THE ASSOCIATION OF PHYSICAL ACTIVITY WITH PREDIABETES/TYPE 2 DIABETES AND CARDIAC AUTONOMIC FUNCTION

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ABSTRACT

Three separate studies were conducted to assess the association of physical activity with prediabetes/type 2 diabetes (pre/T2D) and cardiac autonomic function. The purpose of study 1 was to examine whether using both objectively (accelerometer) and subjectively (questionnaire) measured moderate- to vigorous-intensity physical activity (MVPA) and sedentary time (SED) improves the prediction of pre/T2D using data from the Framingham Heart Study (n=4200). Logistic regression was used to examine the odds ratio of pre/T2D in groups cross-classified by subjective and objective MVPA and SED. The findings demonstrated that low objectively measured MVPA appears more closely associated with pre/T2D risk compared to subjective measures, and there does not appear to be an additive effect of SED on pre/T2D risk after accounting for MVPA. The purpose of study 2 was to examine the effects of 3-6 months of aerobic, resistance, and combined aerobic and resistance exercise training on heart rate recovery (HRR) from three previously reported randomized trials (n=147). A repeated measures ANCOVA was used to examine differences in 1-, 2-, 3-, 4-, and 5-min HRR from pre- to post-intervention and compared to control adjusting for sex, Tanner stage, ethnicity, and training duration. The findings suggest that aerobic exercise training may be a more effective strategy for improving HRR in adolescents with overweight or obesity. The purpose of study 3 was to examine the association of MVPA or SED and pre/T2D with heart rate variability (HRV) in Hispanic adults using data from the Hispanic Community Health Study / Study of Latinos (n=11 209). Multiple linear regression models were used to examine differences in RMSSD and SDNN in groups cross-classified by MVPA or SED with pre/T2D, adjusting for age, body mass index, sex, education, nutrition,

smoking status, alcohol use, cardiovascular disease, and MVPA or SED where appropriate. Having pre/T2D, regardless of MVPA or SED, was associated with lower RMSSD and SDNN. There was an association of high HRV with high MVPA in individuals without pre/T2D, but it did not translate to individuals with pre/T2D. The association of MVPA and SED with HRV in individuals with pre/T2D requires further investigation.

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1. GENERAL INTRODUCTION

Physical activity can be measured using subjective or objective methods. However, there can be discrepancies within and between these methods of measurement (1–4), resulting in discrepancies in findings between studies. In addition, low levels of physical activity have been associated with various chronic conditions and health risk factors, including prediabetes and type 2 diabetes (pre/T2D) (5–9), obesity (10), and impaired cardiac autonomic function (11). However, the association of physical activity with these health outcomes are understudied in certain populations (e.g., pediatric populations with overweight and obesity) and ethnicities (e.g., Hispanic adults), and therefore, require further investigation. The objectives of this dissertation were: 1) to examine the association of objectively (accelerometer) and subjectively (questionnaire) measured physical activity and sedentary time (SED) with pre/T2D in adults, 2) to examine the effects of 3-6 months of aerobic, resistance, or combined aerobic and resistance exercise training on heart rate recovery (HRR) and examine the relationship of HRR with various obesity and cardiometabolic risk factors in adolescents with overweight or obesity, and 3) to examine the association of physical activity, SED, and pre/T2D with heart rate variability (HRV) in Hispanic adults.

2. REVIEW OF THE SCIENTIFIC LITERATURE

2.1. PHYSICAL ACTIVITY AND SEDENTARY TIME

2.1.1. Physical Activity and Sedentary Time Guidelines

The Canadian Society for Exercise Physiology and the American College of Sports Medicine recommend that adults engage in ≥150 minutes of moderate- to vigorous-intensity aerobic exercise per week (12–14). In addition to aerobic exercise, it is recommended that adults perform resistance exercise using major muscle groups on at least 2 days of the week (12–14). Sedentary time (SED) should also be limited to <8 hours per day (14). Adolescents should perform ≥60 minutes of moderate- to vigorous-intensity aerobic exercise per day and resistance exercise at least 3 days per week (12,13,15). Recreational screen time should be limited to ≤2 hours per day and extended periods of sitting should be limited for adolescents (15).

2.1.2. Physical Activity and Sedentary Time Measurement Methods

2.1.2.1. Subjective Methods

Physical activity can be measured using subjective methods, such as questionnaires, physical activity diaries, and behavioural observations (16). Questionnaires are commonly used to gather information on physical activity due to the fact that they are cost effective and can easily be used to gather information from large samples (16). However, the questions being used to gather physical activity information can vary greatly from one questionnaire to another. Some studies will ask participants to report on total physical activity on a typical day (17), while others will ask individuals to report on the amount of time spent performing specific types of activities, such as

occupational (18,19), leisure-time (5–7,18,19), or transport physical activity (19). This can make comparisons between research using different questionnaires challenging.

2.1.2.2. Objective Methods

Physical activity can also be measured using objective methods, such as accelerometers, pedometers, and heart rate monitors (16). Accelerometers are small electronic devices that are worn on the body and generally measure body movement in one or more axes. They have become a common tool for measuring physical activity in free-living environments (16). Most studies will require participants to wear accelerometers for 24 hours of the day and only remove the device for specific activities, such as sleeping, showering, or swimming (19–21). However, there may be differences in the way in which SED is determined using these devices. Sleep time may be captured as SED, so studies have used algorithms (22), self-reported sleep logs (23,24), or have standardized SED to a 16-hour day to differentiate between SED during waking hours versus sleep time (20,21).

2.1.2.3. Difference Between Subjective versus Objective Methods

Although both subjective and objective methods are commonly used for measuring physical activity, errors and discrepancies within and between these methods of measurement can occur. Physical activity measured using self-reported questionnaires has been observed to over- or underestimate physical activity when compared to objective methods (1–4). Since subjective methods require individuals to report on previous physical activity, they can have recall or social desirability bias,

resulting in an over- or underestimation of activity (25). Meanwhile, objective methods are more expensive than subjective methods and they may not detect all upper or lower body movements depending on their wear location. As a result, they have been shown to be limited in their ability to accurately capture certain types of activity, such as cycling (26,27) and resistance exercise (28). These devices also may not be waterproof, and consequently, cannot be used for water-based activities, such as swimming (16). Further, when cut-points and algorithms are being established for accelerometers to measure physical activity, they are typically determined using data gathered in controlled, laboratory settings using small samples of primarily healthy, normal weight individuals (27,29,30). The cut-points and algorithms used in accelerometers may not be applicable to all individuals in free-living conditions, producing inaccurate activity predictions (3). Due to the differences that have been identified between subjective and objective methods, it has been recommended that both subjective and objective methods be used in combination to gain a more complete assessment of physical activity and SED (16). Using both methods may provide unique insight into the relationship between physical activity and various health outcomes.

2.2. PREDIABETES AND TYPE 2 DIABETES

Type 2 diabetes (T2D) is a disease characterized by a progressive loss of insulin secretion from β-cells and peripheral insulin resistance in the body, resulting in insulin deficiency and hyperglycemia in the body (31,32). Prediabetes involves having blood glucose values that are higher than normal, but not high enough to be considered T2D (31,32). The chronic hyperglycemia that occurs with T2D is associated with long-term

microvascular and cardiovascular complications (31). Although insulin resistance is rarely restored to normal in these individuals, insulin resistance may be improved through weight reduction, the pharmacological treatment of hyperglycemia, and/or exercise (32). The Centers for Disease Control and Prevention has demonstrated variations in the prevalence of prediabetes and type 2 diabetes (pre/T2D) among different ethnicities, with Hispanic adults displaying a higher prevalence than non-Hispanic whites, blacks, or Asians in the United States (33).

2.2.1. Diagnostic Tests and Criteria for Prediabetes and Type 2 Diabetes

Pre/T2D can be detected and diagnosed using either fasting plasma glucose, the 2-hour plasma glucose value during a 75 g oral glucose tolerance test (OGTT), or glycated hemoglobin (HbA_{1c}) (32). HbA_{1c} reflects an individual's average glycemia over ~3 months. Prediabetes is diagnosed when one or more of the following criteria are met: fasting glucose ≥5.6 mmol/L, a 2-hour OGTT ≥7.8 mmol/L, or HbA_{1c} ≥5.7% (32). Meanwhile, an individual is diagnosed as having T2D if they have a fasting glucose ≥7.0 mmol/L, a 2-hour OGTT ≥11.1 mmol/L, or HbA_{1c} ≥6.5% (32). Diabetes Canada and the American Diabetes Association (ADA) recommend that adults with T2D maintain a HbA_{1c} of ≤7% to reduce the risk of microvascular and macrovascular complications (34,35).

2.2.2. Physical Activity and Sedentary Time Guidelines for Type 2 Diabetes

Diabetes Canada and the ADA recommend that adults with T2D engage in ≥150 minutes per week of moderate- to vigorous-intensity (>64% of a person's maximum

heart rate) or ≥75 minutes per week of vigorous-intensity (>76% of a person's maximum heart rate) aerobic exercise over at least 3 non-consecutive days of the week (36,37). Adults with T2D should also perform resistance exercise on at least 2 days of the week and should minimize the amount of time spent in SED (36,37).

2.2.3. Effects of Physical Activity and Sedentary Time on Type 2 Diabetes

Physical activity has been shown to increase glucose uptake (38,39) and decrease fasting glucose (40,41), HbA_{1c} (40,41), insulin resistance (42–44), and inflammatory markers, such as interleukin (IL)-6 (40) and IL-18 (40,41). Alternatively, increased SED has been shown to alter glucose metabolism (45) and increase inflammation (46) through independent mechanisms. While both physical activity and SED have been shown to affect various glycemic and inflammatory markers, it has not been determined if low physical activity and high SED would have an additive effect on these parameters and be associated with an increased risk of pre/T2D.

2.3. CARDIAC AUTONOMIC FUNCTION

Heart rate is regulated by the parasympathetic and sympathetic divisions of the autonomic nervous system (47). The cardiovascular center in the medulla oblongata regulates heart rate via changes in parasympathetic and sympathetic nervous system activity (47). Parasympathetic and sympathetic nervous system fibers innervate the sinoatrial node in the heart (47). Parasympathetic fibers in the vagus nerve release acetylcholine that binds to muscarinic acetylcholine receptors at the sinoatrial node, causing a decrease in heart rate (47–49). Sympathetic fibers release epinephrine and

norepinephrine that bind to β-adrenergic receptors at the sinoatrial node, causing an increase in heart rate (47–49). Cardiac autonomic function can be assessed using non-invasive methods, including heart rate recovery (HRR) and heart rate variability (HRV).

2.3.1. Heart Rate Recovery

HRR is the rate at which the heart rate decreases after the cessation of maximal exercise and can be used to assess parasympathetic reactivation and sympathetic withdrawal following exercise (50–52). Parasympathetic reactivation is considered responsible for HRR during the first minute following exercise cessation, while a combination of parasympathetic reactivation and sympathetic withdrawal are associated with HRR at 2 to 5 minutes post-exercise (53,54). A delayed HRR after exercise has been associated with an increased risk of all-cause mortality and sudden cardiac death (52,55). Specifically, a 1-min HRR of less than 15 bpm has been associated with an elevated risk of mortality in adults (52). A delayed HRR has also been observed in individuals with certain chronic conditions, including T2D (56) and obesity (57–59).

2.3.1.1. Effects of Physical Activity on Heart Rate Recovery

Increased physical activity has been associated with a faster HRR (11). Physical activity has been shown to improve the balance and response of parasympathetic and sympathetic activity, resulting in a faster HRR (53,54). Improvements in HRR in healthy adults have been observed following aerobic (60) and resistance (61) exercise training. The effects of physical activity on HRR have also been examined in individuals with overweight or obesity. Twelve to 24 weeks of aerobic exercise has resulted in a faster HRR in adults with overweight or obesity (62–64). One study examined the effects of 6

weeks of aerobic and resistance training on HRR and observed a faster HRR following aerobic, but not resistance exercise, in middle-aged women with obesity (65). Meanwhile, HRR improved following 12 weeks of combined aerobic and resistance training in adults with obesity in a separate study (66). The effects of physical activity on HRR in pediatric populations with overweight or obesity is less examined. In one study, children with obesity completed 16 weeks of exercise training with a hypocaloric diet and displayed a faster HRR at 1 min post-exercise following the intervention, while no changes in HRR were observed in children on a hypocaloric diet alone (67). The limited research that exists in individuals with overweight or obesity displays improvements in HRR following exercise, but most of these studies were conducted in adults performing aerobic exercise (62–64). More research needs to be done to examine the effects of other forms of exercise training, such as resistance training or combined aerobic and resistance training, on HRR in both adult and pediatric populations with overweight and obesity.

2.3.2. Heart Rate Variability

HRV is the beat-to-beat variation in time of consecutive heartbeats or R wave to R wave (NN) intervals in milliseconds (48). HRV represents the balance between parasympathetic and sympathetic activity on the sinoatrial node, and can be used to assess autonomic function (48). HRV can be analyzed in both the time domain and frequency domain (48,68). Reduced HRV is associated with chronic heart failure (69), hypertension (70), fibromyalgia (71), and pre/T2D (72–74), and has been associated with an increased risk of cardiac events and mortality in adults (75–77). Ethnic

differences in HRV have been observed; however, the findings are limited and conflicting (78,79).

2.3.2.1. Time Domain Methods

Time domain parameters assess the change in normal NN intervals over time (68). Some of the most frequently used time domain parameters are the square root of the mean squared successive differences between adjacent NN intervals (RMSSD), the standard deviation of all NN intervals (SDNN), and the percentage of successive interval differences larger than 50 ms (PNN50) (48,68). These parameters are markers of parasympathetic (or vagal) modulation (68). Although these and frequency domain parameters are highly correlated, the Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology have recommended using RMSSD over other HRV measurements, because it has better statistical properties (48).

2.3.2.2. Frequency Domain Methods

Frequency domain, or power spectral analysis, assesses the frequency at which the length of the NN interval changes (68). In a typical heart rate power spectral density curve, three main frequency bands can be observed: very low frequency (VLF), low frequency (LF), and high frequency (HF) (48,68). VLF bands are defined as $\leq$0.04 Hz, LF bands are defined as 0.04-0.15 Hz, and HF bands are defined as 0.15-0.4 Hz (48,68). Parasympathetic activity is considered responsible for the HF bands, while both parasympathetic and sympathetic activity are considered to be responsible for the LF

bands (48,68). The LF/HF ratio can be used to assess sympathovagal balance, primarily providing an indication of sympathetic activity (68). Meanwhile, the physiological mechanisms responsible for the VLF bands remain unknown (48,68).

2.3.2.3. Effects of Physical Activity and Sedentary Time on Heart Rate Variability

Higher physical activity has been associated with increased HRV (80,81). Research has demonstrated that HRV can be improved through physical activity in healthy adults (82–85). One study was conducted to examine the effects of physical activity on Hispanic adults. In a clinical trial, 20 inactive Hispanic adults completed either 12 weeks of moderate-intensity aerobic training or high-intensity interval training (HIIT) (86). The HIIT group displayed significant improvements in SDNN following the 12 weeks of training, demonstrating the beneficial effects of physical activity on HRV in this population (86). However, more research needs to be done to better understand ethnic differences in HRV and the association of physical activity with HRV in Hispanic adults.

Prolonged, uninterrupted bouts of sitting have been associated with decreased HRV (87,88). While one study observed an association between increased occupational sitting with decreased HRV (89), a similar association between SED and HRV was not observed in other studies (90–92). Further, the association of SED and HRV has not yet been examined in Hispanic adults.

2.4. SUMMARY

It is recommended that adults, including those with T2D (36,37), engage in ≥150 minutes of moderate- to vigorous-intensity aerobic exercise per week and resistance

exercise on ≥2 days per week (12–14). Physical activity provides many health benefits, including decreased fasting glucose (40,41), HbA_{1c} (40,41), insulin resistance (42–44), and inflammatory markers (40,41), and increased glucose uptake (38,39), HRR (60–67), and HRV (82–86). In addition, SED should be limited to <8 hours per day (14). High SED may alter glucose metabolism (45), increase inflammation (46), and has been associated with decreased HRV (87,88). Subjective or objective methods can be used to measure physical activity and SED, but discrepancies have been observed within and between methods (1–4). Consequently, it has been recommended that both subjective and objective methods be used to gain a more complete assessment of physical activity and SED. Furthermore, the additive effects physical activity and SED in relation to certain health outcomes, such as T2D, have not been examined.

A delayed HRR has been associated with an increased risk of all-cause mortality and sudden cardiac death (52,55) and has been observed in individuals with obesity (57–59). Physical activity can improve HRR in these individuals (62–67). However, most of these studies have been conducted in adults performing aerobic exercise (62–64). The effects of other forms of exercise training, such as resistance training or combined aerobic and resistance training, on HRR in pediatric populations with overweight and obesity requires further examination.

Reduced HRV has been associated with an increased risk of cardiac events and mortality in adults (75–77) and is associated with chronic heart failure (69), hypertension (70), fibromyalgia (71), and pre/T2D (72–74). Ethnic differences in HRV exist, but the findings are limited and conflicting (78,79). In addition, physical activity has been shown to improve HRV in adults (82–85), but limited research has been conducted in Hispanic

adults (86). Further, the association of SED and HRV in Hispanic adults has not been examined. Hispanic adults also display a higher prevalence of pre/T2D in the United States compared to other ethnicities (33). Therefore, the association of physical activity or SED and pre/T2D with HRV in Hispanic adults requires further investigation.

3. MANUSCRIPT 1

The association of objectively and subjectively measured physical activity and sedentary time with prediabetes and type 2 diabetes in adults: A cross-sectional study in Framingham Heart Study cohorts

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3.1. ABSTRACT

The purpose of this study was to examine whether using both objectively (accelerometer) and subjectively (questionnaire) measured moderate- to vigorous-intensity physical activity (MVPA) and sedentary time (SED) improves the prediction of prediabetes and type 2 diabetes (pre/T2D) using data from the Framingham Heart Study (n=4200). Logistic regression was used to examine the odds ratio of pre/T2D in groups cross-classified by subjective and objective MVPA and SED. Less than half of participants fell into concordant categories of MVPA and SED using subjective and objective measures, with 7.0-9.4% of participants in the extreme discordant categories of high-low or low-high subjective-objective MVPA or SED. Low objective MVPA, regardless of subjective MVPA status, was associated with a higher prevalence of pre/T2D (P<0.05). When cross-classifying by MVPA and SED, the majority of participants fell into concordant categories of MVPA-SED, with <4% of participants in the extreme discordant categories of MVPA-SED. Low objective MVPA, regardless of objective SED, was associated with a higher prevalence of pre/T2D (P<0.05). These findings suggest that low objectively measured MVPA appears more closely associated with pre/T2D risk compared to subjective measures, and there does not appear to be an additive effect of SED on pre/T2D risk after accounting for MVPA.

Keywords: physical activity, sedentary time, prediabetes, type 2 diabetes, questionnaire, accelerometer

3.2. INTRODUCTION

Physical activity can be measured using subjective methods (e.g., questionnaires, physical activity diaries, behavioural observations) and objective methods (e.g., accelerometers, pedometers, heart rate monitors) (16). Although subjective and objective activity measurement methods are correlated, there are differences between the measures and limitations to the use of each measure. Self-reported methods have been shown to over- or underestimate physical activity when compared to objective methods (1–4). Subjective methods can have recall or social desirability bias that results in an over- or underestimation of activity (25), while the cut-points and algorithms used in accelerometers to objectively measure physical activity may not be applicable to all individuals in free-living conditions, producing inaccurate activity predictions (3). Consequently, it has been recommended that both subjective and objective methods be used in combination to gain a more complete assessment of physical activity (16).

Physical activity and sedentary time (SED) have been associated with various health conditions, including prediabetes and type 2 diabetes (pre/T2D) (5–9,22–24,93,94). However, previous studies have only used either subjective or objective methods to measure participants' physical activity and SED, and the combination of subjectively and objectively measured physical activity and SED in relation to pre/T2D has yet to be examined. Thus, the objective of the current study was to examine the association of objectively (accelerometer) and subjectively (questionnaire) measured physical activity and SED with pre/T2D in adults.

3.3. METHODS

3.3.1. Study Population

A retrospective, cross-sectional study was performed using data from the Framingham Heart Study (FHS) Offspring, Generation 3, New Offspring Spouse, Omni 1, and Omni 2 cohorts (95). Data from examination 9 (2011-2014) in the Offspring cohort, examination 2 (2008-2011) in the Generation 3 cohort, examination 2 (2008-2011) in the New Offspring Spouse, examination 4 (2011-2014) in the Omni 1 cohort, and examination 2 (2009-2011) in the Omni 2 cohort was used for analysis as these were the only examination cycles that contained objective physical activity data. Demographic, health, and physical activity data were gathered from a total of 10 070 participants from the 5 cohorts. Participants were excluded from analysis if they were missing activity data or wore accelerometers for <10 hours a day for at least 4 days (n=5846), were missing glycemic data (n=3764), or were missing covariate data (age, body mass index (BMI), sex, smoking status, alcohol use) (n=3752), leaving a final sample of 4200 participants for analysis. All participants provided written informed consent prior to participation in the study. Limited data access was obtained through the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH). This manuscript was prepared using research materials obtained from the NHLBI Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the FHS investigators or the NHLBI. This current study was approved by the York University Research Ethics Board. In order to reduce confirmation bias and opposing evidence, there were no specific hypotheses generated for this study.

3.3.2. Demographics

Participants were asked to report their age, sex, smoking status, and alcohol status. Participants self-identified as male or female. If participants reported smoking cigarettes, pipes, or cigars within the past month, they were categorized as being a current smoker; otherwise, they were categorized as a non-smoker. If participants reported drinking beer, wine, or liquor/spirits at least once a month within the past year, they were categorized as a current drinker; otherwise, they were categorized as a non-drinker.

3.3.3. Anthropometrics

At the in-clinic examination, weight was measured using a scale and recorded to the nearest pound (96,97). Height was measured using a stadiometer and recorded to the nearest ¼ inch (96,97). Height and weight measurements were used to calculate BMI using the following equation: BMI = weight (kg) / [height $(m)^2$].

3.3.4. Physical Activity & Sedentary Time

3.3.4.1. Subjective Physical Activity & Sedentary Time

Physical activity and SED information was gathered using a questionnaire at the in-clinic examination. Participants were asked how many hours were spent sitting and performing light activity, moderate activity, and heavy activity on a typical day (i.e., most days of the week) over the past year (98,99). Sitting time was used to establish subjective SED per day, the sum of time spent performing moderate and heavy activity was used to establish subjective moderate- to vigorous-intensity physical activity

(MVPA) per day, and the total time spent performing heavy activity was used to establish vigorous-intensity physical activity (VIGPA) per day.

3.3.4.2. Objective Physical Activity & Sedentary Time

Participants were also given an omni-directional accelerometer (Actical, model #198-0200-00, Philips Respironics, Murrysville, PA, USA) to wear on their right hip for 8 days following the in-clinic examination (100,101). Participants in the Generation 3, New Offspring Spouse, and Omni 2 cohorts were instructed to wear the device for 24 hours per day and to remove it while bathing or swimming. Participants in the Offspring and Omni 1 cohorts were instructed to wear the device during waking hours and to remove it while sleeping, bathing, or swimming.

Accelerometer data was included in the analysis if the device was worn for ≥10 hours a day for at least 4 days. Accelerometer data was analyzed using established methods (20,21) with MVPA defined as >1486 counts/min (27,30), VIGPA defined as >2779 counts/min (27,30), and SED defined as <200 counts/min (102). SED was standardized to a 16-hour day from 6 AM to 10 PM. Accelerometer data was used to establish objective MVPA per day, objective VIGPA per day, objective SED per day, and total steps per day.

3.3.5. Glycemia

At the in-clinic examination, participants underwent phlebotomy from an antecubital vein while in the supine position following a 12-hour, overnight fast (96,97). Blood samples were stored at -80°C until assay (96,97). Blood samples were used to

determine fasting glucose and glycated hemoglobin (HbA_{1c}). Since only 8.2% (n=346) of participants were categorized as having T2D, participants with pre/T2D were pooled together to form a larger group of individuals with high-risk glucose to use for analysis. Participants were classified as having pre/T2D if their fasting glucose was ≥5.6 mmol/L, HbA_{1c} was ≥5.7%, or if they were taking antidiabetic medication (32).

3.3.6. Statistical Analysis

Participant characteristics were stratified by pre/T2D status. T-tests and chi-square tests were used to determine group differences between individuals with and without pre/T2D for continuous and categorical characteristics, respectively.

Participants were divided into tertiles (low, moderate, and high) for subjective and objective MVPA, VIGPA, and SED. The subjective and objective groups were cross-classified to produce nine subjective-objective MVPA, VIGPA, and SED groups, with the high subjective-high objective group used as the referent group. In addition, the MVPA and SED groups were cross-classified to produce nine subjective MVPA-SED and objective MVPA-SED groups, with the high MVPA-low SED group used as the referent group.

Logistic regression models were used to examine the odds ratio of pre/T2D in the cross-classified subjective and objective activity groups. A logistic regression model was also used to examine the odds ratio of pre/T2D with total steps per day. The referent group was >10 000 steps per day for this model. All models were adjusted for age, BMI, sex, smoking status, and alcohol use. All statistical analyses were performed using SAS

statistical software (version 9.4; SAS Institute, Cary, NC) with significance defined at $P<0.05$.

3.4. RESULTS

3.4.1. Participant Characteristics

Demographic characteristics, health characteristics, and objective and subjective physical activity stratified by pre/T2D status are presented in **Table 1**. Based on objective physical activity measurements, individuals with pre/T2D accumulated less steps (7322 ± 3829 versus 8275 ± 3803 steps/day), less MVPA (20.1 ± 21.9 versus 27.5 ± 22.6 min/day), less VIGPA (1.1 ± 5.9 versus 2.4 ± 7.3 min/day), and more SED (801.0 ± 64.0 versus 785.6 ± 60.6 min/day) than individuals without pre/T2D ($P<0.0001$). However, there was no significant difference in MVPA, VIGPA, or SED between groups from subjective measurements ($P>0.05$).

Table 1. Participant Characteristics. Demographic characteristics, health characteristics, and objective (accelerometer) and subjective (questionnaire) physical activity data stratified by prediabetes/type 2 diabetes (T2D) status. Data are presented as mean ± SD or frequency (%). *P* values are displayed for comparison of the Prediabetes or T2D group and the No Prediabetes or T2D group.

Variable	Prediabetes or T2D (n = 1910)	No Prediabetes or T2D (n = 2290)	*P* value
Demographic Characteristics			
Age (years)	59.3 ± 12.7	50.4 ± 12.9	*<0.0001*
Male (*n*, %)	1037 (54)	904 (39)	*<0.0001*
BMI (kg/m^2)	29.2 ± 5.5	26.2 ± 4.7	*<0.0001*
Health Characteristics			
Smoking Status (*n*, %)	168 (9)	186 (8)	0.43
Alcohol Use (*n*, %)	1347 (71)	1840 (80)	*<0.0001*
Glycemic Characteristics			
Fasting Glucose (mmol/L)	6.0 ± 1.3	5.0 ± 0.3	*<0.0001*
HbA_{1c} (%)	5.9 ± 0.6	5.3 ± 0.2	*<0.0001*
Objective Physical Activity Data			
Total Steps/day	7322 ± 3829	8275 ± 3803	*<0.0001*
MVPA min/day	20.1 ± 21.9	27.5 ± 22.6	*<0.0001*
VIGPA min/day	1.1 ± 5.9	2.4 ± 7.3	*<0.0001*
SED min/day [standardized to 6 AM-10 PM]	801.0 ± 64.0	785.6 ± 60.6	*<0.0001*
Longest Sedentary Bout (min)	114.5 ± 58.1	110.2 ± 51.2	*0.01*
Accelerometer Wear Time (min)	860.1 ± 113.3	892.7 ± 105.2	*<0.0001*
Subjective Physical Activity Data			
MVPA min/day	260.6 ± 164.6	260.5 ± 160.7	0.99
VIGPA min/day	63.0 ± 91.2	62.7 ± 80.9	0.89
SED min/day	449.0 ± 195.9	438.6 ± 196.5	0.09

BMI, body mass index; HbA_{1c}, glycated hemoglobin; MVPA, moderate- to vigorous-intensity physical activity; SED, sedentary time; T2D, type 2 diabetes; VIGPA, vigorous-intensity physical activity

3.4.2. Frequency of Participants in Groups

For the cross-classified subjective-objective MVPA tertiles, participants were fairly evenly distributed across the nine groups, with each group containing between 8.7-14.7% of the total participants and 34.1% categorized into the concordant categories of low, moderate, or high subjective-objective MVPA (**Figure 1A**). The extreme discordant categories of high subjective-low objective or low subjective-high objective contained 9.4% and 8.7% of total participants, respectively (**Figure 1A**). There was slightly more variation between subjective-objective SED groups, with 7.0-16.2% of total participants distributed across the nine groups (**Figure 1B**), and 42.0% of participants categorized into the concordant categories of low, moderate, or high subjective-objective SED. Similar to MVPA, 7.0 and 7.5% of participants fell into the extreme discordant categories of high subjective-low objective or low subjective-high objective SED, respectively (**Figure 1B**).

When cross-classifying MVPA-SED tertiles using subjective and objective measures, the majority of participants fell into the concordant categories of high MVPA-low SED, moderate MVPA-moderate SED, or low MVPA-high SED groups (subjective MVPA-SED: 56.8%; objective MVPA-SED: 55.0%; **Figure 1C** and **1D**). Only a small percentage of participants fell into the extreme discordant categories of high MVPA-high SED (subjective MVPA-SED: 0.8%; objective MVPA-SED: 2.5%) or low MVPA-low SED (subjective MVPA-SED: 3.5%; objective MVPA-SED: 2.9%; **Figure 1C** and **1D**).

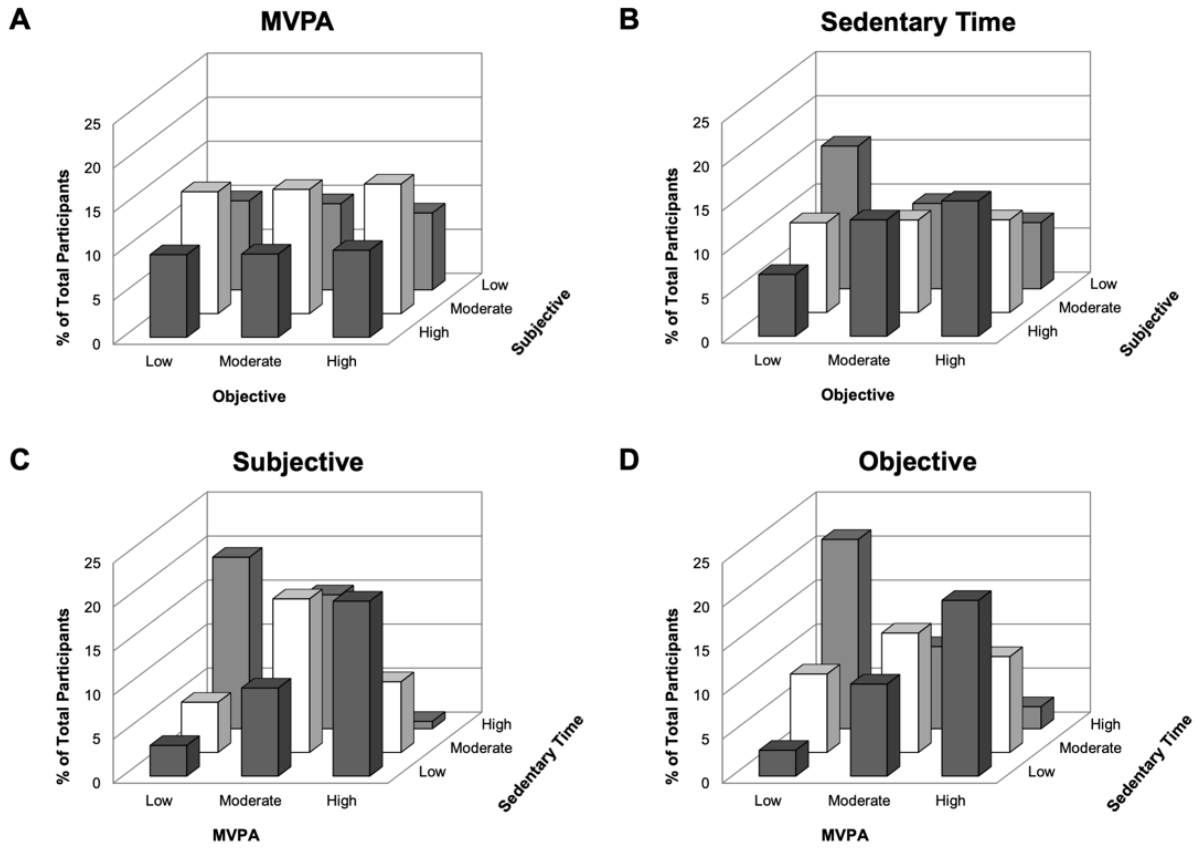

Figure 1. Percentage of total participants in the cross-classified tertiles of MVPA (A), sedentary time (B), subjective (C), and objective (D) groups (n=4200). MVPA, moderate- to vigorous-intensity physical activity.

3.4.3. Association of Physical Activity or Sedentary Time with Prediabetes & T2D

There was no interaction effect for subjective and objective MVPA or VIGPA groups on the odds of having pre/T2D (**Figure 2A**, *P*>0.05). There was a significant negative main effect of objective MVPA (*P*<0.0001) and VIGPA (*P*=0.01), but no significant effect of subjective MVPA (*P*=0.27) or VIGPA (*P*=0.44), on the odds of having prevalent pre/T2D (**Figure 2A**). Low objective MVPA and VIGPA, independent of subjective MVPA or VIGPA status, was associated with a higher prevalence of pre/T2D (**Figure 2A & Appendix A**, *P*<0.05). There were no main effects or interaction effects for subjective or objective SED on the odds of having prevalent pre/T2D (**Figure 2B & Appendix A**, *P*>0.05).

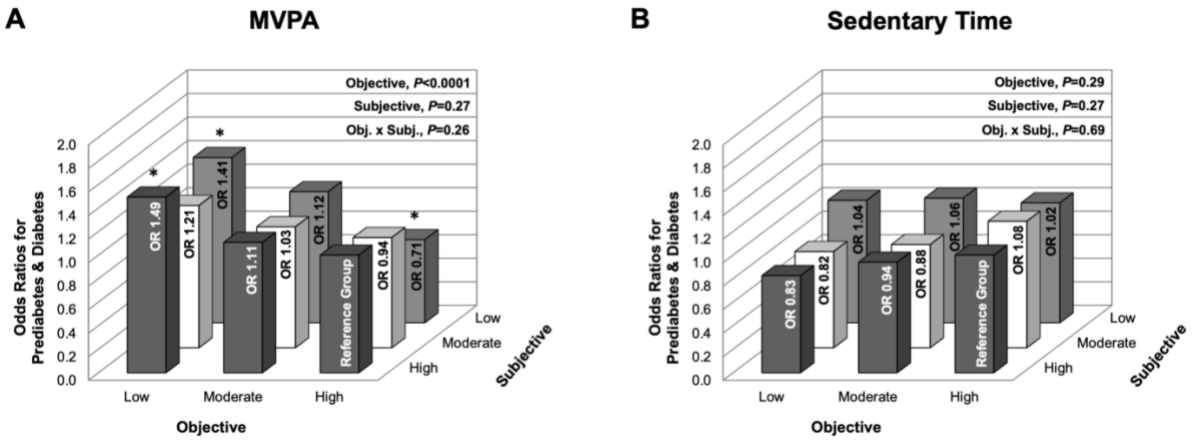

Figure 2. Odds ratios for prediabetes and type 2 diabetes by subjective (questionnaire) and objective (accelerometer) MVPA (A) and sedentary time (B) status (n=4200). **P*<0.05 compared to reference group. MVPA, moderate- to vigorous-intensity physical activity.

3.4.4. Association of Physical Activity & Sedentary Time with Prediabetes & T2D

When examining the cross-classified subjective MVPA-SED groups, there was no main effect or interaction effect of subjective MVPA and SED on the odds of having prevalent pre/T2D (**Figure 3A & Appendix B**, *P*>0.05). For the cross-classified objective MVPA-SED analysis, there was no main effect of objective SED status and no interaction effect of objective MVPA and SED on the odds of prevalent pre/T2D (**Figure 3B**, *P*>0.05). However, there was a significant negative main effect of objective MVPA on the odds of prevalent pre/T2D (**Figure 3B**, *P*=0.0002). Low objective MVPA, regardless of objective SED status, was associated with a higher prevalence of pre/T2D (**Figure 3B & Appendix B**, *P*<0.05).

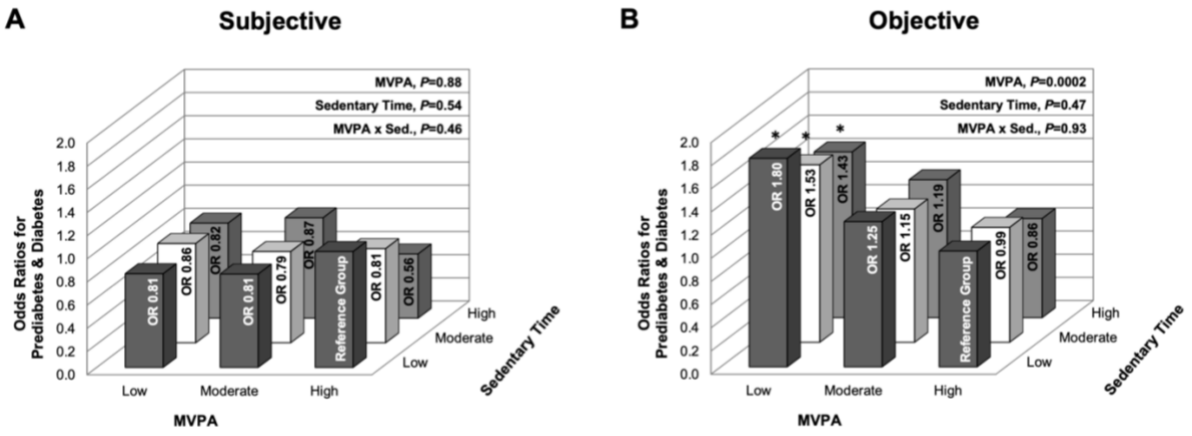

Figure 3. Odds ratios for prediabetes and type 2 diabetes by subjective (questionnaire) (A) and objective (accelerometer) (B) MVPA and sedentary time status (n=4200). **P*<0.05 compared to reference group. MVPA, moderate- to vigorous-intensity physical activity.

3.4.5. Association of Total Steps with Prediabetes & T2D

There was no association of steps per day with the odds of prevalent pre/T2D (data not shown, $P>0.05$).

3.5. DISCUSSION

The principal findings are that objectively measured low MVPA is associated with a higher prevalence of pre/T2D, but there was no association with subjectively measured MVPA or subjectively and objectively measured SED. Previous studies have recommended using both subjective and objective methods, which may provide a more complete assessment of physical activity and SED (16). However, our findings suggest that only objective physical activity measurements are significantly associated with prevalent pre/T2D. Future work should examine whether these observations hold true for other health outcomes.

Although subjective and objective activity measurement methods are correlated, there is generally substantive variation between the methods (1–3). Studies have demonstrated that self-reported physical activity can be over- or underestimated when compared to objective methods (1–4), and our study was no exception. The current analysis demonstrates that when using both subjective and objective methods, only 34.1% of participants were categorized into the same MVPA level and 42.0% of participants were categorized into the same SED level by both measures. This means that the majority of individuals may have a different physical activity or SED rating when using subjective versus objective measures. Subjective methods can have recall or social desirability bias, that can result in an over- or underestimation of past physical

activity (25). Objective measures are typically viewed to be superior; however, they are known to be limited in their ability to capture certain types of activity (e.g., cycling (26,27), resistance exercise (28), etc.). Further, the cut-points and algorithms used to predict physical activity using accelerometers are typically determined using data gathered in a controlled, laboratory setting using small samples of primarily healthy, normal weight individuals (27,29,30). As a result, their applicability to free-living individuals, particularly those with overweight or obesity, are not as clear. One study has shown that objective methods may underestimate physical activity levels in individuals with overweight or obesity (3). Consequently, studies have recommended using both subjective and objective methods to assess physical activity and SED (16).

Based on existing literature (5–9), we expected to see an association of MVPA with pre/T2D. However, our findings demonstrate that only objectively measured MVPA was associated with pre/T2D, while subjectively measured MVPA status was not significantly associated with the odds of having pre/T2D. The lack of association of subjective MVPA measures with pre/T2D may be due to differences in the questionnaires used to gather this information between studies. The current study asked participants to report the number of hours spent performing activities at light, moderate, and high intensities over 24 hours, which should, in theory, be more akin with accelerometer measures than other studies who have generally limited activity to leisure-time physical activity (5–7). Given that individuals of low socioeconomic status (SES) are less likely to perform leisure-time physical activity (103) and are more likely to have higher occupational physical activity than individuals of high SES (103), the association between leisure-time physical activity and T2D may be confounded by SES.

As a result, individuals of low SES may be represented as having low physical activity in studies that only examine leisure-time physical activity, even though their total daily physical activity may be similar to those of high SES when method of transport and occupational physical activity are taken into account. Theoretically, the context of the physical activity should not matter for T2D risk, and so an approach that captures all physical activity should be superior to restricting to certain types of activity. Together, these observations demonstrate the limitations of using certain subjective measurement methods and suggest objective methods may be more closely associated with T2D risk.

We also expected to see an association of SED with pre/T2D (5,22–24,93,94). However, our findings demonstrate that neither subjectively or objectively measured SED is associated with pre/T2D. Differences in the accelerometers and methods used to determine SED could account for the differences in objective SED findings between studies. In this study, SED was standardized to a 16-hour day from 6 AM to 10 PM to reduce the possibility of capturing sleep as SED time; however, sleep time may be captured as SED in some instances. Other studies have used algorithms or self-reported sleep logs to differentiate between SED during waking hours versus sleep (22–24). The algorithms used do not exhibit 100% accuracy in differentiating between waking hours and sleep, and self-report measures may display recall bias (22,104). Differences in the questionnaires used between studies may also contribute to discrepancies. In the current study, SED was determined using self-reported total time spent sitting over 24 hours. However, many of the previous studies have examined specific sedentary behaviours, such as watching TV, but did not adjust for diet (5,93,94). Given that TV watching is associated with an unhealthy diet (5) and diet is

shown to be strongly associated with an increased risk of T2D (105,106), it is unclear whether SED is linked directly with T2D risk or via its association with diet.

Physical activity has been observed to increase glucose uptake (38,39) and to reduce insulin resistance (42–44), while SED alters glucose metabolism (45) and increases inflammation (46) through independent mechanisms. In fact, current physical activity guidelines now incorporate SED limits (14). Thus, individuals who meet the guidelines for physical activity may be at a higher health risk if they exceed SED guidelines. Conversely, those who meet SED guidelines, but are not meeting the guidelines for physical activity, may similarly display a higher health risk compared to those achieving both the physical activity and SED recommendations. However, the predicted additive effects of physical activity and SED on pre/T2D risk was not observed in this study. It is also important to consider that MVPA and SED are well correlated (107,108). Consequently, the number of people who are active and sedentary or inactive and not sedentary are relatively rare, with less than 4% of participants falling into the extreme discordant categories of high MVPA-high SED or low MVPA-low SED in this study. Thus, the importance of studying SED as a health factor separate from physical activity is unclear. Further, whether this observation holds true for other health outcomes has yet to be determined and should be examined in future research.

The strengths and limitations of this study warrant mention. A strength of this study is the use of both subjective and objective physical activity data gathered from a large sample of adults from five cohorts in the FHS for analyses. To our knowledge, this is the first study to examine the association of both subjective and objective physical activity and SED with pre/T2D in adults. While the accelerometers used in this study are

generally considered an objective measure of physical activity, it is important to recognize that there are some subjective assumptions involved in the conversion of acceleration counts to physical activity in minutes. Further, we recognize SES and diet as being potential confounding factors in the relationship between physical activity and SED with pre/T2D. However, data on SES and diet were not available for all five of the FHS cohorts used, so we were unable to adjust for these factors in our analyses. Limitations of this study also include the use of a primarily Caucasian sample of adults associated with the original cohort of the FHS. This limits the generalizability of the results of our study, but it should not affect the internal validity. The homogeneity of our study sample in ethnicity is a benefit, because it reduces the likelihood of confounding by this factor. Finally, conducting cross-sectional analyses prevents us from inferring a causal relationship between physical activity or SED with pre/T2D.

3.6. CONCLUSION

Our findings suggest that objectively measured low MVPA appears more closely associated with pre/T2D risk as compared to subjective measures. In addition, low objective MVPA, and not objective SED status, is associated with prevalent pre/T2D. Thus, there does not appear to be an additive effect of SED beyond the effects of MVPA on pre/T2D risk. Future studies should examine whether the findings for subjectively and objectively measured physical activity and SED observed in this study hold true for other health outcomes.

3.7. ACKNOWLEDGEMENTS

RP and JLK were responsible for the data analysis. RP wrote the manuscript. All authors were involved in the study design, critical revision of the manuscript, and approval of the final manuscript.

3.8. FUNDING

There was no specific funding for this work.

3.9. DATA AVAILABILITY STATEMENT

Data analyzed during this study are available through a data sharing agreement with the National Heart, Lung, and Blood Institute of the National Institutes of Health: https://biolincc.nhlbi.nih.gov/home/

4. MANUSCRIPT 2

The effects of 3-6 months of aerobic, resistance, and combined aerobic and resistance exercise training on heart rate recovery in adolescents with overweight and obesity

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Figures: 1

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4.1. ABSTRACT

The purpose of this study was to examine the effects of 3-6 months of aerobic, resistance, and combined aerobic and resistance exercise training on heart rate recovery (HRR) and examine the relationship of HRR with various obesity and cardiometabolic risk factors in adolescents with overweight or obesity from three previously reported randomized trials (n=147). A repeated measures ANCOVA was used to examine differences in 1-, 2-, 3-, 4-, and 5-min HRR from pre- to post-intervention and compared to control adjusting for sex, Tanner stage, ethnicity, and training duration. Multiple linear regression models were used to examine the relationship between changes in HRR and changes in VO_2 peak, body weight, waist circumference, body fat percentage, total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein, very low-density lipoprotein, systolic blood pressure, and diastolic blood pressure adjusting for sex, Tanner stage, ethnicity, training duration, and training intervention. A faster 2-, 3-, 4-, and 5-min HRR was observed following all three exercise interventions compared to pre-intervention ($P<0.05$). Aerobic exercise training was the only intervention to display a significantly faster 1-, 2-, 3-, 4-, and 5-min HRR compared to a non-exercise control group ($P<0.05$). There was a negative relationship between the change in 2-, 3-, 4-, and 5-min HRR with the change in VO_2 peak ($P<0.05$), but changes in HRR were not associated with changes in most obesity or cardiometabolic risk factors with exercise ($P>0.05$). Aerobic exercise training may be a more effective strategy for improving HRR in adolescents with overweight or obesity.

Keywords: aerobic, resistance, heart rate recovery, adolescents, overweight, obesity

4.2. INTRODUCTION

Heart rate recovery (HRR) is the rate at which heart rate declines following the cessation of exercise and is a non-invasive method of determining autonomic control. A delayed HRR is a cardiovascular risk factor that has been associated with an increased risk of all-cause mortality and sudden cardiac death in adults (52,55,109). While a delayed HRR has been observed in adolescents and adults with overweight or obesity (57–59), only a few studies have been conducted in these individuals to examine the effects of regular exercise on HRR (62–65). These studies demonstrate that regular aerobic exercise can improve HRR in adults with overweight or obesity (62–65). However, it has not been established whether other forms of exercise, such as resistance training or combined aerobic and resistance training, would also be effective for improving HRR, or if these observations hold true in adolescent populations. The objective of this study was to examine the effects of 3-6 months of aerobic, resistance, or combined aerobic and resistance exercise training on HRR and examine the relationship of HRR with various obesity and cardiometabolic risk factors in adolescents with overweight or obesity.

4.3. METHODS

4.3.1. Study Population

A retrospective study was performed using data obtained from adolescents with overweight or obesity between 2007 and 2017 at UPMC Children's Hospital of Pittsburgh (Clinicaltrials.gov registration numbers: NCT00739180, NCT01323088, NCT01938950) (110–112). Two hundred and seven participants were recruited and

randomly assigned to 3 or 6 months of aerobic exercise, resistance exercise, combined aerobic and resistance exercise, or a non-exercise control group. The inclusion criteria were that participants be 12-18 years of age, with overweight or obesity (body mass index [BMI] >85th percentile) (113,114), pubertal (Tanner stages II-V), physically inactive (i.e., no structured physical activity for 3 months prior to study except school physical education classes), and non-smokers. The exclusion criteria were significant weight change (BMI >2 kg/m^2) within 3 months prior to the study, having an endocrine disorder, or taking medication affecting body composition, lipids, or glucose metabolism. Participants were excluded from analysis if they were missing all 5 min of HRR at pre-intervention (n=4), all 5 min of HRR at post-intervention (n=47), or covariate data (n=9), leaving a final sample of 147 participants for analysis. All participants provided written parental informed consent and child assent prior to participation in the study. The institutional review board from the University of Pittsburgh approved the study (110–112). To reduce confirmation bias and opposing evidence, there were no specific hypotheses generated for this study.

4.3.2. Exercise Interventions

Participants were randomly assigned to one of the following groups: aerobic exercise, resistance exercise, combined aerobic and resistance exercise, or a non-exercise control group as reported previously (110–112). The exercise groups exercised at either the downtown Pittsburgh YMCA exercise facility or the exercise laboratory at the Children's Hospital of Pittsburgh. All participants were asked to complete exercise sessions 3 times per week for 60 min per session for 3 (111,112) or 6 months (110). A

single session of aerobic exercise consisted of continuous, moderate-intensity (50-75% of peak volume of oxygen consumption [VO_2 peak]) exercise performed on a treadmill, elliptical, or cycle ergometer for 60 min. A single session of resistance exercise consisted of 2 sets (60 min) of 8 exercises (leg press, leg extension, leg flexion, chest press, latissimus pull-down, seated row, bicep curl, triceps extension) performed for 12-15 reps per set using weight machines. The resistance exercise also included modified push-ups and abdominal crunches performed to exhaustion. A single session of the combined aerobic and resistance exercise consisted of continuous, moderate-intensity (50-65% of VO_2 peak) exercise performed on a treadmill or elliptical for 30 min, 1 set (30 min) of the same 8 exercises as the resistance group, and modified push-ups and abdominal crunches performed to exhaustion. The control group (3-month control group) were asked not to participate in structured physical activity throughout the study. Average attendance at the exercise sessions was ≥89% (110–112).

4.3.3. Demographics

A certified nurse practitioner conducted a physical examination and identified pubertal development according to Tanner criteria (genital development and pubic hair) (110–112,115). Participants self-identified their ethnicity and were categorized as being of white ethnicity or non-white ethnicity for analysis.

4.3.4. Anthropometrics

Body weight was measured and recorded to the nearest 0.1 kg and height was measured and recorded to the nearest 0.1 cm using standardized equipment (110–

112,115). Height and weight measurements were used to calculate BMI using the following equation: BMI = weight (kg) / [height $(m)^2$]. Waist circumference was measured in a standing position at the superior edge of the iliac crest after a normal expiration to the nearest 0.1 cm (110,112). The average of two waist circumference measurements was used for analysis (110,112). Body fat was assessed by dual-energy X-ray absorptiometry using Lunar iDXA (GE Healthcare, Madison, Wisconsin) (116).

4.3.5. Fasting Lipids

Heated-hand arterialized venous blood was obtained for lipid analysis following a minimum 8-hour, overnight fast (115). Fasting plasma lipids were measured in the Nutrition Laboratory of the University of Pittsburgh Graduate School of Public Health, certified by the Centers for Disease Control and Prevention-National Heart, Lung, and Blood Institute Lipid Standardization Program (115).

4.3.6. Blood Pressure

Following an overnight hospital stay, blood pressure was measured in the supine position every 10 minutes between 6 AM to 7 AM before awakening with an automated sphygmomanometer (Dynamap, GE Medical Systems Information Technologies, Inc., Milwaukee, Wisconsin) by a trained nurse (115). The average of seven blood pressure measurements was used for analysis (115).

4.3.7. VO_2 Peak Test

Cardiorespiratory fitness was assessed in participants before and after the exercise intervention using a modified Balke graded maximal treadmill test with the use of standard open-circuit spirometry techniques until volitional exhaustion (110–112). The treadmill was set at a brisk but comfortable walking speed and was held constant for the duration of the test. For the first 2 minutes of the test, the treadmill grade was set at 0%, followed by a 2% grade for the third minute, and then it was increased by 1% every minute until exhaustion. Participants were considered to have attained VO_2 peak when at least two of the three following criteria were achieved: 1) a change in VO_2 <2.1 ml/kg/min with increasing exercise intensity at near-maximal treadmill stages, 2) a respiratory exchange ratio >1.05, and/or 3) heart rate >90% of age-predicted heart rate maximum. After completing the test, participants performed a 5 min cool-down on the treadmill at 2 mph and 0% grade. Heart rate was measured during the test and the 5 min cool-down (110–112). Heart rate collected during the 5 min cool-down was used to determine HRR using the following equation: $HRR_{y\ min}$ = heart rate at *y* min post-exercise - peak heart rate

4.3.8. Statistical Analysis

Baseline characteristics were stratified by exercise training group. One-way analysis of variance (ANOVA) with Tukey's honestly significant difference post-hoc tests and chi-square tests were used to determine between-group differences for continuous and categorical characteristics, respectively.

A repeated measures analysis of covariance (ANCOVA) adjusting for sex, Tanner stage, ethnicity, and training duration was used to examine differences in HRR compared to control and pre-post differences in HRR. Multiple linear regression models were used to examine the relationship between the change in HRR and the change in VO_2 peak, body weight, waist circumference, body fat percentage, total cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), systolic blood pressure, and diastolic blood pressure in all exercise interventions collapsed together. All regression models were adjusted for sex, Tanner stage, ethnicity, training duration, and training intervention. Deterministic regression imputation was used to calculate missing HRR values for analysis. All statistical analyses were performed using SAS statistical software (version 9.4; SAS Institute, Cary, NC) with significance defined at $P<0.05$.

4.4. RESULTS

4.4.1. Participant Characteristics

Participant characteristics at baseline stratified by exercise intervention group are presented in **Table 2**. There were no significant differences in age, sex, Tanner stage, ethnicity, body weight, waist circumference, body fat percentage, VO_2 peak, total cholesterol, HDL, or LDL between groups ($P>0.05$). The Aerobic + Resistance group had a significantly lower baseline BMI than the Control group ($P=0.03$) and a significantly lower baseline BMI percentile than the Aerobic, Resistance, and Control groups ($P=0.001$). The Aerobic + Resistance group had significantly lower baseline triglycerides and VLDL than the Aerobic group ($P=0.007$). The Resistance group had a

significantly lower baseline systolic blood pressure than the Control group (*P*=0.03) and a significantly lower baseline diastolic blood pressure than the Aerobic group (*P*=0.047).

Table 2. Participant Characteristics. Participant characteristics at baseline stratified by exercise intervention group. Data are presented as mean ± SD or frequency (%). *P* values are displayed for comparison between intervention groups. [a] *P*<0.05 compared to Control. [b] *P*<0.05 compared to Aerobic. [c] *P*<0.05 compared to Resistance.

Variable	Control (n = 19)	Aerobic (n = 52)	Resistance (n = 51)	Aerobic + Resistance (n = 25)	*P* value
Demographic Characteristics					
Age (years)	14.7 ± 1.7	14.7 ± 1.8	14.5 ± 1.6	14.7 ± 1.7	0.90
Male (*n*, %)	11 (58)	20 (38)	26 (51)	9 (36)	0.29
Tanner Stage, II-IV / V (*n*)	4/15	18/34	19/32	7/18	0.57
White Ethnicity (*n*, %)	8 (42)	27 (52)	21 (41)	8 (32)	0.40
Aerobic Fitness					
VO_2 peak (mL/kg/min)	28.3 ± 4.7	26.3 ± 4.6	25.6 ± 5.4	24.7 ± 4.5	0.09
Body Composition					
Body Weight (kg)	97.9 ± 14.2	95.1 ± 18.6	93.4 ± 14.0	88.7 ± 15.3	0.25
BMI (kg/m^2)	34.7 ± 4.5	33.9 ± 4.8	34.0 ± 3.2	31.4 ± 3.9[a]	*0.03*
BMI (percentile)	98.7 ± 1.2	98.2 ± 1.7	98.6 ± 1.0	97.0 ± 3.0[a,b,c]	*0.001*
Waist Circumference (cm)	110.7 ± 11.6	108.9 ± 11.8	109.2 ± 9.2	104.5 ± 11.2	0.22
Body Fat (%)	42.8 ± 7.0	41.7 ± 4.9	42.6 ± 4.6	40.7 ± 5.6	0.41
Lipids					
Total Cholesterol (mg/dL)	146.6 ± 21.4	155.1 ± 32.0	142.3 ± 24.4	143.4 ± 22.3	0.08
Triglycerides (mg/dL)	85.3 ± 36.4	115.8 ± 84.1	95.0 ± 44.3	66.1 ± 30.6[b]	*0.007*
HDL Cholesterol (mg/dL)	40.6 ± 6.6	43.7 ± 10.6	41.1 ± 7.3	45.2 ± 9.2	0.16
LDL Cholesterol (mg/dL)	88.9 ± 20.5	88.8 ± 25.3	82.2 ± 21.5	84.9 ± 24.1	0.49
VLDL Cholesterol (mg/dL)	17.1 ± 7.3	23.2 ± 16.8	19.0 ± 8.9	13.2 ± 6.1[b]	*0.007*
Blood Pressure					
Systolic BP (mmHg)	116 ± 12	112 ± 10	108 ± 11[a]	110 ± 8	*0.03*
Diastolic BP (mmHg)	60 ± 6	61 ± 6	58 ± 6[b]	60 ± 5	*0.047*

BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; VO_2 peak, peak volume of oxygen consumption

4.4.2. Heart Rate Recovery

All exercise intervention groups had a significantly faster 2-, 3-, 4-, and 5-min HRR after the intervention, with no difference in Control (**Figure 4**, $P<0.05$). The Aerobic and Resistance groups also had a significantly faster HRR at 1 min post-exercise compared to pre-intervention (**Figure 4**, $P<0.05$). However, as compared to Control, the Aerobic exercise group was the only group to display a significantly faster 1-, 2-, 3-, 4-, and 5-min HRR (**Figure 4**, $P<0.05$).

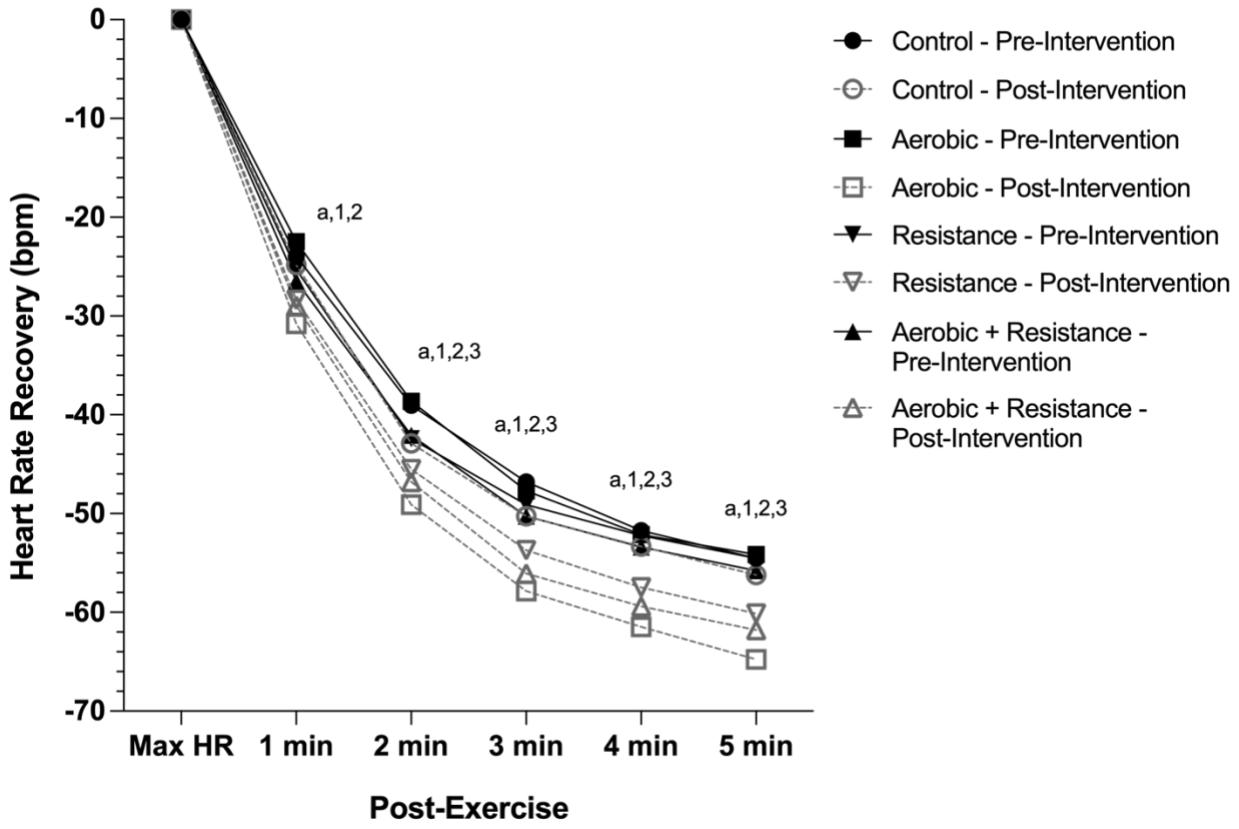

Figure 4. Heart Rate Recovery. Heart rate recovery for adolescents with overweight or obesity before and after 3 or 6 months of aerobic exercise (n=52), resistance exercise (n=51), combined aerobic and resistance exercise (n=25), or non-exercise control (n=19). Model was adjusted for sex, Tanner stage, ethnicity, and training duration. Data are presented as adjusted least squared means.

[a] *P*<0.05 Aerobic Post versus Control Post

[1] *P*<0.05 Aerobic Pre versus Post

[2] *P*<0.05 Resistance Pre versus Post

[3] *P*<0.05 Aerobic + Resistance Pre versus Post

There were no pre-post differences in Control

4.4.3. Heart Rate Recovery & Change in VO_2 Peak

There was no association between the change in 1-min HRR and the change in VO_2 peak from pre- to post-intervention with or without adjustment for covariates and intervention group (**Table 3,** *P*>0.05). There was a negative relationship between the change in 2-, 3-, 4-, and 5-min HRR with the change in VO_2 peak with adjustment for sex, Tanner stage, ethnicity, training duration, and intervention group (**Table 3,** *P*<0.0001).

Table 3. Change in Heart Rate Recovery & Change in VO_2 Peak, Body Composition, Lipids, and Blood Pressure. The association of the change in heart rate recovery with the change in VO_2 peak, body weight, waist circumference, body fat percentage, total cholesterol, triglycerides, HDL, LDL, VLDL, systolic blood pressure, and diastolic blood pressure in adolescents with overweight or obesity after 3 or 6 months of aerobic exercise (n=52), resistance exercise (n=51), or combined aerobic and resistance exercise (n=25). Models were adjusted for sex, Tanner stage, ethnicity, training duration, and training intervention.

	1-min HRR			2-min HRR			3-min HRR			4-min HRR			5-min HRR		
	β	**Std Error**	***P* value**	**β**	**Std Error**	***P* value**	**β**	**Std Error**	***P* value**	**β**	**Std Error**	***P* value**	**β**	**Std Error**	***P* value**
VO_2 Peak	-0.31	0.25	0.22	-1.06	0.21	**<0.0001**	-1.24	0.18	**<0.0001**	-1.21	0.16	**<0.0001**	-1.17	0.15	**<0.0001**
Body Weight	0.63	0.25	**0.01**	0.43	0.23	0.07	0.34	0.21	0.11	0.31	0.20	0.12	0.33	0.19	0.08
Waist Circumference	0.48	0.32	0.14	0.15	0.30	0.61	0.02	0.27	0.94	-0.08	0.25	0.76	-0.09	0.24	0.70
Body Fat Percentage	0.78	0.57	0.17	0.68	0.52	0.20	0.70	0.47	0.14	0.83	0.43	0.06	0.63	0.42	0.13
Total Cholesterol	0.01	0.07	0.93	0.003	0.06	0.96	0.01	0.05	0.91	-0.01	0.05	0.81	-0.004	0.05	0.94
Triglycerides	0.0003	0.01	0.98	-0.01	0.01	0.42	-0.003	0.01	0.84	-0.01	0.01	0.39	-0.003	0.01	0.79
HDL Cholesterol	-0.39	0.21	0.07	-0.06	0.20	0.75	-0.10	0.18	0.58	-0.19	0.17	0.25	-0.27	0.16	0.09
LDL Cholesterol	0.06	0.09	0.51	0.05	0.08	0.56	0.03	0.07	0.72	0.03	0.07	0.60	0.02	0.06	0.75
VLDL Cholesterol	0.002	0.07	0.98	-0.05	0.07	0.42	-0.01	0.06	0.84	-0.05	0.06	0.39	-0.01	0.05	0.79
Systolic BP	-0.11	0.10	0.29	-0.23	0.09	**0.01**	-0.19	0.08	**0.02**	-0.11	0.08	0.16	-0.07	0.07	0.32
Diastolic BP	-0.29	0.15	0.06	-0.31	0.14	**0.03**	-0.20	0.12	0.11	-0.15	0.12	0.19	-0.13	0.11	0.26

BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; VO_2 peak, peak volume of oxygen consumption

4.4.4. Heart Rate Recovery & Change in Obesity

There was no association between the change in HRR with the change in waist circumference or body fat percentage with or without adjustment for covariates and intervention group (**Table 3,** *P*>0.05). A positive relationship between the change in 1-min HRR and the change in body weight was observed with adjustment for covariates and intervention group (**Table 3,** *P*=0.01).

4.4.5. Heart Rate Recovery & Change in Cardiometabolic Risk Factors

No association was observed between the change in HRR with the change in total cholesterol, triglycerides, HDL, LDL, or VLDL with or without adjustment for covariates and intervention group (**Table 3,** *P*>0.05). There was a negative relationship between the change in 2- and 3-min HRR with the change in systolic blood pressure and the change in 2-min HRR with the change in diastolic blood pressure with adjustment for covariates and intervention group (**Table 3,** *P*<0.05).

4.5. DISCUSSION

To our knowledge, this is the first study to examine the effects of aerobic, resistance, and combined aerobic and resistance exercise training on HRR in adolescents with overweight or obesity**.** The principal findings are that aerobic, resistance, and combined aerobic and resistance exercise are associated with improvements in HRR after 3-6 months of training, but only aerobic exercise is associated with significant improvements in HRR when compared to a control group. A delayed HRR following exercise has been observed in individuals with overweight and

obesity (57–59) and is associated with an increased risk of mortality and sudden cardiac death in adults (52,55). Our findings suggest that aerobic training is an effective strategy for improving HRR in adolescents with overweight or obesity.

Previous studies have observed improvements in HRR following aerobic exercise training in adults with overweight or obesity (62–65). In middle-aged women with obesity, improvements in HRR were only observed following aerobic training, but not resistance training (65). Although we observed reductions in HRR in all exercise groups, only the aerobic exercise group was associated with a significantly faster HRR compared to control. These findings suggest that aerobic training may be a more effective strategy for improving HRR in adolescents with overweight or obesity.

Reduced parasympathetic activation during the first minute following exercise cessation is considered to be responsible for impaired 1-min HRR (53,54). Meanwhile, a delayed HRR during 2 to 5 minutes post-exercise is caused by reduced parasympathetic activation and a slow withdrawal of sympathetic activity through the delayed clearance of catecholamines, such as norepinephrine (53,54). Aerobic exercise can improve the balance and response of parasympathetic and sympathetic activity, resulting in a faster HRR (53,54). There is some evidence to suggest that the upregulation of nitric oxide synthase 1 in intracardiac parasympathetic ganglia may play a key role in mediating the improvements in parasympathetic function following aerobic training (117,118).

Previous research has demonstrated that a 1-min HRR of less than 15 bpm is associated with an elevated risk of mortality in adults (52). Children have been shown to display a faster 1-min HRR than adults (119), and in the current study, the mean 1-min

HRR at baseline in all intervention groups was greater than 20 bpm. Although these values are higher than the adult threshold, HRR has been shown to decline with age (120). By improving HRR earlier in life, it may delay the decrease in HRR that can occur in individuals with overweight and obesity.

In the current study, there was a negative relationship between the change in 2-, 3-, 4-, and 5-min HRR with the change in VO_2 peak following aerobic, resistance, or combined aerobic and resistance exercise training. This suggests that the change in VO_2 peak that occurs with exercise training is more closely related to the parasympathetic reactivation and sympathetic withdrawal that is associated with HRR at 2 to 5 minutes post-exercise rather than the parasympathetic reactivation alone that occurs during the first minute of HRR. Our findings further demonstrate that there was no association between the change in HRR and the change in most obesity or cardiometabolic risk factors. Similarly, a previous study involving combined aerobic and resistance exercise did not observe associations between the change in 1-min HRR with the change in most obesity or cardiometabolic risk factors in children and adolescents (121). Findings from cross-sectional research has displayed an association of HRR with various obesity and cardiometabolic factors in children, but no associations were observed in adolescents (122). This suggests that the physiological and hormonal changes occurring during adolescence may be concealing the association of HRR with these risk factors (122). Further research is required to confirm these hypotheses. In our study, an association was observed between the change in 2- and 3-min HRR with the change in systolic blood pressure and the change in 2-min HRR with the change in diastolic blood pressure. Given that blood pressure is also regulated by the autonomic

nervous system (123,124), it is logical for an association to exist between HRR and blood pressure.

The strengths and limitations of this study warrant mention. A strength of this study is the use of a large sample of adolescents with overweight or obesity. However, the study sample consisted of adolescents primarily of black or white ethnicity. Consequently, the findings of this study may not be generalizable to adolescents in other ethnic groups. While HRR has been validated as a measure of cardiac autonomic function (125), it would be useful to confirm these findings using other measures of autonomic function, such as heart rate variability (e.g., SDNN, RMSSD, etc.).

4.6. CONCLUSION

A delayed HRR following exercise is associated with an increased risk of mortality and sudden cardiac death in adults (52,55) and has been observed in individuals with overweight and obesity (57–59). Our findings suggest that aerobic exercise training may be an effective strategy for improving HRR in adolescents with overweight or obesity. The change in 2-, 3-, 4-, and 5-min HRR is negatively associated with the change in VO_2 peak following exercise training, but HRR does not appear to be associated with most obesity or cardiometabolic risk factors.

4.7. ACKNOWLEDGEMENTS

RP and JLK were responsible for the data analysis. RP wrote the manuscript. SL designed the original studies, obtained funding, and carried out the original experiments. All authors were involved in the study design, critical revision of the manuscript, and approved the final manuscript.

4.8. FUNDING

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4.9. DATA AVAILABILITY STATEMENT

Data availability is subject to approval by the principal investigator (Dr. SoJung Lee) and ethical approval from the requestor committee institution.

5. MANUSCRIPT 3

The association of physical activity, sedentary time, and prediabetes/type 2 diabetes with heart rate variability in Hispanic adults

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5.1. ABSTRACT

There is a higher prevalence of prediabetes and type 2 diabetes (pre/T2D) in Hispanic adults compared to other ethnicities. Pre/T2D has been associated with reduced heart rate variability (HRV), and increased physical activity has been associated with improved HRV. The purpose of this study was to examine the association of moderate- to vigorous-intensity physical activity (MVPA) or sedentary time (SED) and pre/T2D with HRV in Hispanic adults using data from the Hispanic Community Health Study / Study of Latinos (n=11 209). Multiple linear regression models were used to examine differences in the square root of the mean squared successive differences between adjacent NN intervals (RMSSD) and the standard deviation of all NN intervals (SDNN) in groups cross-classified by MVPA or SED and pre/T2D, adjusting for age, body mass index, sex, education, nutrition, smoking status, alcohol use, cardiovascular disease, and MVPA or SED where appropriate. Having pre/T2D, regardless of MVPA or SED, was associated with lower RMSSD and SDNN (P<0.05). High MVPA was associated with high RMSSD and SDNN in individuals without pre/T2D (P<0.05), but not in individuals with pre/T2D (P>0.05). These findings suggest that the association of high HRV with high MVPA observed in individuals without pre/T2D may not translate to individuals with pre/T2D.

Keywords: physical activity, sedentary time, prediabetes, type 2 diabetes, heart rate variability, Hispanic

5.2. INTRODUCTION

Heart rate variability (HRV) is the beat-to-beat variation in time of consecutive heartbeats or R-to-R intervals in milliseconds and is a non-invasive method of assessing autonomic function (48). The square root of the mean squared successive differences between adjacent NN intervals (RMSSD) and the standard deviation of all NN intervals (SDNN) are commonly used time domain indices of HRV (48,68). Reduced HRV has been associated with an increased risk of cardiac events and mortality in adults (75–77).

Hispanic adults have displayed a higher prevalence of prediabetes and type 2 diabetes (pre/T2D) than non-Hispanic whites, blacks, or Asians in the United States (33) and pre/T2D has been associated with reduced HRV (72–74). Physical activity has been shown to improve HRV in healthy adults (82–85). Research examining the effects of physical activity on HRV in Hispanic adults is limited. However, improvements in SDNN have been observed following 12 weeks of high-intensity interval training in these individuals (86). In addition, physical activity has been shown to reduce fasting glucose (40,41), glycated hemoglobin (HbA_{1c}) (40,41), insulin resistance (42), and inflammatory markers (40,41) in adults with pre/T2D. However, the association of physical activity or sedentary time (SED) and pre/T2D with HRV in Hispanic adults has not been examined. The objective of this study was to examine the association of moderate- to vigorous-intensity physical activity (MVPA) or SED and pre/T2D with HRV in Hispanic adults.

5.3. METHODS

5.3.1. Study Population

A retrospective, cross-sectional study was performed using data from the Hispanic Community Health Study / Study of Latinos (HCHS/SOL). The HCHS/SOL consists of data gathered from individuals of Mexican, Cuban, Puerto Rican, Dominican, Central American, and South American heritage recruited from four field centers in Miami, FL, San Diego, CA, Chicago, IL, and Bronx, NY in the United States (126). Demographic, health, and physical activity data were gathered from a total of 16,052 participants between 2008 to 2011 (126,127). Participants were excluded from analysis if they were missing subjective or objective physical activity data or wore accelerometers for <10 hours a day for at least 3 days (n=3655), glycemic data (n=632), HRV data (n=769), or covariate data (age, body mass index [BMI], sex, education, nutrition, smoking status, alcohol use, cardiovascular disease [CVD], MVPA, SED) (n=985), leaving a final sample of 11,209 participants for analysis. All participants provided written informed consent prior to participation in the study. The institutional review board at all field centers, coordinating centers, central labs, and reading centers approved the study. Limited data access was obtained through the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health. This manuscript was prepared using research materials obtained from the NHLBI Data Repository Information Coordinating Center and does not necessarily reflect the opinions or views of the HCHS/SOL investigators or the NHLBI. This current study was approved by the York University Research Ethics Board. To reduce confirmation bias and opposing evidence, there were no specific hypotheses generated for this study.

5.3.2. Demographics

Participants self-reported their age, sex, education, smoking status, and alcohol status. Participants self-identified as male or female. If participants reported receiving an associate degree, bachelor's degree, master's degree, professional degree, or doctorate degree, they were categorized as high education; otherwise, they were categorized as having low education. If participants reported smoking at least 100 cigarettes in their entire life and currently smoking daily or some days, they were categorized as being a current smoker; otherwise, they were categorized as a non-smoker. If participants reported currently drinking alcoholic beverages, they were categorized as a current drinker; otherwise, they were categorized as a non-drinker. Participants were classified as having CVD if they reported having coronary heart disease (including angina), cerebrovascular disease, carotid revascularization, myocardial infarction, stroke, or transient ischemic attack, if they reported having had a balloon angioplasty, a stent, or bypass surgery, or if they reported taking antianginal, antiarrhythmic, antiplatelet, beta blockers, cardiac glycosides, or clopidogrel medication.

5.3.3. Anthropometrics

Body weight was measured using the Tanita TBF-300A Body Composition Analyzer scale (Tanita Corporation, Tokyo, Japan) to the nearest 0.1 kg and height was measured using a wall-mounted stadiometer to the nearest cm (128). These measurements were used to calculate BMI using the following equation: BMI = weight (kg) / [height $(m)^2$].

5.3.4. Nutrition

Participants completed a 24-hour dietary recall on a weekday or weekend day (129). This data was used to calculate a score on the Alternative Healthy Eating Index (AHEI-2010), which assigns a score based on 11 components of diet (vegetables without potatoes, whole fruit, whole grains, sugar sweetened beverages and fruit juice, nuts and legumes, red/processed meat, trans fat, long-chain (n-3) fats (EPA+DHA), polyunsaturated fatty acids, sodium, alcohol). AHEI-2010 scores range from 0 to 110. Lower scores represent unhealthy eating habits, while higher scores represent healthy eating habits (129).

5.3.5. Physical Activity & Sedentary Time

5.3.5.1. Subjective Physical Activity & Sedentary Time

Physical activity and SED information was gathered using questionnaires. Participants were asked how many minutes were spent sitting or reclining (subjective SED) and performing moderate and vigorous physical activity on a typical day (subjective MVPA).

5.3.5.2. Objective Physical Activity & Sedentary Time

Participants were given an Actical accelerometer (model #198-0200-03, Philips Respironics, Murrysville, PA, USA) to wear on their right hip above the iliac crest for 7 days (127). Participants were instructed to wear the device continuously for 7 days and only remove it while swimming, showering, or sleeping.

Accelerometer data was included in the analysis if the device was worn for ≥10 hours a day for at least 3 days. Accelerometer data was analyzed using established methods (19) with SED defined as <100 counts/min (130) and MVPA defined as ≥1535 counts/min (29). Accelerometer data was used to establish objective MVPA per day and objective SED per day.

5.3.6. Glycemia

Participants were required to fast for at least 8 hours prior to attending an in-clinic examination (131,132). At the in-clinic examination, participants underwent phlebotomy from an antecubital vein while sitting upright. Plasma blood samples were collected, processed, and frozen towards the start of the in-clinic visit and 2 hours after administration of a 75 g glucose drink for an oral glucose tolerance test (OGTT). If participants did not fast for at least 8 hours, had a fasting glucose ≥8.3 mmol/L, or had been previously diagnosed with T2D, they did not complete the OGTT (131,132). Blood samples were used to determine fasting glucose, 2-hour OGTT, and HbA_{1c}. Participants with pre/T2D were pooled together to form a larger group of individuals with high-risk glucose to use for analysis. Participants were classified as having pre/T2D if their fasting glucose was ≥5.6 mmol/L, 2-hour OGTT was ≥7.8 mmol/L, HbA_{1c} was ≥5.7%, or if they were taking antidiabetic medication (32).

5.3.7. Heart Rate Variability

At the in-clinic examination, 10-second epoch HRV measurements were taken at rest while supine using a standard, 12-lead electrocardiogram (ECG) (133–135). During

the recording, participants were breathing freely while lying in the supine position and were instructed to not speak. The GE MAC 1200 electrograph (GE, Milwaukee, Wisconsin) with a 10mm/mV calibration at a speed of 25 mm/s was used to record ECG data. All ECG data was centrally processed using the GE 12-SL Marquette Version 2001 (GE, Milwaukee, Wisconsin) at the Epidemiology Cardiology Research Center in Winston Salem, North Carolina. The median duration of the RR interval across all 12 leads was used to determine HRV using the following equations for square root of the mean squared successive differences between adjacent RR intervals (RMSSD) and standard deviation of all RR intervals (SDNN):

$$\text{RMSSD} = \{ [\sum_{j=1}^{n} (RR_{j+1} - RR_j)^2] / n \}^{0.5}$$

$$\text{SDNN} = \{ [\sum_{j=1}^{n} (RR_{mean} - RR_j)^2] / (n - 1) \}^{0.5} \quad (133–135)$$

Ultra-short (i.e., 10 sec) ECG recordings have displayed high validity when compared to the gold standard 5-minute measurements for RMSSD and SDNN (136).

5.3.8. Statistical Analysis

Participant characteristics were stratified by pre/T2D status. Participants were divided into low and high groups of subjective or objective MVPA and SED using medians. The MVPA (subjective and objective) groups were cross-classified with pre/T2D status to produce four MVPA-pre/T2D groups, with the high MVPA-no pre/T2D group (healthy) used as the referent group. The SED (subjective and objective) groups were cross-classified with pre/T2D status to produce four SED-pre/T2D groups, with the low SED-no pre/T2D group (healthy) used as the referent group.

Multiple linear regression models were used to examine differences in RMSSD and SDNN in the cross-classified MVPA-pre/T2D and SED-pre/T2D groups, adjusting for age, BMI, sex, education, nutrition, smoking status, alcohol use, and CVD. MVPA models were additionally adjusted for SED, while SED models were additionally adjusted for MVPA. Sampling weights, clusters, and strata were used in all analyses. Inverse probability weighting was used to account for missing accelerometer data, as previously described (19). All statistical analyses were performed using SAS statistical software (version 9.4; SAS Institute, Cary, NC) with significance defined at $P<0.05$.

5.4. RESULTS

5.4.1. Participant Characteristics

Demographic characteristics, health characteristics, and objective and subjective MVPA and SED stratified by pre/T2D status are presented in **Table 4**. Individuals with pre/T2D were significantly higher in age, BMI, nutrition score on the AHEI-2010, prevalence of CVD, fasting glucose, 2-hour OGTT, and HbA_{1c} and lower in education than those without pre/T2D ($P<0.05$). Individuals with pre/T2D accumulated fewer minutes of objectively measured MVPA and subjectively measured SED than individuals without pre/T2D ($P<0.05$). Lower RMSSD and SDNN was also observed in individuals with pre/T2D as compared to individuals without pre/T2D ($P<0.0001$).

Table 4. Demographic characteristics, health characteristics, and objective (accelerometer) and subjective (questionnaire) physical activity and sedentary time data stratified by prediabetes/type 2 diabetes (T2D) status.

Variable	No Prediabetes or T2D	Prediabetes or T2D	*P* value
Weighted *n*	7397	7323	
Demographic Characteristics			
Age (years)	35.3 ± 0.4	46.8 ± 0.8	*<0.0001*
Male (*n*, %)	3489 (47)	3773 (52)	0.24
BMI (kg/m^2)	28.1 ± 0.3	30.9 ± 0.2	*<0.0001*
High Education (*n*, %)	1505 (20)	1145 (16)	*0.03*
Health Characteristics			
Nutrition Score	46.4 ± 0.3	48.4 ± 0.4	*<0.0001*
Smokers (*n*, %)	1381 (19)	1464 (20)	0.53
Drinkers (*n*, %)	4176 (56)	3786 (52)	0.20
Cardiovascular Disease (*n*, %)	339 (5)	1082 (15)	*<0.0001*
Glycemic Characteristics			
Fasting Glucose (mmol/L)	5.0 ± 0.0	6.3 ± 0.1	*<0.0001*
OGTT (mmol/L)*	5.5 ± 0.0	7.9 ± 0.1	*<0.0001*
HbA_{1c} (%)	5.2 ± 0.0	6.2 ± 0.1	*<0.0001*
Objective Physical Activity Data			
MVPA min/day	26.9 ± 1.0	23.1 ± 0.9	*0.002*
SED min/day	695.0 ± 6.5	701.4 ± 9.8	0.57
Accelerometer Wear Time (hr)	15.9 ± 0.1	15.7 ± 0.2	0.33
Subjective Physical Activity Data			
MVPA min/day	151.1 ± 8.8	163.6 ± 37.7	0.75
SED min/day	273.7 ± 6.0	248.3 ± 7.5	*0.006*
Heart Rate Variability			
RMSSD (ms)	46.8 ± 1.3	30.9 ± 1.0	*<0.0001*
SDNN (ms)	37.7 ± 1.0	26.1 ± 0.8	*<0.0001*

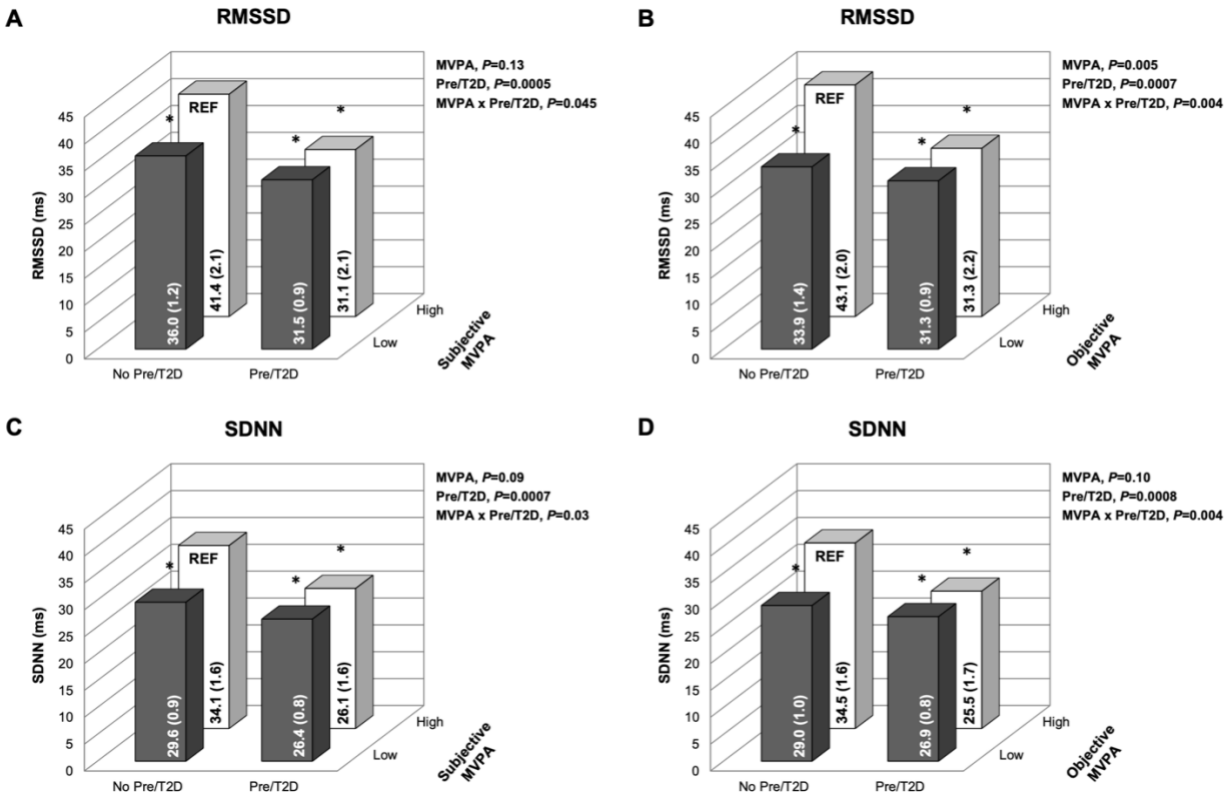
Data are presented as weighted means ± SE or weighted frequency (%). *P* values are displayed for comparison of the Prediabetes or T2D group and the No Prediabetes or T2D group.
BMI, body mass index; HbA_{1c}, glycated hemoglobin; MVPA, moderate- to vigorous-intensity physical activity; OGTT, oral glucose tolerance test; RMSSD, square root of the mean squared difference of successive NN intervals; SDNN, standard deviation of NN intervals; SED, sedentary time; T2D, type 2 diabetes
* n = 9396

5.4.2. Physical Activity & Prediabetes/Type 2 Diabetes

The association between subjective and objective MVPA and pre/T2D with HRV (RMSSD and SDNN) adjusted for age, BMI, sex, education, nutrition, smoking status, alcohol use, CVD, and SED is shown in **Figure 5**. All subjective and objective MVPA-pre/T2D groups displayed a 5.4-11.8 ms lower RMSSD than the high MVPA-no pre/T2D group with adjustment for covariates (**Figure 5A & 5B**, main effect and interaction: $P<0.05$). The low MVPA group had a 5.4-9.2 ms lower RMSSD than the high MVPA group in individuals without pre/T2D, but there was no difference in RMSSD between the low and high MVPA groups in those with pre/T2D (**Figure 5A & 5B**).

All subjective and objective MVPA-pre/T2D groups displayed a 4.5-9.0 ms lower SDNN than the high MVPA-no pre/T2D group with adjustment for covariates (**Figure 5C & 5D**, main effect and interaction: $P<0.05$). The low MVPA group displayed a 4.5-5.5 ms lower SDNN than the high MVPA group in those without pre/T2D, but no difference was observed in SDNN between the low and high MVPA groups in individuals with pre/T2D (**Figure 5C & 5D**).

Figure 5. RMSSD (A+B) and SDNN (C+D) for subjective (A+C) and objective (B+D) moderate- to vigorous-intensity physical activity (MVPA) by prediabetes/type 2 diabetes (pre/T2D) status. Models were adjusted for age, body mass index, sex, education, nutrition, smoking status, alcohol use, cardiovascular disease, and sedentary time. Data are presented as adjusted least squared means (SE). *P<0.05 compared to High MVPA-No pre/T2D.



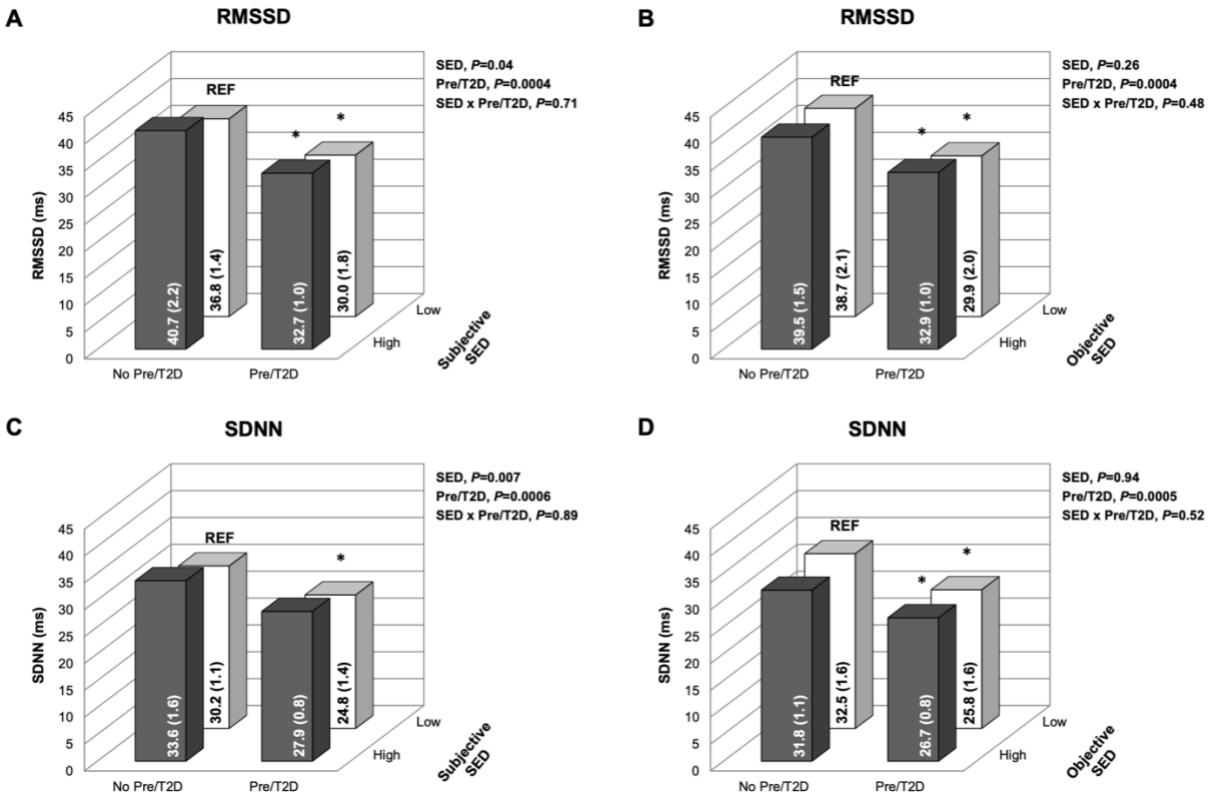
MVPA, moderate- to vigorous-intensity physical activity; RMSSD, square root of the mean squared difference of successive NN intervals; SDNN, standard deviation of NN intervals; Pre/T2D, prediabetes/type 2 diabetes

5.4.3. Sedentary Time & Prediabetes/Type 2 Diabetes

The association between subjective and objective SED and pre/T2D with HRV (RMSSD and SDNN) adjusted for age, BMI, sex, education, nutrition, smoking status, alcohol use, CVD, and MVPA is shown in **Figure 6**. The pre/T2D groups, regardless of subjective or objective SED status, displayed a 4.1-8.8 ms lower RMSSD than the low SED-no pre/T2D group with adjustment for covariates (**Figure 6A & 6B**, main effect: $P<0.05$).

The low subjective SED-pre/T2D group displayed a 5.4 ms lower SDNN than the low subjective SED-no pre/T2D group with adjustment for covariates (**Figure 6C**, main effect: $P<0.05$). The pre/T2D groups, independent of objective SED status, exhibited a 5.8-6.7 ms lower SDNN than the low objective SED-no pre/T2D group with adjustment for covariates (**Figure 6D**, main effect: $P<0.05$).

Figure 6. RMSSD (A+B) and SDNN (C+D) for subjective (A+C) and objective (B+D) sedentary time by prediabetes/type 2 diabetes (pre/T2D) status. Models were adjusted for age, body mass index, sex, education, nutrition, smoking status, alcohol use, cardiovascular disease, and moderate- to vigorous-intensity physical activity. Data are presented as adjusted least squared means (SE). *P<0.05 compared to Low sedentary time-No pre/T2D.



RMSSD, square root of the mean squared difference of successive NN intervals; SDNN, standard deviation of NN intervals; SED, sedentary time; Pre/T2D, prediabetes/type 2 diabetes

5.5. DISCUSSION

To our knowledge, this is the first study to examine the association of physical activity or SED and pre/T2D with HRV in Hispanic adults. The principal findings are that having pre/T2D, regardless of MVPA, is associated with lower RMSSD and SDNN. Having high MVPA is associated with higher RMSSD and SDNN in individuals without pre/T2D, but there is no association of high MVPA with HRV in individuals with pre/T2D. In addition, having pre/T2D, regardless of SED, is associated with lower RMSSD and SDNN. These findings were confirmed using both subjective and objective measures of MVPA and SED. Our findings suggest that pre/T2D is associated with reduced HRV, independent of MVPA or SED, in Hispanic adults. Further, high MVPA is associated with high HRV in individuals without pre/T2D, but not in those with pre/T2D.

Reduced HRV has been observed in individuals with pre/T2D (72–74) and has been associated with an increased risk of cardiac events and mortality in adults (75,77,137); however, ethnicity was not taken into consideration. Similarly, our study in Hispanic adults demonstrated that having pre/T2D was significantly associated with lower RMSSD and SDNN. Hyperinsulinemia has been associated with decreased parasympathetic activity (138) and increased sympathetic nervous system activity (139,140), which could contribute to impairments in cardiac autonomic function in individuals with pre/T2D. This may be the result of elevated levels of glycation that occur in these individuals due to chronic hyperglycemia. Glycation leads to the formation of advanced glycation end-products (141), which have been associated with increased autonomic dysfunction (142).

According to the Centers for Disease Control and Prevention, the prevalence of pre/T2D is higher among Hispanic adults than non-Hispanic whites, blacks, or Asians in the United States (33). Limited and conflicting findings have been observed when examining ethnic differences in HRV in Hispanic adults when compared to other ethnicities (78,79). However, it has been demonstrated that physical activity can improve SDNN in healthy Hispanic adults (86).

Pre/T2D and low levels of physical activity have separately been associated with decreased HRV (72–74,80) and higher HbA_{1c} (143). Our findings demonstrate that having pre/T2D, regardless of MVPA or SED, is associated with lower RMSSD and SDNN in Hispanic adults. Physical activity has been shown to improve glucose control (144,145) and lower advanced glycation end-products (146,147), but our findings suggest that higher levels of physical activity are not associated with higher cardiac autonomic function in Hispanic adults with pre/T2D. While a 0.3% lower HbA_{1c} was observed in individuals with pre/T2D and high MVPA compared to low MVPA (data not shown), these changes may not translate to improvements in autonomic function. Alternatively, greater doses of physical activity may be required in those with pre/T2D in order to offset the negative effects of pre/T2D and improve autonomic function in individuals with pre/T2D. Although no differences in HRV were observed between MVPA levels in individuals with pre/T2D, high MVPA was associated with better HRV in those without pre/T2D. Similarly, another study observed significant associations of moderate-intensity physical activity with SDNN and vigorous-intensity physical activity with RMSSD and SDNN in healthy men (81). These improvements in HRV have been attributed to improvements in the central regulation of parasympathetic output and

baroceptor sensitivity, which have been shown to improve with exercise (148). However, our findings suggest that these improvements may not translate to individuals with pre/T2D.

It has previously been demonstrated that bouts of prolonged, uninterrupted sitting result in decreased HRV (87,88). However, with the exception of one study that observed an association between increased occupational sitting with reduced RMSSD and SDNN (89), an association between SED and HRV has not been observed in other studies (90–92). In the current study, individuals with pre/T2D displayed significantly lower RMSSD and SDNN than individuals without pre/T2D and, unexpectedly, individuals with high SED displayed a higher HRV than those with low SED. However, there are several factors that need to be considered. First, the difference in HRV between the low and high subjective SED groups is much smaller than the difference observed for objective MVPA with RMSSD in the no pre/T2D group (difference of ~3 versus 9 ms). It is unclear whether this small difference in HRV with SED is clinically significant. Further, the main effect of SED was only observed with subjective SED and not objective SED. Overall, these findings demonstrate that further investigation is needed to clarify the association between SED and HRV.

Substantial variations have previously been observed between subjective and objective measures of physical activity (1–3). In a previous study, we observed that ≥58% of individuals had a different physical activity or SED rating when using a subjective (questionnaire) versus an objective (accelerometer) measure of activity (149). Due to these discrepancies, it has been recommended that both subjective and objective methods be used to gain a more complete assessment of physical activity and

SED (16). In the current study, both individuals with and without pre/T2D had a significantly higher subjective MVPA and lower subjective SED compared to objective measures. However, in our analyses for MVPA-pre/T2D and SED-pre/T2D with HRV, the findings were similar using subjective and objective methods with some small variations. The discrepancy in physical activity and SED categorization that has previously been observed (149) could contribute to the variations between the main effects of subjective and objective SED observed in the current study. Although the validity of subjective measures has been questioned, it is important to consider that questionnaires are far more economical and less labour intensive than objective measures, particularly for large datasets. Future work should continue to determine how best to use subjective and objective methods for the optimal assessment of physical activity in different populations and in relation to different health outcomes.

The strengths and limitations of this study warrant mention. A strength of this study is the use of both subjective and objective measures of physical activity for analyses. It is important to recognize that although the accelerometers used in this study are generally considered an objective measure of physical activity, the conversion of acceleration counts to physical activity in minutes involves some subjective assumptions. Frequency domain analysis could not be performed using 10-second epoch ECG measurements. It is recommended that ≥5-minute ECG recordings be used to determine HRV (48). Frequency domain indices should be examined in future research to differentiate between parasympathetic and sympathetic modulation of cardiac autonomic function. Our analytical sample was significantly older (41.0 vs. 38.0 years) and had a slightly better nutrition score (47.4 vs. 45.3) than those who were

excluded from analysis, but there were no other significant differences in variables or covariates between groups. Finally, the cross-sectional nature of the analyses prevents us from inferring a causal relationship between MVPA-pre/T2D or SED-pre/T2D with HRV.

5.6. CONCLUSION

Our findings suggest that pre/T2D is associated with lower RMSSD and SDNN, independent of MVPA or SED, in Hispanic adults. In addition, high MVPA is associated with higher RMSSD and SDNN in individuals without pre/T2D, but not in individuals with pre/T2D. This demonstrates that the high HRV associated with high MVPA observed in individuals without pre/T2D may not translate to individuals with pre/T2D.

5.7. ACKNOWLEDGEMENTS

RP and JLK were responsible for the data analysis. RP wrote the manuscript. All authors were involved in the study design, critical revision of the manuscript, and approval of the final manuscript.

5.8. FUNDING

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5.9. DATA AVAILABILITY STATEMENT

Data analyzed during this study are available through a data sharing agreement with the National Heart, Lung, and Blood Institute of the National Institutes of Health: https://biolincc.nhlbi.nih.gov/home/

6. GENERAL DISCUSSION

It has been recommended that both subjective and objective methods be used to gain a more complete assessment of physical activity and SED (16) due to the observed discrepancies between subjective and objective methods of measuring physical activity and SED in the literature (1–4). Using data from the FHS, we observed that low objective MVPA, but not subjective MVPA, was associated with pre/T2D risk. Further, there was a main effect of subjective SED on HRV in data from the HCHS/SOL, but this was not observed with objective SED. These discrepancies highlight the observed differences between subjective and objective methods when examining the association of physical activity and SED with different health outcomes. While subjective methods can be more cost effective and less labour intensive than objective methods, future research needs to consider and utilize the method that will display the most accurate association of physical activity and SED with these and other health outcomes, which our findings suggest may be objective methods.

The higher prevalence of pre/T2D in Hispanic adults (33), along with the association of low objective MVPA with the higher prevalence of pre/T2D that we observed in adults in the FHS, highlight the importance of promoting physical activity to reduce the prevalence of pre/T2D in the general population and also in racial and ethnic minorities. In order to improve the promotion and adoption of physical activity, a number of barriers need to be addressed. Individual and neighbourhood poverty have been shown to be more closely associated with decreased physical activity than race (150). Findings from longitudinal cohort studies and natural experiments have demonstrated that increased accessibility to different types of locations, access to public

transportation, and land use mix are associated with increased physical activity (151). Creating diverse residential areas where housing is mixed with commercial, public, and recreational locations can help to increase daily physical activity (151). In addition, developing more infrastructure for active modes of transportation, such as walking, cycling, and public transportation, may also help to increase physical activity levels (151). There is evidence that changing built environments to be more usable results in increased overall physical activity when compared to a control group (152). A lack of social support from friends, family, and healthcare professionals has also been identified as a barrier to physical activity in individuals with T2D (153,154). Receiving support from a general practitioner has been shown to increase minutes per week of physical activity in patients, demonstrating the importance of receiving social support from healthcare providers (155). Addressing inequities produced by poverty, changing built environments, and increasing social support are barriers that need to be addressed in order to help increase physical activity and help lower the prevalence of pre/T2D.

Our findings from the HCHS/SOL data demonstrate that pre/T2D status, regardless of physical activity levels, is associated with lower HRV in adults, and that physical activity was only associated with better HRV in those without pre/T2D. This suggests that the negative effects of hyperglycemia may have more longstanding/permanent effects on HRV that may not be reversed by physical activity. Consequently, utilizing interventions that focus on improving glycemic control and preventing T2D may be more beneficial for improving autonomic control in individuals. Nevertheless, research has demonstrated that physical activity may have other health effects and using a combination of standard care with a lifestyle intervention that

includes physical activity results in greater reductions in HbA_{1c} and 2-hour OGTT than standard care alone (156). Interventions that examine whether physical activity may be a beneficial method of improving autonomic function in individuals with pre/T2D requires further investigation.

7. SUMMARY & CONCLUSIONS

Our findings from study 1 suggest that objectively measured low MVPA appears more closely associated with pre/T2D risk as compared to subjective measures. Low objective MVPA, but not objective SED status, is associated with pre/T2D prevalence. Thus, there does not appear to be an additive effect of SED beyond the effects of MVPA on pre/T2D risk.

Findings from study 2 suggest that aerobic exercise training may be a more effective strategy for improving HRR in adolescents with overweight or obesity than resistance or a combination of aerobic and resistance exercise. The change in 2-, 3-, 4-, and 5-min HRR is negatively associated with the change in VO_2 peak following exercise training, but HRR does not appear to be associated with most obesity or cardiometabolic risk factors.

Our findings from study 3 suggest that pre/T2D is associated with lower RMSSD and SDNN, regardless of MVPA or SED, in Hispanic adults. High MVPA is associated with higher RMSSD and SDNN in individuals without pre/T2D, but not in individuals with pre/T2D. This demonstrates that the high HRV associated with high MVPA observed in individuals without pre/T2D may not translate to individuals with pre/T2D.

Future studies should determine and utilize the most accurate and appropriate method for measuring physical activity and SED when examining their association with different health outcomes, which our findings suggest may be objective methods. In addition, future work should focus on addressing inequities produced by poverty, changing built environments, and increasing social support in order to help increase physical activity levels and help lower the prevalence of T2D and CVD risk.

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9. ABBREVIATIONS

ADA	American Diabetes Association
AHEI-2010	Alternative Healthy Eating Index
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BMI	Body mass index
CVD	Cardiovascular disease
ECG	Electrocardiogram
FHS	Framingham Heart Study
HbA_{1c}	Glycated hemoglobin
HCHS/SOL	Hispanic Community Health Study / Study of Latinos
HDL	High-density lipoprotein
HF	High frequency
HIIT	High-intensity interval training
HRR	Heart rate recovery
HRV	Heart rate variability
IL	Interleukin
LDL	Low-density lipoprotein
LF	Low frequency
MVPA	Moderate- to vigorous-intensity physical activity
NHLBI	National Heart, Lung, and Blood Institute
NIH	National Institutes of Health
NN	R wave to R wave
OGTT	Oral glucose tolerance test
PNN50	Percentage of successive interval differences larger than 50 ms
Pre/T2D	Prediabetes and type 2 diabetes
RMSSD	Square root of the mean squared successive differences between adjacent RR intervals
SDNN	Standard deviation of all RR intervals
SED	Sedentary time
SES	Socioeconomic status
T2D	Type 2 diabetes
VIGPA	Vigorous-intensity physical activity
VLDL	Very low-density lipoprotein
VLF	Very low frequency
VO_2 peak	Peak volume of oxygen consumption

10. APPENDICES

Appendix A. Odds ratios (95% CI) for prediabetes and type 2 diabetes by subjective (questionnaire) and objective (accelerometer) MVPA and sedentary time status (n=4200). The high subjective-high objective group was used as the reference group. *P<0.05 compared to reference group.

		MVPA			Sedentary Time		
		Objective			Objective		
		Low	Moderate	High	Low	Moderate	High
Subjective	Low	1.41 (1.0-1.9)*	1.12 (0.8-1.5)	0.71 (0.5-1.0)*	1.04 (0.8-1.3)	1.06 (0.8-1.4)	1.02 (0.8-1.4)
	Moderate	1.21 (0.9-1.6)	1.03 (0.8-1.4)	0.94 (0.7-1.2)	0.82 (0.6-1.1)	0.88 (0.7-1.2)	1.08 (0.8-1.4)
	High	1.49 (1.1-2.1)*	1.11 (0.8-1.5)	1.00 (0.0-0.0)	0.83 (0.6-1.1)	0.94 (0.7-1.2)	1.00 (0.0-0.0)

MVPA, moderate- to vigorous-intensity physical activity

Appendix B. Odds ratios (95% CI) for prediabetes and type 2 diabetes by subjective (questionnaire) and objective (accelerometer) MVPA and sedentary time status (n=4200). The high MVPA-low sedentary time group was used as the reference group. *P<0.05 compared to reference group.

		Subjective			Objective		
		MVPA			MVPA		
		Low	Moderate	High	Low	Moderate	High
Sedentary Time	High	0.82 (0.7-1.0)	0.87 (0.7-1.1)	0.56 (0.3-1.2)	1.43 (1.1-1.8)*	1.19 (0.9-1.6)	0.86 (0.5-1.4)
	Moderate	0.86 (0.6-1.2)	0.79 (0.6-1.0)	0.81 (0.6-1.1)	1.53 (1.2-2.0)*	1.15 (0.9-1.5)	0.99 (0.8-1.3)
	Low	0.81 (0.5-1.2)	0.81 (0.6-1.1)	1.00 (0.0-0.0)	1.80 (1.2-2.8)*	1.25 (1.0-1.6)	1.00 (0.0-0.0)

MVPA, moderate- to vigorous-intensity physical activity