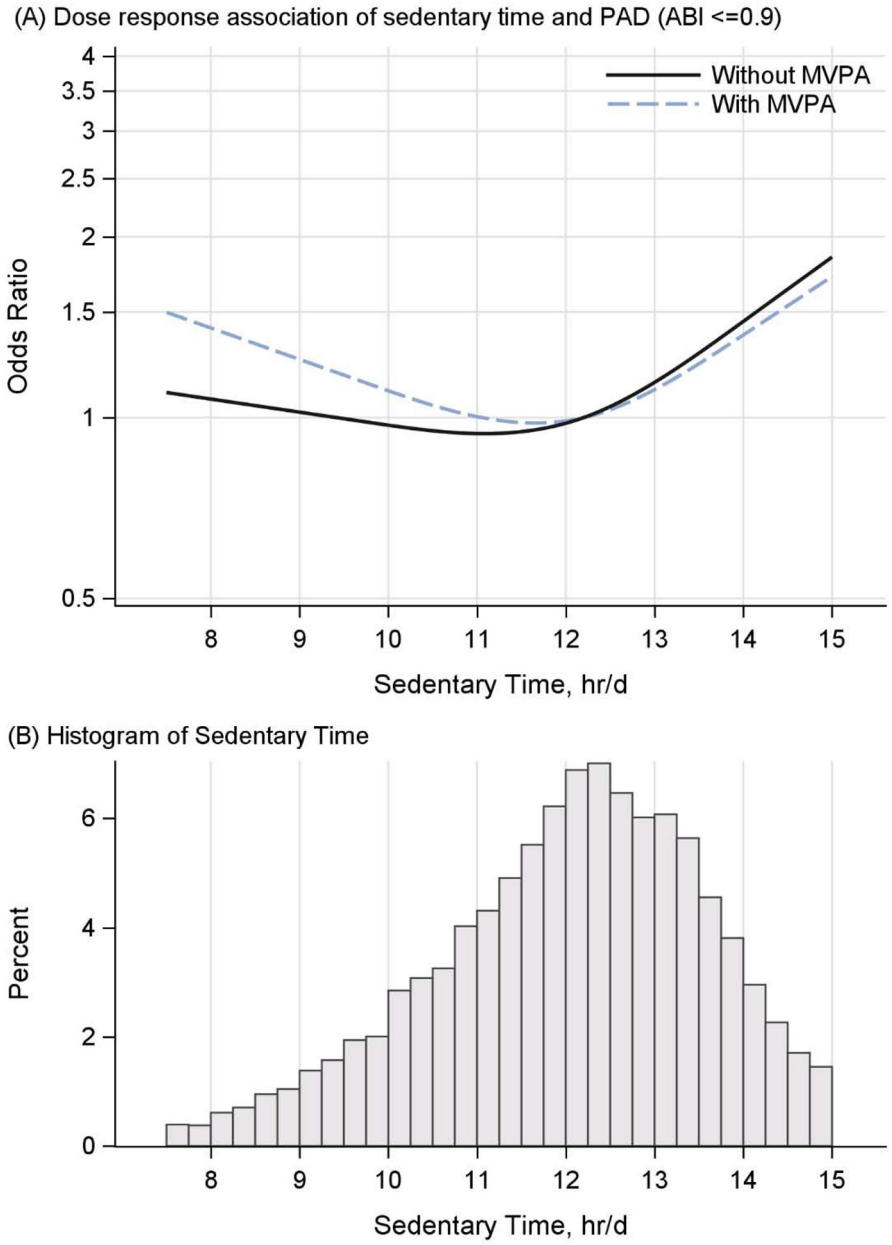

Figure 1. Continuous Dose-Response Associations of Sedentary Time and Peripheral Artery Disease (ABI ≤ 0.9) in the Hispanic Community Health Study/ Study of Latinos (2008–2011)

A, Association of Sedentary Time with PAD (ABI ≤0.9) B, Distribution of Sedentary Time (hr/d) for the HCHS/SOL cohort. All associations were estimated using multivariable restricted cubic splines logistic regression adjusting for age, sex, field center, Hispanic/ Latino background group, education, marital status, cigarette smoking, alcohol use, diet quality, hypertension, diabetes, stroke, coronary heart disease, dyslipidemia, kidney function, body mass index, leg pain with movement, arthritis and physical function (black solid line). Blue dotted line shows additional adjustment for MVPA. The reference point was set at median sedentary time (12.2 hr/d). Respective odds ratios (OR) and 95% CI for 11.2, 13.2, 14.2 and 15.2 hours per day of sedentary time were: not adjusted for MVPA 0.94

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(0.86–1.03), 1.20 (1.06–1.34), 1.52 (1.15–2.01), 1.94 (1.24–3.05); adjusted for MVPA 0.99 (0.89–1.10), 1.16 (1.02–1.31), 1.44 (1.06–1.94), 1.80 (1.11–2.90). Results were trimmed at the 1st and 99th percentiles. **Abbreviations**: ABI, Ankle brachial index; HCHS/SOL, Hispanic Community Health Study/Study of Latinos; MVPA, Moderate-to-vigorous physical activity; PAD, Peripheral artery disease.

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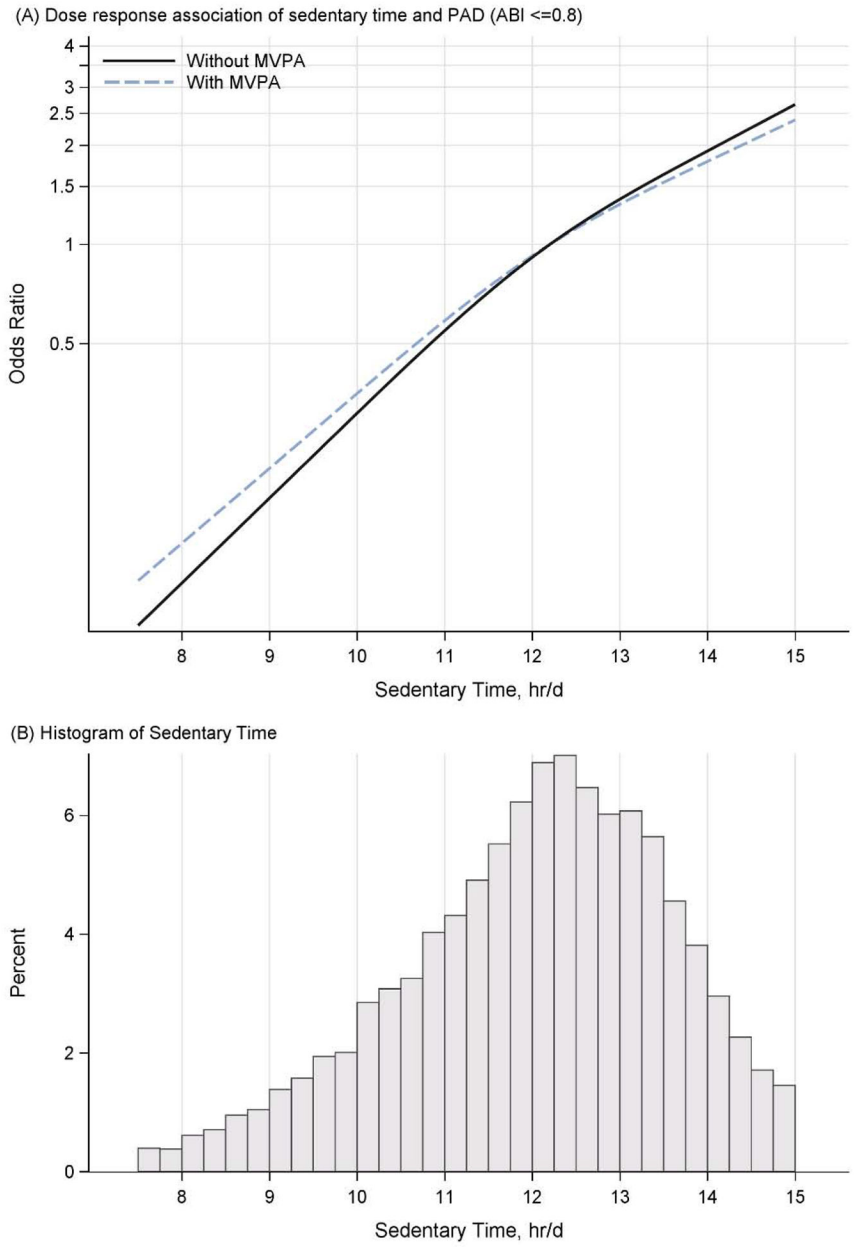

Figure 2. Continuous Dose-Response Associations of Sedentary Time and Peripheral Artery Disease (ABI ≤ 0.8) in the Hispanic Community Health Study/ Study of Latinos (2008–2011)

A, Association of Sedentary Time with PAD (ABI ≤0.8) B, Distribution of Sedentary Time (hr/d) for the HCHS/SOL cohort. All associations were estimated using multivariable restricted cubic splines logistic regression adjusting for age, sex, field center, Hispanic/ Latino background group, education, marital status, cigarette smoking, alcohol use, diet quality, hypertension, diabetes, stroke, coronary heart disease, dyslipidemia, kidney function, body mass index, leg pain with movement, arthritis and physical function (black solid line). Blue dotted line shows additional adjustment for MVPA. The reference point was set at median sedentary time (12.2 hr/d). Respective odds ratios (OR) and 95% CI for 11.2, 13.2, 14.2 and 15.2 hours per day of sedentary time were: not adjusted for MVPA 0.61

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(0.40–0.94), 1.47 (1.18–1.84), 2.05 (1.16–3.62), 2.84 (1.09–7.38); adjusted for MVPA 0.65 (0.43–0.97), 1.41 (1.10–1.81), 1.89 (0.99–3.61), 2.53 (0.86–7.39). Results were trimmed at the 1st and 99th percentiles. **Abbreviations**: ABI, Ankle brachial index; HCHS/SOL, Hispanic Community Health Study/Study of Latinos; MVPA, Moderate-to-vigorous physical activity; PAD, Peripheral artery disease.

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Table 1.

Characteristics of the HCHS/SOL (n= 7,609) by Quartiles of Sedentary Time (2008–2011)

Variable	QUARTILES OF SEDENTARY TIME*† 1 (LOW)	2	3	4 (HIGH)	p-value
Age [years], mean (95% CI)	53.2 (52.8–53.7)	55.0 (54.4–55.6)	57.3 (56.7–57.9)	59.4 (58.8–60.1)	<0.001
Gender, % (95% CI)					<0.001
Female	46.2 (42.7–49.8)	56.7 (53.4–60.0)	60.8 (57.6–63.9)	57.0 (53.9–60.1)	
Male	53.8 (50.2–57.3)	43.3 (40.0–46.6)	39.2 (36.1–42.4)	43.0 (39.9–46.1)	
Hispanic Background, % (95% CI)					<0.001
Dominican	6.3 (4.6–8.0)	6.1 (4.7–7.5)	9.3 (6.6–12.0)	16.2 (13.2–19.2)	
Central American	7.5 (5.9–9.1)	5.1 (3.9–6.2)	7.6 (6.1–9.1)	6.5 (5.1–7.9)	
Cuban	23.1 (18.3–27.9)	28.7 (23.5–33.9)	30.4 (25.8–35.1)	27.6 (22.4–32.7)	
Mexican	41.6 (37.0–46.3)	36.7 (32.1–41.3)	27.6 (23.4–31.8)	17.3 (13.9–20.8)	
Puerto Rican	15.3 (11.5–19.1)	15.5 (12.6–18.4)	17.0 (14.5–19.6)	24.7 (21.3–28.2)	
South American	3.9 (2.9–4.9)	6.1 (4.6–7.6)	6.4 (4.9–7.9)	5.4 (3.9–6.8)	
Mixed/Other	2.2 (1.3–3.2)	1.9 (0.9–2.8)	1.6 (1.0–2.2)	2.3 (1.4–3.2)	
Center, % (95% CI)					<0.001
Bronx	18.4 (14.4–22.4)	19.4 (16.1–22.6)	24.7 (20.9–28.5)	43.7 (38.3–49.1)	
Chicago	18.2 (15.1–21.2)	11.3 (9.4–13.2)	10.6 (8.6–12.5)	9.9 (8.1–11.6)	
Miami	31.8 (26.7–36.9)	38.5 (32.9–44.2)	41.4 (35.9–46.8)	35.7 (29.8–41.6)	
San Diego	31.6 (26.8–36.4)	30.8 (26.3–35.2)	23.4 (18.9–27.8)	10.7 (8.2–13.2)	
Education, % (95% CI)					0.006
Less than High School	38.9 (35.1–42.7)	36.2 (32.6–39.9)	38.4 (35.2–41.7)	45.0 (41.3–48.7)	
High School/Equivalent	22.8 (20.2–25.4)	20.5 (17.8–23.2)	22.5 (19.5–25.5)	19.0 (16.4–21.6)	
Greater than High School/Equivalent	38.3 (34.6–42.1)	43.3 (40.0–46.6)	39.1 (35.7–42.5)	36.0 (32.4–39.6)	
Marital Status, % (95% CI)					<0.001
Single	17.8 (14.2–21.4)	18.3 (15.8–20.8)	15.8 (13.5–18.1)	18.1 (15.3–20.9)	
Married or living with a partner	59.0 (55.0–63.1)	54.3 (50.7–58.0)	53.7 (50.3–57.1)	45.0 (41.0–48.9)	
Separated, divorced, or widow(er)	23.1 (20.1–26.2)	27.4 (24.4–30.3)	30.5 (27.3–33.7)	36.9 (33.0–40.9)	
Cigarette Use, % (95% CI)					0.285
Never	52.6 (48.8–56.4)	52.2 (48.7–55.6)	54.4 (50.8–57.9)	55.2 (51.7–58.8)	
Former	24.1 (20.9–27.4)	26.3 (23.2–29.5)	26.4 (23.3–29.5)	26.3 (23.4–29.2)	
Current	23.3 (19.8–26.7)	21.5 (18.8–24.2)	19.3 (16.2–22.3)	18.5 (15.8–21.1)	
Alcohol Use, % (95% CI)					<0.001
Never	18.9 (15.4–22.3)	22.5 (19.5–25.5)	25.7 (22.8–28.6)	25.1 (22.0–28.3)	
Former	30.0 (26.4–33.7)	30.3 (27.4–33.3)	35.2 (31.8–38.5)	35.3 (31.838.8)	
Current	51.1 (47.3–55.0)	47.2 (43.7–50.6)	39.1 (36.1–42.2)	39.6 (35.8–43.4)	
AHEI-2010, mean (95% CI)	50.6 (50.0–51.2)	50.3 (49.7–51.0)	50.3 (49.6–50.9)	49.5 (49.0–50.0)	<0.001
Diabetes, % (95% CI)					<0.001
Normal	30.5 (27.0–34.0)	30.6 (27.6–33.5)	24.1 (21.5–26.6)	18.6 (15.9–21.3)	
Impaired glucose tolerance	47.2 (43.8–50.5)	49.3 (45.9–52.6)	47.1 (43.7–50.6)	42.9 (39.4–46.5)	
Diabetes	22.4 (19.4–25.4)	20.2 (17.7–22.7)	28.8 (25.6–31.9)	38.5 (35.1–41.9)	

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Variable	QUARTILES OF SEDENTARY TIME*†				p-value
	1 (LOW)	2	3	4 (HIGH)	
Stroke, % (95% CI)	1.3 (0.6–2.1)	1.9 (0.9–3.0)	2.0 (1.1–2.9)	4.2 (2.8–5.6)	0.001
Hypertension, % (95% CI)	33.9 (30.6–37.2)	37.4 (34.4–40.5)	44.7 (41.4–47.9)	52.3 (48.9–55.8)	<0.001
Coronary Heart Disease, % (95% CI)	5.6 (4.3–7.0)	8.3 (6.6–10.1)	8.3 (6.8–9.9)	15.9 (13.3–18.5)	<0.001
Dyslipidemia, % (95% CI)	43.5 (39.8–47.3)	42.7 (39.4–46.1)	46.7 (43.3–50.1)	43.5 (40.0–46.9)	0.392
Arthritis, % (95% CI)	15.7 (13.2–18.3)	22.4 (19.6–25.2)	25.1 (22.1–28.1)	29.8 (26.5–33.1)	<0.001
Leg Pain with Movement, % (95% CI)	37.9 (33.9–41.9)	40.8 (37.6–44.0)	44.7 (40.8–48.5)	52.6 (48.6–56.5)	<0.001
BMI [kg/m^2], mean (95% CI)	28.9 (28.6–29.2)	29.5 (29.2–29.9)	29.9 (29.5–30.2)	30.8 (30.4–31.2)	<0.001
eGFR [ml/min/1.73m^2], mean (95% CI)	93.1 (91.7–94.5)	90.3 (89.2–91.5)	86.8 (85.6–88.1)	82.3 (81.3–83.4)	<0.001
SF-12 physical function, mean (95% CI)	49.2 (48.5–49.9)	48.5 (47.8–49.2)	46.5 (45.7–47.4)	43.4 (42.5–44.3)	<0.001
MVPA [min/day], mean (95% CI)	37.2 (34.2–40.3)	19.5 (18.2–20.9)	13.6 (12.4–14.7)	8.4 (7.6–9.2)	<0.001

Data are presented as predicted marginal means (95% CI) or percent (95% CI). All analyses account for the complex sample design of the HCHS/SOL.

*Quartile median (range) [hr/d]: Q1: 10.1 (0.9–11.1), Q2: 11.8 (11.1–12.3), Q3: 12.8 (12.3–13.3), Q4 13.9 (13.3–16.7).

†Sedentary time was adjusted for wear time using the residuals method.

Abbreviations: ABI, ankle brachial index; AHEI-2010, Alternative Healthy Eating Index 2010; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HCHS/SOL, Hispanic Community Health Study/Study of Latinos; MVPA, moderate-to-vigorous intensity physical activity; SF-12, short form 12.

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Table 2.

Associations of Sedentary Time Quartiles and Peripheral Artery Disease (ABI ≤ 0.9) in the HCHS/SOL (2008–2011)

Sedentary Time*†	Model 1 (n=7,486)	Model 2 (n=7,421)	Model 3 (n=7,247)	Model 4 (n=7,247)
Quartile 1	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Quartile 2	0.72 (0.46–1.12)	0.73 (0.47–1.16)	0.69 (0.44–1.10)	0.64 (0.40–1.02)
Quartile 3	1.19 (0.77–1.82)	1.16 (0.75–1.79)	1.12 (0.73–1.73)	0.99 (0.64–1.53)
Quartile 4	1.49 (1.02–2.18)	1.33 (0.91–1.93)	1.28 (0.87–1.89)	1.09 (0.71–1.67)
p-overall	0.003	0.037	0.030	0.073
p-value for trend‡	0.004	0.026	0.040	0.130
# with ABI ≤ 0.9	348	344	335	335

Data are odds ratio (95% confidence interval) from logistic regression using ABI (0.9–1.4) as reference group.

*Quartile median (range) [hr/d]: Q1: 10.1 (0.9–11.1), Q2: 11.8 (11.1–12.3), Q3: 12.8 (12.3–13.3), Q4 13.9 (13.3–16.7).

†Sedentary time was adjusted for wear time using the residuals method.

‡Sedentary time treated as continuous linear variable (hr/d) in logistic regression model.

Model 1 adjusts for age, sex, center, Hispanic/Latino background, education, marital status, smoking, alcohol use, AHEI-2010.

Model 2 adjusts for Model 1 + hypertension, diabetes, stroke, CHD, dyslipidemia, eGFR and BMI.

Model 3 adjusts for Model 2 + leg pain with movement, arthritis and physical function.

Model 4 adjusts for Model 3 + MVPA.

Abbreviations: ABI, ankle brachial index; AHEI-2010, Alternative Healthy Eating Index 2010; BMI, body mass index; CI, confidence interval; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HCHS/SOL, Hispanic Community Health Study/Study of Latinos; MVPA, moderate-to-vigorous intensity physical activity.

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Table 3.

Select Odds Ratios from Non-Linear Associations Between Daily Sedentary Time and Peripheral Artery Disease (ABI ≤ 0.9) in the HCHS/SOL (2008–2011)

Sedentary Time [hr/d]*†	Model 1 (n=7,492)	Model 2 (n=7,427)	Model 3 (n=7,253)	Model 4 (n=7,253)
9.2 (−3)	0.95 (0.64–1.40)	0.99 (0.65–1.49)	1.01 (0.68–1.51)	1.22 (0.80–1.86)
10.2 (−2)	0.91 (0.73–1.15)	0.95 (0.74–1.20)	0.96 (0.76–1.22)	1.08 (0.84–1.39)
11.2 (−1)	0.91 (0.83–1.00)	0.93 (0.85–1.03)	0.94 (0.86–1.03)	0.99 (0.89–1.10)
12.2 (median)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
13.2 (+1)	1.26 (1.12–1.42)	1.20 (1.07–1.35)	1.20 (1.06–1.34)	1.16 (1.02–1.31)
14.2 (+2)	1.72 (1.30–2.27)	1.54 (1.17–2.04)	1.52 (1.15–2.01)	1.44 (1.06–1.94)
15.2 (+3)	2.36 (1.51–3.69)	1.99 (1.27–3.12)	1.94 (1.24–3.05)	1.80 (1.11–2.90)
p-overall	<0.001	0.007	0.012	0.048
p-non-linear	0.017	0.053	0.049	0.024

Data are odds ratio (95% confidence interval) from logistic regression using ABI (0.9–1.4) as reference group. Median daily sedentary time (12.2 hr/d) was set as reference point.

*Sedentary time was adjusted for wear time using the residuals method.

†Sedentary time treated as continuous non-linear variable (hr/d) in a restricted cubic spline logistic regression model with 3 knots (10^{th}, 50^{th}, and 90^{th} percentile).

Model 1 adjusts for age, sex, center, Hispanic/Latino background, education, marital status, smoking, alcohol use, AHEI-2010.

Model 2 adjusts for Model 1 + hypertension, diabetes, stroke, CHD, dyslipidemia, eGFR and BMI.

Model 3 adjusts for Model 2 + leg pain with movement, arthritis and physical function.

Model 4 adjusts for Model 3 + MVPA.

Abbreviations: ABI, ankle brachial index; AHEI-2010, Alternative Healthy Eating Index 2010; BMI, body mass index; CI, confidence interval; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HCHS/SOL, Hispanic Community Health Study/Study of Latinos; MVPA, moderate-to-vigorous intensity physical activity.

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Table 4.

Sensitivity Analysis of Associations of Sedentary Time Quartiles and Peripheral Artery Disease (ABI ≤ 0.8) in the HCHS/SOL (2008–2011)

Sedentary Time*†	Model 1 (n=7,486)	Model 2 (n=7,421)	Model 3 (n=7,247)	Model 4 (n=7,247)
Quartile 1	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Quartile 2	3.96 (1.51–10.35)	4.40 (1.61–12.04)	3.58 (1.32–9.69)	3.13 (1.17–8.37)
Quartile 3	6.40 (2.58–15.87)	6.52 (2.46–17.29)	6.77 (2.67–17.15)	5.44 (2.31–12.81)
Quartile 4	7.41 (3.25–16.87)	6.28 (2.73–14.45)	6.61 (2.84–15.40)	5.08 (2.05–12.57)
p-value for trend‡	<0.001	<0.001	<0.001	0.002
# with ABI ≤ 0.8	89	88	87	87

Data are odds ratio (95% confidence interval) from logistic regression using ABI (0.8–1.4) as reference group.

*Quartile median (range) [hr/d]: Q1: 10.1 (0.9–11.1), Q2: 11.8 (11.1–12.3), Q3: 12.8 (12.3–13.3), Q4 13.9 (13.3–16.7).

†Sedentary time was adjusted for wear time using the residuals method.

‡Sedentary time treated as continuous linear variable (hr/d) in logistic regression model.

Model 1 adjusts for age, sex, center, Hispanic/Latino background, education, marital status, smoking, alcohol use, AHEI-2010.

Model 2 adjusts for Model 1 + hypertension, diabetes, stroke, CHD, dyslipidemia, eGFR and BMI.

Model 3 adjusts for Model 2 + leg pain with movement, arthritis and physical function.

Model 4 adjusts for Model 3 + MVPA.

Abbreviations: ABI, ankle brachial index; AHEI-2010, Alternative Healthy Eating Index 2010; BMI, body mass index; CI, confidence interval; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HCHS/SOL, Hispanic Community Health Study/Study of Latinos; MVPA, moderate-to-vigorous intensity physical activity.