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Inactivity, Inflammation, and Insulin Resistance in Type 2 Diabetes and the Metabolic Syndrome

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INACTIVITY, INFLAMMATION, AND INSULIN RESISTANCE IN TYPE 2 DIABETES AND THE METABOLIC SYNDROME

By

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Both type 2 diabetes (T2D) and the the metabolic syndrome (MetS) have been shown to increase the risk of cardiovascular disease (CVD). Inflammation and insulin resistance have each been associated with the development of MetS and the onset of T2D as well as the risk of CVD. Inflammation and insulin resistance are therefore suitable targets for public health initiatives and interventions in persons at risk for or living with CVD. Physical inactivity is a major risk factor for CVD as well as MetS and T2D. Conversely, increased physical activity is associated with improved health outcomes for individuals with a high risk for developing CVD. Two possible mechanisms for the deleterious effects of inactivity on health are inflammation and insulin resistance. Researchers have hypothesized that increased adiposity and reduced fitness are partially responsible for the associations between inactivity, inflammation, and insulin resistance. However, these relationships have not been studied extensively in overweight/obese individuals, who are often unfit and sedentary. The purpose of this study was to further examine the relationship between baseline measures of walking activity and sedentary behavior, and inflammation and insulin resistance in a sample of adults with type 2 diabetes and/or metabolic syndrome. This thesis examined baseline data from participants enrolled in either of two studies of patients with T2D (n = 116) or MetS without T2D (n = 126).

Participants included low income men and women (not pregnant or nursing) between the ages of 18 and 70 who either show depressed affect (BDI > 11), and were overweight (BMI $\geq$ 27 kg/m^2) and had type 2 diabetes or had at least 3 components of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) classification of the metabolic syndrome (MetS). Structural equation modeling was used to determine if physical inactivity is associated with inflammation or insulin resistance in these conditions. Possible mediational roles of adiposity and low cardiorespiratory fitness were also examined. Additional analyses were conducted to determine if these relationships can be estimated equally in MetS and T2D conditions. Activity was indirectly related to abdominal adiposity via an indirect, positive association with cardiorespiratory fitness. Abdominal adiposity was positively related to both inflammation and insulin resistance. There were no direct associations between activity and inflammation or insulin resistance in this population. Therefore, walking may be negatively related to cardiovascular risk, insofar as it reduces abdominal adiposity.

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Chapter 1: Introduction

Diabetes and Metabolic syndrome: Epidemiology and Impact

The increasing prevalence of obesity as well as type 2 diabetes (T2D) and metabolic syndrome (MetS) is a growing public health problem both in the United States and worldwide. Approximately 34% of the US population meets criteria for MetS (American Heart Association [AHA], 2010), while 9.3% are living with T2D (Pradhan, 2007).Additionally, it is estimated that 2/3 of the American population is overweight or obese (AHA, 2010).Both T2D and the MetS have been shown to increase the risk of CVD. In fact, CVD is the leading cause of death in individuals with diabetes with heart disease and stroke accounting for about 65% of deaths in this population (AHA, 2010). Diabetics have been shown to have 2-4 times the risk of developing CVD, which includes both coronary heart disease (CHD) and stroke, than non-diabetics (Eckel, Kahn, Robertson, & Rizza, 2006). Additionally, studies have suggested the risk of myocardial infarction (MI) in diabetics is equal to that of people who have had previous MI (Haffner, Lehto, Rönnemaa, Pyörälä, & Laakso, 1998). The co-occurrence of MetS andT2D represents an even greater risk. For example, the prevalence of CVD in diabetics has been shown to increase with MetS criteria such that individuals with more risk factors have a greater risk of having or developing CVD (Guzder, Gatling, Mullee & Byrne, 2006). One study showed that among newly diagnosed diabetics, the presence of all 5 criteria for MetS was associated with almost 5 times the risk of developing CVD compared to the presence of only one of these criteria. Additionally, components of MetS at baseline predicted CVD incidence over 5 years after diagnosis (Guzder et al., 2006).

Inflammation, Metabolic Syndrome, and Diabetes

Inflammation has been implicated in both the development of the MetS and T2D (Haffner, 2003; Dandona, Aljada, & Bandyopadhyay, 2004; Pradhan, 2007). Numerous cross-sectional and longitudinal studies have shown that inflammation is associated with insulin resistance (Shoelson, Lee, & Goldfine, 2006; Paolisso, Rizzo, Mazziotti, Tagliamonte, Gambardella, Rotondi, et al., 1998; Pradhan, Buring, Manson, & Ridker, 2003; Festa, D'Agostino, Howard, Mykkänen, Tracy, & Haffner, 2000). For example, c-reactive protein(CRP) is related to fasting insulin (Pradhan et al., 2003) and insulin sensitivity (Festa et al., 2000) and tumor necrosis factor- alpha (TNF-α) is inversely related to whole body glucose disposal (Paolisso et al., 1998). Levels of inflammatory markers have been shown to increase with the presence of MetS components (Festa et al., 2000; Ridker, Buring, Cook, & Rifai, 2003). Additionally, several inflammatory markers have been linked to the development of diabetes. These include CRP (Pradhan, Manson, Rifai, Buring & Ridker, 2001; Barzilay, Abraham, Heckbert, Cushman, Kuller & Resnick et al., 2001; Thorand, B., Löwel, H., Schneider, A., Kolb, H., Meisinger, C., Fröhlich, M., et al., 2003; Spranger, J., Kroke, A., Möhlig, M., Hoffmann, K., Bergmann, M., Ristow, M., et al.,2003; Laaksonen, D., Niskanen, L., Nyyssönen, K., Punnonen, K., Tuomainen, T., Valkonen, V, et al., 2004), interleukin-6(IL-6) (Pradhan et al., 2001), fibrinogen (Festa, D'Agostino, Tracy & Haffner, 2002), plasminogen activator inhibitor (PAI-1)(Festa et al., 2002), and white blood cell count (WBC)(Schmidt, M., Duncan, B., Sharrett, A., Lindberg, G., Savage, P., Offenbacher, S., et al.,1999).

Inflammation and CVD in MetS and T2D.

Inflammation also increases the risk of CVD among diabetics and individuals with MetS (Ridker et al., 2003; Sattar, Gaw, Scherbakova, Ford, O'Reilly, Haffner, et al.,

2003; Malik. Wong, Franklin, Pio, Fairchild & Chen, 2005; Pradhan, 2007). For example, CRP predicted CHD mortality in Finnish men with diabetes over 6 years (Soinio, Marniemi, Laakso, Lehto, & Rönnemaa,2006). Additionally, increased inflammation is associated with increased risk of diabetes among individuals with MetS (Sattar et al, 2003). Inflammation is therefore a suitable target for public health initiatives and interventions in persons at risk for or living with CVD (Pearson, Mensah, Hong, & Smith, 2004).

Inactivity and Inflammation

Numerous studies have demonstrated that an inactive lifestyle is associated with increased levels of inflammation when compared to more active lifestyles(Ford, 2002; Geffken, Cushman, Burke, Polak, Sakkinen, & Tracy, 2001; Mcfarlin, Flynn, Campbell, Craig, Robinson, Stewart et al., 2006). This relationship has been examined in many population-based studies. For example, results of the NHANES III survey indicated that sedentary participants had higher risk for elevated CRP compared to those who were vigorously active. Inactivity was also associated with increased fibrinogen and decreased albumin compared to vigorous activity. Effects of light and moderate activity were insignificant (Ford, 2002). Similarly, Autenrieth et al. (2009) found that CRP and fibrinogen were inversely related to moderate and vigorous activity when compared to inactivity. Again, light activity was not associated with decreased inflammation (Autenrieth, Schneider, Döring, Meisinger, Herder, Koenig, et al., 2009). However, the INCHIANTI study reported significant differences in inflammation (CRP, fibrinogen, and erythrocyte sedimentation rate) between lightly active and sedentary individuals in a

representative sample of elderly participants (Elosua, Bartali, Ordovas, Corsi, Lauretani, & Ferrucci, 2005).

Inactivity and Inflammation in MetS and T2D

Physical inactivity has been associated with increased inflammation in both T2D and MetS. For example in a sample of persons with MetS, sedentary individuals exhibited significantly greater circulating concentrations of CRP (36%), IL-6 (30%), WBC (15%), serum amyloid A (SAA) (19%), TNF-alpha (15%), and fibrinogen (15%) compared to active participants. Additionally, moderately active participants had significantly less circulating CRP and fibrinogen when compared to sedentary participants with metabolic syndrome (Pitsavos, Panagiotakos, Chrysohoou, Kavouras, & Stefanadis, 2005). Furthermore, increasing activity has been shown to result in reduction of inflammatory markers in obese, previously sedentary individuals (Ziccardi, Nappo, Giugliano, Esposito, Marfella, Cioffi, et al.,2002; Nicklas, Ambrosius, Messier, Miller, Penninx, Loeser, et al., 2004; Lakka, T., Lakka, H., Rankinen, Leon, Rao, Skinner, et al., 2005). Taken together, these data indicate that increased engagement in physical activity may slow the development of MetS and T2D and also reduce cardiovascular risk in these populations via the reduction of inflammation.

Sedentary behavior and disease

In addition to comparing active and inactive individuals, sedentary behavior has been independently associated with all-cause mortality (Katzmarzyk, 2010) as well as with cardiovascular risk as indicated by several large scale studies. For example, the Canadian Fitness Survey (Katzmarzyk, Church, Craig, & Bouchard, 2009) reported that time spent sitting was related to mortality and cardiovascular disease in a sample of over

17,000 Canadians. The Australian Diabetes, Obesity & Lifestyle Study (AusDiab) (Dunstan, Barr, Healy, Salmon, Shaw, Balkau, et al., 2010), and the European Prospective Investigation of Cancer (EPIC) (Jakes, Day, Khaw, Luben, Oakes, Welch, et al., 2003) found similar associations between time spent watching television and mortality and CVD risk. The Aerobics Center Longitudinal Study found similar results using a measure of time spent riding in a car (Warren, Barry, Hooker, Sui, Church, & Blair, 2010). Importantly, these associations exist *even after* adjustment for physical activity. Sedentary behavior as indicated by estimated hours watching television per day has been linked to the development of MetS (Ford, Kohl, Mokdad, & Ajani, 2005; Hamilton et al., 2007; Sisson, Camhi, Church, Martin, Tudor-Locke, & Bouchard, 2009; Hu, Li, Colditz, Willett, & Manson, 2003) as well as type 2 diabetes (Hu et al., 2003; Hamilton et al., 2007). Sisson et al. (2010) reported that individuals who described their daily activities as 'mostly sitting' were at an increased risk for the development of MetS (Sisson et al., 2010).

Non-exercise activity and disease

Recent research has begun to focus on non-traditional measures of activity such as non-exercise activity thermogenesis (NEAT) and ambulatory (walking) activity (Katzmarzyk, 2010).Such measures are important in assessing activity in sedentary individuals and have been associated with a number of risk factors for cardiovascular disease (Hamilton, Hamilton, & Zderic, 2007). For example, results of the NHANES 2005-2006 study revealed significant differences in steps taken per day between obese, overweight and normal weight individuals, as well as significant differences in time spent engaging in sedentary, light, moderate and vigorous activity (Tudor-Locke, Brashear,

Johnson, & Katzmarzyk, 2010). Few steps per day has also been associated with the risk of developing MetS. One study estimated a 10-12% reduction in risk of metabolic syndrome for every 1,000 step increment increase in daily walking activity. Additionally, compared to individuals who took less than 5,000 steps per day, those taking 5,000-10,000 steps per day had a 40% reduction in having MetS, and 10,000 or more steps was associated with a 72% reduction in risk (Sisson, Camhi, Church, Tudor-Locke, Johnson, & Katzmarzyk, 2010). Reduction of ambulatory activity has also been shown to result in a decrease in insulin sensitivity after as little as 2 weeks (Krogh-Madsen, Thyfault, Broholm, Mortensen, Olsen, Mounier, 2010).

Direct and Indirect Links between Inactivity and Inflammation

Adiposity

There are several mechanisms by which low levels of activity may contribute to inflammation. Research has suggested that obesity is at least partially responsible for the correlation between inactivity and inflammation (Nicklas, You, & Pahor et al., 2005). It is now accepted that adipose tissue actively secretes a number of biologically active molecules. Additionally, secretion of these factors is abnormal in patients with MetS (Fernández-Real& Ricart, 2003; Dandona, Aljada, Chaudhuri, Mohanty, & Garg, 2005; Jiamsripong, Mookadam, M., Honda, Khandheria, & Mookadam, F., 2008). Excess accumulation of visceral adipose tissue, adipocyte enlargement, insulin resistance, and macrophage infiltration of adipose tissue have all been associated with increased inflammation. This is characterized by an increase in proinflammatory cytokines such as IL-6, TNF-alpha, CRP, PAI-1, leptin and resistin and a decrease in the secretion of anti-inflammatory protein adiponectin (Fernandez-Real et al., 2003; Dandona et al., 2005;

Jiamsripong et al., 2008; Goossens, 2008).Obesity is associated with increased inflammation in MetS and T2D populations; weight-loss, via exercise and/or diet, results in a significant reduction of inflammatory markers. For example, in the Finnish Diabetes Prevention Study (2009), increasing activity resulted in decreased CRP and IL-6 in adults at high risk for developing diabetes. While the reduction in CRP was explained by change in BMI, changes in IL-6 remained significant after adjustment (Herder, Peltonen, Koenig, Sütfels, Lindström, Martin, et al., 2009). Similarly other interventions have found reductions in inflammatory markers that were independent of changes in body composition (Nicklas, Hsu, Brinkley, Church, Goodpaster, Kritchevsky, et al., 2008). This suggests that while some inflammatory mediators may be more closely linked to adiposity, others are affected by inactivity via different mechanisms.

Low cardiorespiratory fitness

Low levels of aerobic fitness often observed in sedentary individuals can also contribute to increased inflammation (Nicklaset al., 2005). Among sedentary, hypertensive, men, activity was inversely related to levels of the inflammatory marker E-selectin, while elevated CRP was associated with low fitness (Hjelstuen, Anderssen, Holme, Seljeflot, & Klemsdal, 2006). Low fitness has also been associated with greater levels of inflammation in MetS. Aronson et al. (2004) found evidence to suggest that the inverse relationship between CRP and cardiorespiratory fitness is stronger in individuals with MetS than those with a normal metabolic profile (Aronson, Sella, Sheikh-Ahmad, Kerner, Avizohar, Rispler, et al., 2004). Similarly, in a representative sample of adults, Borodulin et al. (2005) found self-rated fitness and aerobic fitness to be inversely related to inflammation (Borodulin, Laatikainen, Salomaa, & Jousilahti, 2005).Studies have also

shown that interventions that increase aerobic fitness also result in decreased inflammation. For example, Kadoglou et al. (2007) found that decreases in IL-18 following an exercise intervention in participants with T2D were predicted by increased VO_{2max} (Kadoglou, Iliadis, Angelopoulou, Perrea, Ampatzidis, Liapis, et al., 2007). Similarly, amongst previously sedentary but healthy adults, training that improved low aerobic fitness also resulted in decreased inflammatory monocytes and TNF-alpha (Timmerman, 2008). However, some researchers have postulated that this effect is related to reduction in trunk fat associated with aerobic exercise. For example, Vieira et al. (2009) discovered that improvements in VO_{2max} following aerobic exercise resulted in decreased visceral fat as well as decreased CRP in previously sedentary subjects (Vieira, Hu, Valentine, McAuley, Evans, Baynard, et al., 2009).

Other mechanisms

It is likely that the effects of sedentary behavior on inflammation and insulin resistance are not entirely explained by adiposity and low aerobic fitness. One study showed that in previously sedentary individuals with high baseline concentrations of CRP (>3mg/L), exercise training resulted in a 29% decrease in CRP that was significant even after adjustment for changes in BMI and VO_{2max} (Lakka et al., 2005). Similar to adipose tissue, skeletal muscle is also thought to have endocrine functions, releasing anti-inflammatory myokines during contraction (Bruunsgaard, 2005). In addition, several studies have found that exercise is related to decreased expression of inflammatory factors in muscle tissue of congestive heart failure (CHF) patients (Gielen, Adams, Möbius-Winkler, Linke, Erbs, Yu, 2003), and in elderly (Greiwe, Cheng, Rubin,

Yarasheski, & Semenkovich, 2001) and obese populations (Lambert, Wright, Finck, & Villareal, 2008).

Cardiorespiratory Fitness, Abdominal Adiposity, and Insulin Resistance

Physical inactivity may also promote CVD by promoting insulin resistance. Insulin resistance, as assessed by the homeostatic model and the euglycaemic insulin clamp, has been found to be independently associated with CVD risk (Coulston, Fada, & Peragallo-Dittko, 2005; Reddy, Singh, Bangit, & Batsell, 2010). This increased risk may be related to endothelial dysfunction and inflammation, dyslipidemia and/or hypercoagulability which are often observed in individuals who are insulin resistant and contribute to atherosclerotic processes (Reddy et al., 2010).

Numerous studies have reported on a positive relationship between physical activity and insulin sensitivity in both cross-sectional (Mayer-Davis, D'Agostino, Karter, Haffner, Rewers, & Sasd et al., 1998; Wannamethee, Shaper, & Alberti , 2000; Borodulin, Tuomilehto, Peltonen, Lakka, Sundvall, & Jousilahti, 2006; Holt, Wild, Eareham, Ekelund, Umpleby, Shojaee-Moradie, & Byrne et al., 2007) and longitudinal analyses (Miyatake, Nishikawa, Morishita, Kunitomi, Wada, Suzuki, & Fujii et al., 2002; Balkau, Mhamdi, Oppert, Nolan, Golay, Porcellati, & Ferrannini, 2008; Dwyer, Ponsonby, Ukoumunne, Pezic, Venn, Dunstan, & Shaw, 2011). Cardiorespiratory fitness is also associated with improved insulin sensitivity (Messier, Malita, Rabasa-Lhoret, Brochu, & Karelis, 2008). In fact, improvements in insulin sensitivity following increases in physical activity are often mediated by increases in cardiorespiratory fitness (Gan, Kriketos, Ellis, Thompson, Kraegen, & Chisholm, 2003; O'Leary, Marchetti, Krishnan, Stetzer, Gonzalez, & Kirwan, 2006). Studies have also shown that effects of physical

inactivity on insulin resistance are mediated by adiposity (Balkau et al, 2008; Dwyer et al., 2011). However, some researchers have found the relationship, although slightly weaker, remains after adjustments for adiposity (Racette, Evans, Weiss, Hagberg, & Hollosy, 2006). Additionally, Borodulin et al., (2006) found evidence to suggest that physical inactivity may have a greater metabolic effect in individuals with a higher degree of abdominal adiposity (Borodulin et al., 2006).

The observed relationship between cardiorespiratory fitness and insulin sensitivity is also often attributed to differences in adiposity (Christou, Gentile, DeSouza, Seals & Gates, 2005). Research has found that controlling for BMI typically weakens the relationship (Racette et al., 2006). Studies that have employed more robust indicators of adiposity or measures of abdominal adiposity have found that the relationship between cardiorespiratory fitness and insulin sensitivity is completely mediated by adiposity (Christou et al., 2005; Messier et al., 2008). In addition, studies that have compared the associations between adiposity and insulin resistance, and cardiorespiratory fitness and insulin resistance have shown that adiposity is the stronger predictor of the two (Christou et al., 2005; Racette et al., 2006; Usui, Asaka, Kawano, Aoyama, Ishijima, Sakamoto & Higuchi, 2010). Interestingly, a study by Holt et al., (2007) concluded that cardiorespiratory fitness may be more closely related to liver insulin sensitivity, while adiposity is closely associated with whole body insulin resistance (Holt et al., 2007).

Decreased adiposity and improved cardiorespiratory fitness represent possible links between exercise and inflammation. However, less is known about the links between sedentary behavior or non-exercise related activity and inflammation and/or insulin resistance in sedentary individuals. For example, although regular, brisk, walking

is associated with a number of health benefits related to cardiovascular risk (Murphy, Nevill, Murtagh, & Holder, 2007); there is limited research on the relationship between cardiovascular risk and ordinary walking. Similarly, the mechanisms by which sedentary activity promotes death and disease are not entirely understood.

The present study

The purpose of this thesis was to examine the relationship between baseline measures of physical activity and sedentary behavior, and inflammation and insulin resistance in a sample of adults with T2D and/or MetS. This study examined baseline data from participants enrolled in either of two studies in patients with MetS (n = 126) or T2D (n = 116). Because these individuals do not typically engage in regular exercise, this study describes how physical activity relates to cardiovascular risk at levels that are below recommended levels of intensity and frequency. Additionally, inclusion of data from subjects with MetS and T2D allowed for examination of these relationships in a sample with a broad spectrum of elevated cardiovascular risk. Participants included low income men and women (not pregnant or nursing) between the ages of 18 and 70 who are either depressed (BDI > 11), overweight (BMI ≥ 27 kg/m^2) and have T2D or who do not have diabetes but have at least 3 components of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) classification of the MetS. These criteria include impaired fasting blood glucose (100-125 mg/dL), abdominal obesity measured as waist circumference (for males > 40 inches and females > 35 inches), high triglyceride levels (≥ 150 mg/dL), low HDL-C (< 40 mg/dL for males and < 50 mg/dL for females), or hypertension (blood pressure ≥ 130 and/or ≥ 85 or treated hypertension).

Primary Aim 1. To describe demographic (ethnicity, language, marital status, employment status, education & income), biological (age, BMI, girth, cardiorespiratory fitness, triglycerides, inflammation, & current medications), psychological (depression) and behavioral (physical activity and sedentary behavior) characteristics of participants enrolled in the CHARMS and CALM-D programs.

Hypothesis 1a. CHARMS and CALM-D participants will have low levels of cardiorespiratory fitness and elevations in a number of other biological risk factors for cardiovascular disease including BMI, girth, triglycerides, and inflammation.

Hypothesis 1b. CHARMS and CALM-D participants will show behavioral characteristics that are associated with increased cardiovascular risk including low levels of physical activity and high levels of sedentary behavior.

Hypothesis 1c. CHARMS and CALM-D participants are likely to be using medications to manage blood pressure and lipids. Additionally, CALM-D participants are more likely to be using medication to regulate blood glucose.

Primary Aim 2. To describe differences between CHARMS and CALM-D participants in terms of demographic, biological, psychological and behavioral characteristics.

Hypothesis 2a. CHARMS and CALM-D participants will not differ in terms of ethnicity, language, marital status, education or income.

Hypothesis 2b. Compared to CHARMS participants, CALM-D participants will be less likely to be employed and more likely to be on medical disability.

Hypothesis 2c. Compared to CHARMS participants, CALM-D participants will be older, have greater BMIs and girths, lower cardiorespiratory fitness, greater triglycerides and inflammation and be prescribed more medications.

Hypothesis 2d. Participants in CALM-D will have higher BDI scores compared to participants in CHARMS.

Hypothesis 2e. Participants in CHARMS and CALM-D will not differ significantly in terms of physical activity or sedentary behavior.

Primary Aim 3. To determine if sedentary behavior and low levels of physical activity represent opposite ends of a single continuum or if they contribute to cardiovascular risk independently in CHARMS and CALM-D participants.

Hypothesis 4. Sedentary behavior will have a unique association with cardiovascular risk after accounting for low levels of physical activity.

Primary Aim 4. To examine the relationship between a latent measure of physical activity and cardiovascular risk in CHARMS and CALM-D participants.

Hypothesis 3. Increased physical activity will be associated with decreased cardiovascular risk as measured by abdominal adiposity and cardiorespiratory fitness.

Primary Aim 5. To examine direct and indirect associations between physical activity, insulin resistance and inflammation in CHARMS and CALM-D participants.

Hypothesis 5a. Physical activity will be indirectly associated with reduced inflammation and insulin resistance via reduced adiposity and increased cardiorespiratory fitness.

Primary Aim 6. To determine if the relationships among these variables are comparable in CHARMS and CALM-D participants.

Hypothesis 6a. There will be no significant differences in the associations between physical activity and inflammation between CHARMS and CALM-D participants.

Chapter 2: Method

Participants

Baseline data from 242 participants enrolled in either of two larger studies were used for this analysis. Participants included low-income men and women between the ages of 18 and 70 who were either depressed (BDI > 11), overweight (BMI ≥ 27 kg/m^2), and had T2D (n = 116), or had been found to have MetS as defined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III), but did not have T2D (n = 126).

Measures

All data were collected from participants during 2 baseline assessment visits. During these visits, demographic information as well anthropometric measurements including height, weight, and waist circumference were obtained. Participants were also asked about physical activity using the 7-Day Physical Activity Recall questionnaire. Additionally, blood samples were taken and participants were given an exercise stress test. Participants were also given an pedometer/activity monitor to return at the following assessment visit a week later.

Physical activity and sedentary behavior.

Self-reported activity and sedentary behavior.

A questionnaire was used to assess self-reported activity and sedentary behavior. Participants were asked how many days during the past week they walked or rode a bicycle for at least 10 minutes, and the average amount of time they spent walking or riding per day. Participants were also asked how much time they spent sitting or reclining per day during the past week.

Pedometer data.

Participants were given either the New Lifestyle (NL-2000) activity monitor or the Omron to assess total steps. Both devices contain automatic memory and storage and step counts reset each night. The Omron is also capable of recording aerobic walking time, or time spent walking of 10 minutes duration or greater. Participants were shown how to use the devices and instructed to wear them each day for the following week.

Cardiorespiratory fitness.

Cardiorespiratory fitness was evaluated during an exercise stress test using a cycle ergometer. Maximal oxygen uptake (VO_{2max}) obtained at 75% estimated max heart rate was used as an indicator of cardiorespiratory fitness.

Inflammation.

Blood samples were drawn after a 12-hour fast. Nephelometric assays were used to assess levels of CRP.

Insulin resistance.

Insulin resistance was assessed using the homeostatic model based on fasting insulin and fasting glucose.

Statistical Analysis

SAS version 9.2 was used for data preparation and descriptive analysis. Mplus version 6.0 was used for all structural equation modeling.

Data preparation.

Physical activity.

Total self-reported minutes of walking per week was calculated based on participant responses to the Physical Activity Questionnaire. Sedentary time during the

week was also calculated in this manner. Average steps taken per day was derived from pedometer data for participants who wore the pedometer a minimum of four days.

Excluded values.

Participants who reported less than 2 hours of sedentary time per day were entered as missing as this is likely an underestimate (n = 52). Participants who wore the pedometer for less than 4 days were entered as missing (n = 25). Additionally, participants who had an average of less than 1000 steps/day were entered as missing, as it is likely these participants did not wear the pedometer for the duration of the day (n = 16). CRP values greater than 20 are likely a sign of infection and, therefore were not used for this analysis. Additionally, an outlier was identified among participant girth observations (i.e. girth = 78.7 inches). Analysis of BMI, weight, and height of the individual revealed this was likely an error and the girth for this subject was entered as missing.

Transformations.

A natural log transformation was used to correct for skewness in the data. Variables that were transformed included self-reported walking, self-reported sedentary time, CRP, and HOMA-IR values, resulting in normal distributions.

Descriptive analysis.

Chi-square tests of independence were performed to examine any association between gender and several demographic variables including marital status, ethnicity, language, education, employment and income among participants from CHARMS and CALM-D. Chi-square tests of independence were also performed to determine if there was a relationship between study and demographic variables as well as prescribed

medications in men and women. Continuous variables (i.e. age, girth, BMI, VO_{2max}, blood pressure, steps, triglycerides, CRP, HOMA-IR, and BDI scores) were entered into a two way analysis of variance with gender and study as predictors. Bivariate correlations were also obtained for measures of activity, sedentary behavior, cardiorespiratory fitness, abdominal adiposity, inflammation, and insulin resistance.

Measurement model.

A latent variable was tested as an measure of activity. The latent variable combined self-reported minutes of walking, self-reported minutes of sedentary behavior,pedometer-recorded steps per day, and pedometer-recorded aerobic walking time. Pedometer-recorded aerobic walking time was used to set the metric for this variable. In order to test the validity of this measure, direct paths from activity to girth and VO_{2max} were tested.

Path analysis.

Following the measurement model, direct paths between activity and inflammation and activity and insulin resistance were evaluated using path analysis. Next, models specifying paths from activity to girth and $VO_{2max,}$ and from girth and VO_{2max} to log CRP and log HOMA-IR, were tested. Insignificant paths were removed from the model without a significant decline in model fit. This model was then tested in CALMD and CHARMS participants separately. Initially, all intercepts and path coefficients were allowed to vary freely between groups. Chi-square difference tests were used to determine which parameters could be estimated equally between the two groups.

Chapter 3: Results

Sample Characteristics

Tables 1 and 2 display demographic and biological characteristics of the sample. Of the 242 participants approximately 48% had T2D. The mean age of the sample was 53 ± 8.13, (51.34 ± 8.48; CALMD 54.82 ± 7.35). Approximately 85% were Hispanic and about 75% spoke Spanish only. Sixty-one percent reported being unemployed for the past 3 months. Fifty-six percent reported completing 12 years of education or less. Additionally, 56% reported an annual income between $5,000 and $20,000. Mean waist circumference among men and women indicated the sample was primarily overweight to obese. Low levels of cardiorespiratory fitness as indicated by VO_{2max} were also observed for men and women. Triglycerides and blood pressure were elevated. The sample also exhibited elevated fasting glucose and insulin resistance as indicated by HOMA-IR values. Mean levels of CRP indicated a proinflammatory state. Additionally, an average of 4234 steps per day indicated a predominantly inactive sample.

Subsample Comparisons

Chi-square tests of independence by gender.

Chi square tests of independence indicated a significant relationship between marital status and gender in CHARMS participants $\chi^2(4, N = 126) = 9.48, p = .05$. Women were more likely to be widowed or divorced than men in this sample; men were more likely to be married. However, women also tended to be older than men in this sample. The relationship between gender and language was significant $\chi^2(2, N = 126) = 7.62, p < .05$. CHARMS men were more likely to be bilingual than CHARMS women. These associations were not observed within CALMD participants. There was no

interaction between gender and ethnicity, education, employment status or income in CHARMS or CALMD.

Chi-square tests of independence by study: CALMD vs. CHARMS.

Among men, CHARMS participants were more likely to have been employed within the past 3 months $\chi^2(1, N = 87) = 6.44, p < .05$. There were no differences in employment according to study within women. Marital status, ethnicity, language, education and income did not vary by study in men or women. CALM-D participants were more likely to be prescribed anti-glycemic medications among men $\chi^2(1, N = 91) = 78.82$, and women, $\chi^2(1, N = 151) = 98.66, p < .05$. In women, CALM-D participants were more likely to be prescribed anti-lipidemic medications $\chi^2(1, N = 151) = 9.61, p < .05$. There were no differences in anti-lipidemic medications according to study among men. CALM-D women were also more likely to be prescribed anti-hypertensive medications, $\chi^2(1, N = 151) = 6.27, p < .05$. There were no differences in prescription of anti-hypertensive medications among men. There were no differences according to study in the prescription of anti-inflammatory medications according to study in men or women.

Analysis of variance by study and gender.

A two-way analysis of variance with study (CALMD, CHARMS) and gender entered as independent variables did not predict systolic blood pressure, $F(3, 234) = 1.22, p > .05$, diastolic blood pressure, $F(3, 234) = 1.51, p > .05$, BMI, $F(3, 234) = 1.43, p > .05$ or total steps recorded per week, $F(3, 166) = 1.21, p > .05$, indicating that there were no reliable between group differences in these variables according to gender or study.

The overall ANOVA on age was significant, F (3, 238) = 5.83, $p < .05$. There were significant associations with both gender and study, $p < .05$. Overall, CALMD participants (M = 54.82 years, SD = 7.35) were significantly older than CHARMS participants (M = 51.34 years, SD = 8.48). Also, women (M = 54.16 years, SD = 7.31) were significantly older than men (M = 51.10 years, SD = 9.05). The effect of the interaction was not significant. Girth was also predicted by the ANOVA, F (3, 229) = 10.31, $p < .05$. There was a significant main effect of gender, $p <.05$, such that men (M = 109.12 cm, SD = 9.71) had greater waist circumferences than women (M = 102.21 cm, SD = 9.32). The interaction effect was not significant. The ANOVA predicted VO_{2max} values, F (3, 205) = 25.19, $p < .05$. There were significant main effects of both gender and study, $p< .05$. The effect of the interaction was also significant, $p<.05$. Men (M = 17.74 ml/kg/min, SD =3.78) had greater aerobic capacity than women (M = 13.90 ml/kg/min, SD = 3.20) in both studies. Among men, CALMD participants had lower aerobic capacity compared to CHARMS participants (D = -2.59, t = 3.07, p < .05); study was not related to VO_{2max} values in women (D = -0.54, t = -0.96, p > .05).

The overall ANOVA significantly predicted HDL values, F (3, 230) = 19.33, $p <$ .05. There was a significant main effect of study and gender, $p< .05$. CALMD participants(M = 42.12 mg/dL, SD = 9.28) had significantly higher HDL values than CHARMS participants (M = 39.12 mg/dL , SD = 8.88). Also, females (M = 43.68 mg/dL, SD = 8.88) had higher values when compared to men (M = 35.44 mg/dL, SD = 7.16). There was no interaction effect. The overall ANOVA predicted LDL values, F(3, 229) = 7.01, $p < .05$. The main effect of study was significant, p<.05. CHARMS (M = 124.86 mg/dL, SD = 33.52) participants had higher LDL values than CALMD (M = 105.34

mg/dL, *SD* = 35.04) participants. However, there was no association between LDL and gender. The effect of the interaction was not significant. The overall ANOVA also significantly predicted total cholesterol, F (3, 230) = 8.22, $p < .05$. The main effect of study was significant, $p < .05$. CHARMS participants (M = 205.20 mg/dL, SD = 35.37) had higher total cholesterol when compared to CALMD participants (M = 182.41 mg/dL, SD = 40.95). Neither gender, nor the interaction between study and gender was associated with total cholesterol. The overall ANOVA significantly predicted log-transformed triglyceride values, F (3, 230) = 5.30, p < .05. The main effect of study was significant, p <.05. CHARMS participants (M = 5.24 mg/dL, SD = .42) had significantly higher log-transformed triglyceride values than CALMD participants (M = 5.03 mg/dL, SD = .49). The effect of gender was not significant, although there was a trend for higher values among men. There was no interaction effect. The ANOVA predicted log CRP values F (3, 228) = 6.84, $p < .05$. The main effect of gender was significant. Women (M = 1.40 mg/L, SD = .85) had higher log CRP values compared to men (M = .91 mg/L, SD = .84). The effect of study was not significant. There was no significant interaction.

Fasting Insulin was predicted by the ANOVA, F (3, 229) = 4.04, $p < .05$. The main effects of both study and gender were significant, $p < .05$. The effect of the interaction was also significant, $p < .05$. In CALMD participants, men had greater fasting insulin than women (D = 8.30 mIU/mL, t = 2.09, p <.05). Among men, CALMD participants had greater fasting insulin than CHARMS (D = 9.02 mIU/mL, t = 2.23, p < .05). Women in CHARMS did not differ from women in CALMD (D =0.06 mIU/mL, t = 0.03, p >.05) or men in CHARMS (D = -0.64 mIU/mL, t = -.31, p >.05). The ANOVA also significantly predicted fasting glucose, F (3, 222) = 45.29, $p < .05$. The main effect

of study was significant. CALMD participants (M = 129.87 mg/dL, SD = 35.58) had significantly higher fasting glucose than CHARMS participants (M = 90.07 mg/dL, SD = 9.60). There was no association between fasting glucose and gender. The effect of the interaction between gender and study was not significant. The overall ANOVA on log HOMA-IR was significant, F (3, 217) = 11.94, p < .05. There were significant associations with both gender and study. The effect of the interaction was also significant. Among CALMD participants, men had significantly greater log HOMA-IR values than women (D = 0.30, t = 2.00, p <.05); however, the log HOMA-IR values did not differ between men and women among CHARMS participants (D = .08, t = .71, p <.05). CALMD participants (M = 1.59, SD = .72) were more insulin resistant than CHARMS participants (M = 1.10, SD = .60) in both genders.

The overall ANOVA significantly predicted BDI scores, F (3, 236) = 32.04, p < .05. Both main effects of gender and study were significant, p< .05. Women (M = 17.24, SD = 9.38) had significantly higher scores than men (M = 11.60, SD = 8.84). CALMD participants (M = 20.04, SD = 7.00) reported more depressive symptoms than CHARMS participants (M = 10.56, SD = 9.37). The interaction was not significant.

Bivariate correlations.

Table 3 displays bivariate correlations among indicators of activity, sedentary behavior, cardiorespiratory fitness, abdominal adiposity, inflammation, and insulin resistance. The correlation between self-reported sedentary behavior and CRP revealed a trend, p = .08. Self-reported walking time was positively associated with pedometer-recorded aerobic time, p< .05. The relationship between self-reported walking time and

steps per day showed a trend, $p = .07$. Aerobic time was positively related to steps per day, $p < .01$. The negative relationship between girth and VO_{2max} showed a trend, $p = .06$.

Structural equation modeling.

Measurement models.

A latent measure of physical activity was specified. Pedometer-recorded aerobic time, pedometer-recorded steps per day, self-reported time walking, and self-reported sedentary time were included as indicators. Aerobic time was used to set the metric for activity. This model did not fit the data well, χ^2 (2) = 6.214, p=.0447, CFI = .820, RMSEA = .093 [90% C.I. = .012, .180], SRMR = .077. While significant loadings were observed for both self-reported time walking (B = .790) and pedometer-recorded steps per day (B = 1.110), p< .05; the factor loading for self-reported sedentary time was not significant, B = -.088, p = .116. A second latent measure without self-reported sedentary time was also specified. The model was saturated and therefore fit indices were not obtained. A significant loading was observed for self-reported time walking, B = 1.694, $p < .05$. The loading for pedometer-recorded steps per day was a trend, B = 1.656, $p = .055$.

Structural models.

A structural model was specified to determine if either the latent measure of physical activity or self-reported sedentary time was directly related to girth or VO_{2max}. The model had good fit, χ^2 (6) = 1.880, p=.9304, CFI = 1.000, RMSEA = <.001 [90% C.I. = .000, .027], SRMR = .028. Sedentary time was not significantly related to girth, B = 66.855, $p = .386$ or VO_{2max}, B = -8.935, $p = .772$. Activity was significantly associated with VO2max, B = .633, $p < .05$, but not girth, B = -.851, $p = .190$.

A structural model was specified to examine direct links between self-reported sedentary time and physical activity, and log-transformed CRP and log-transformed HOMA-IR, activity. The model fit the data, χ^2 (6) = 4.207, p=.6487, CFI = 1.000, RMSEA = <.001 [90% C.I. = .000, .075], SRMR = .033. The latent measure of physical activity was not directly associated with log-transformed CRP, B = -.033, *p* =.573 or log-transformed HOMA-IR, B = -.029, *p* = .538. Similarly, Self-reported sedentary time was not significantly associated with log-transformed CRP, B = 3.345, *p* = .610 or log-transformed HOMA-IR, B = -1.449, *p* = .779.

Girth and VO_{2max} were added to the model linking activity with log HOMA-IR and log CRP. Age was included as a control variable for VO_{2max} and sex was included as a control variable for VO_{2max}, girth, and log CRP. The model had good overall fit, χ^2 (18) = 10.862 p=.9001, CFI = 1.000, RMSEA = <.001 [90% C.I. = .000, .025], SRMR = .034. However, paths from VO_{2max} to log CRP and log HOMA-IR were not significant. Therefore, an alternative model with these paths eliminated was tested. The chi-square difference test indicated no significant decrease in overall model fit, χ^2_{diff} = 1.516, df = 2, *p*> .05. This model was retained. Indices indicated overall good fit of the model, χ^2 (20) = 12.378, p=.9024 CFI = 1.000, RMSEA = <.001 [90% C.I. = .000, .023], SRMR = .036. VO_{2max} was positively related to activity, B = .764, *p* < .05. There was no association between girth and activity, B = -1.097, *p* = .080. VO_{2max} was also inversely related to girth, B = -.639, *p* < .01. Girth was also associated with both CRP, B= .025, p < .001, and HOMA-IR, B = .016, p < .01.

The resulting model with activity associated with girth and VO_{2max}, and girth associated with VO_{2max}, log CRP and log HOMA-IR was tested in participants with MetS

and T2D separately. Intercepts of VO_{2max}, log CRP, and log HOMA-IR were constrained equal between groups without significant decline in model fit, $\chi^2_{diff} = 2.82$, df = 3, $p > .05$. However, convergence was not achieved with intercepts for girth constrained as equal. Chi-square difference tests were also used to determine which paths could be constrained between groups while maintaining model fit. The associations between sex and girth, VO_{2max}, and log CRP were consistent between groups, $\chi^2_{diff} = 1.865$, df = 3, $p > .05$. The relationship between age and VO_{2max} was also comparable between the two groups, $\chi^2_{diff} = 2.839$, df = 1, $p > .05$. Additionally, paths from activity to girth and VO_{2max} were estimated as equal between groups, $\chi^2_{diff} = 3.423$, df = 2, $p > .05$. The association between girth and log CRP was also comparable between groups, $\chi^2_{diff} = 1.499$, df = 1, $p > .05$.Also, the relationship between girth and VO_{2max} was equal between groups, $\chi^2_{diff} = .394$, df = 1, $p > .05$. Additionally, the relationship between girth and log HOMA-IR was significantly different among participants with T2D and MetS, $\chi^2_{diff} = 28.121$, df = 1, $p < .05$. Finally, the non-significant path from activity to girth was removed without significant decline in model fit, $\chi^2_{diff} = 1.603$, df = 1, $p > .05$

Figure 1a and figure 1b display the final models for each group. Fit indices indicated good fit, χ^2 (55) = 63.376, p=.2324, CFI = .959, RMSEA .033 [90% C.I. = .000, .067], SRMR = .097. Parameter estimates for the final model are displayed in Table 4. Activity and VO_{2max} were positively associated, B = .885, p < .01. VO_{2max} was also inversely related to girth B = -0.786, p < .001 after controlling for age and sex. Girth was positively associated with log CRP in both groups, B = 0.025, p < .001. Girth was also positively related to log HOMA-IR in T2D, B = 0.017, p < .001, and MetS, B = 0.013, p

< .01. The correlation between log CRP and log HOMA-IR was not significant in either group.

The indirect inverse association between activity and girth was significant, B =-.695, *p* .05. An inverse, indirect association between activity and log CRP was also observed, B = -.018, *p*< .05. VO_{2max} was also negatively related to log HOMA-IR via girth in T2D, B = -.014, *p*< .01, and MetS, B = -.010, *p*< .05. There was a trend for a negative, indirect relationship between activity and log HOMA-IR in T2D, B = -.012, *p* = .053, and MetS, B = -.009, *p* = .076. The model accounted for 28.8%, 17.8%, 6.8% and 13.8% of the variance observed in VO_{2max}, girth, HOMA-IR and log CRP, respectively among participants with T2D. This model accounted for 49.3%, 20.6%, 4.1% *(not significant)* and 16.6% of the observed variance in VO_{2max}, girth, log HOMA-IR and log CRP, respectively among participants with MetS.

Chapter 4: Discussion

The present study found that walking is positively related to cardiorespiratory fitness in men and women both with T2D and/or MetS. Increased cardiorespiratory fitness is, in turn, associated with decreased abdominal adiposity. Decreased abdominal adiposity is positively related to both insulin resistance and inflammation. Walking, however, was not directly related to abdominal adiposity, insulin resistance, or inflammation. Also, cardiorespiratory fitness was not directly associated with either insulin resistance or inflammation. Associations between walking and cardiorespiratory fitness, cardiorespiratory fitness and abdominal adiposity, and abdominal adiposity and inflammation were comparable between individuals with and without T2D. However, the relationship between abdominal adiposity and insulin resistance appears to differ between these groups. Abdominal adiposity may be more closely associated with insulin resistance in individuals with T2D compared with individuals with MetS.

Walking and Cardiorespiratory Fitness

The observed positive association between physical activity and fitness has been reported in many studies using both self-reported and objectively recorded measures of activity. Similarly, aerobic walking interventions have been shown to have positive effects on fitness (Murphy et al., 2007), even at a moderate intensity (Duscha et al., 2005). Whereas moderate to vigorous intensity aerobic activity is generally recommended to improve cardiorespiratory fitness, the type of activity employed in this analysis (walking or biking for at least 10 minutes), is reflective of activity that is of moderate intensity at best. Variations in frequency or intensity of activity were not taken into account in this analysis. These data are consistent with previous research indicating

that self-reported frequency of activity (Hulens et al., 2002; Ramadan & Barac-Nieto, 2003), as well as pedometer-recorded steps accumulated per day (Le Masurier & Corbin, 2006) are associated with improved aerobic fitness.

Walking and Insulin Resistance

These results support previous research that indicates associations between activity or fitness and insulin resistance are mediated by differences in abdominal adiposity. A number of studies have reported an inverse association between self-reported physical activity and insulin resistance (Mayer-Davis et al., 1998; Wannamethee et al., 2000; Gill, 2007). Similarly, pedometer-recorded walking has also been found to be positively related to insulin resistance (Balkau et al., 2008; Dwyer et al., 2011; Miyatake et al., 2002). Other studies have reported on an inverse relationship between fitness and insulin resistance (Bruce et al., 2003; Thamer et al., 2003; Christou et al., 2005; Racette et al., 2006). Although some studies have reported an independent effect of fitness or activity on insulin resistance after adjustment for adiposity, the relationship is usually attenuated (Racette et al., 2006; Balkau et al., 2008) and often eliminated after such adjustment (Usui et al., 2010; Dwyer et al., 2011). Furthermore, Christou et al., (2005) showed that while VO_{2max} was associated with insulin resistance after controlling for BMI, they relationship was no longer significant after adjustment for waist circumference.

Walking and Inflammation

Crossectional and longitudinal studies have provided evidence for an inverse association between self-reported activity and inflammation, (Kasapis & Thompson, 2005; Plaisance & Grandjean, 2006). This analysis supports previous findings that

indicate these relationships are largely related to differences in adiposity (Pischon, 2003; Verdaet et al., 2004, Arsenault et al., 2009). However, a number of other studies have reported significant relationships between self-reported physical activity and inflammation even after correcting for adiposity (Geffken et al., 2001; Abramson & Vaccarino, 2002; Wannamethee et al., 2002; Ford, 2003; King et al., 2003; Reuben et al., 2003; Colbert 2004; Albert et al., 2004; Pitsavos et al., 2005; Borodulin et al., 2006; Autenrieth et al., 2009; Majka et al., 2009). Pedometer-based assessments of walking have yielded less consistent results. In individuals with impaired glucose tolerance, Yates et al., (2010) found that CRP was not significantly related to walking behavior. However, in a sample of healthy women, accumulating 7,500 steps per day or more was associated with decreased CRP compared to accumulating less than 7,500 steps (Woolf et al., 2008). It is possible that these relationships are only observed at higher levels of activity, whereas individuals in this study accumulated an average of about 4,000 steps per day.

In the present analysis, the association between cardiorespiratory fitness and CRP was mediated by waist circumference. In contrast, previous studieshave shown associations between cardiorespiratory fitness and CRP even after adjustments for adiposity (Church et al., 2002; Aronson et al., 2004; Kullo et al., 2007; Jae et al., 2009). However, these analyses were conducted on samples of healthy subjects (Church et al., 2002; Kullo et al., 2007) or within samples with a greater range of cardiorespiratory fitness (Aronson et al., 2004; Jae et al., 2009), whereas levels of cardiorespiratory fitness in this sample were predominantly especially low and levels of abdominal adiposity were high. Therefore, observed associations between fitness and inflammation would have been faint in comparison to associations between adiposity and inflammation.

Walking, Cardiorespiratory Fitness, and Adiposity

The present study documented an indirect pathway between physical activity and adiposity. Numerous other studies have described a direct, inverse relationship between activity and adiposity. Some studies have reported this relationship using self-report measures of physical activity (Ramadan et al., 2003) although none have reported on associations with self-reported measures of walking alone. Walking as measured by pedometer-recorded steps per day has also been related to adiposity (Miyatake et al., 2002; Dwyer et al., 2011). This relationship was not significant in the present analysis. Measurement based on accumulation of physical activity and caloric expenditure may be more closely related to abdominal adiposity than aerobic walking time which was used to set the metric for physical activity in this study. The lack of a direct association between walking and adiposity may also be due to limited power. Differences in abdominal adiposity as a function of physical activity in this analysis were expected to be small as the participants in this sample are primarily overweight and inactive. Also, our ability to detect such differences was limited due to a restricted sample size. Finally, the relationship between walking and adiposity may be limited by our reliance on self-reported activity, as pedometer-recorded data was not available for many participants. In contrast, cardiorespiratory fitness, which may be a more sensitive measure, was inversely related to abdominal adiposity.

Advantages and Limitations

Structural equation modeling provides a unique advantage in that multiple relationships among a set of variables can be examined at once. However, use of this technique often requires substantial sample sizes. In the present analysis, participants

from two separate studies (CHARMS and CALMD) were combined in an effort to ensure adequate sample size. Many of the hypothesized relationships were observed in spite of the restricted sample size. However, it is likely that these associations would be strengthened in a larger sample. Also, a larger sample would allow for a more in-depth evaluation of potential moderators of these relationships, i.e. the examination of these associations in men and women separately. Such analysis would be informative as some studies have reported differences in relationships according to gender (Albert et al., 2004; Borodulin, 2006).

Between study differences.

Several between group differences were noted among CHARMS and CALMD participants due to differences in study inclusion criteria. All CALMD participants were overweight, with T2D and depression (BDI > 11); whereas CHARMS participants did not have T2D but met at least three of five criteria for MetS. In comparison to CHARMS participants, CALMD participants showed greater fasting insulin, fasting glucose and HOMA-IR values. CALMD participants also tended to be older with decreased cardiorespiratory fitness compared to CHARMS participants. CHARMS participants displayed more signs of dyslipidemia as indicated by decreased HDL and increased LDL, total cholesterol and triglycerides in comparison to CALMD participants. CHARMS participants also reported less symptoms of depression.

The observed relationship between abdominal adiposity and HOMA-IR was significantly stronger in CALMD than CHARMS. However, there was less variability in HOMA-IR values within CHARMS participants when compared to CALMD as a consequence of study inclusion criteria. All CHARMS participants had fasting glucose

values less than 126 mg/dL. This ceiling effect may have resulted in a weaker statistical relationship in this group.

Physical activity assessment.

While most of the available literature concerning physical activity and cardiovascular risk focuses on one measure of activity, in the present study multiple indicators of physical activity were combined. Latent measures capture the covariation of multiple indicators in order to improve the measurement of a single construct. Furthermore, while many studies typically utilize either self-reported or objectively-recorded data, the present analysis evaluated their shared variability in relation to cardiovascular risk.

Missing physical activity data.

A major limitation in this study was the prevalence of missing data related to physical activity. Pedometer-recorded data were only available for about half of the participants included in the study, while the other half either did not receive a pedometer or did not wear it for a sufficient period of time. Additionally, only about half of the participants reported walking continuously for 10 minutes or more during the typical week. This item is designed to be reflective of moderate intensity activity. Assessment of activity of even lighter intensity is warranted as it has been reported that in high-risk individuals, total accumulation of activity may be more closely related to cardiovascular risk than activity intensity (Duscha et al., 2005).

Self-reported sedentary behavior.

While multiple indicators of physical activity were available for this analysis, sedentary behavior was assessed only by self-reported time sitting. The validity of this

variable is questionable as it was not significantly related to other variables included in the analysis. Similarly, self-reported sedentary time did not have a significant loading on the latent measure of physical activity. This suggests sedentary behavior did not share a significant portion of variance with the indicators of physical activity (self-reported walking, pedometer-recorded aerobic time, and pedometer-recorded steps per day) used in the model and supports the hypothesis that physical activity and sedentary behavior represent separate constructs. However, the lack of significance could also be due to inadequate measurement of sedentary behavior. An objective measure of sedentary behavior (i.e. accelerometer-derived) would likely provide more reliable and valid data. Such measures of sedentary behavior should be further developed and compared to both subjective reports of sedentary behavior, as well as cardiovascular risk variables.

Chapter 5: Conclusions

In the present study, structural equation modeling was used to test a latent measurement model of physical activity and a path model relating physical activity to cardiorespiratory fitness, abdominal adiposity, inflammation and insulin resistance in a sample of individuals with MetS and/or T2D. The final model demonstrated good fit of the data for both groups. Both self-reported and pedometer-recorded indicators of activity had significant loadings on the latent measure of physical activity whereas, self-reported sedentary time did not. The final path model revealed significant path coefficients for all hypothesized associations. Additionally, these relationships were strikingly similar among participants with MetS and those with T2D, as most associations were estimated equally for both groups without significant decline in model fit.

There was no evidence for a direct association between walking and abdominal adiposity, inflammation, or insulin resistance. Walking was related to improved cardiorespiratory fitness. Cardiorespiratory fitness, in turn, was inversely associated with abdominal adiposity. Abdominal adiposity was positively related to inflammation and insulin resistance. However, abdominal adiposity may be more closely related to insulin resistance in individuals with T2D when compared to individuals with MetS. In conclusion, walking may be related to cardiovascular risk, insofar as it indirectly reduces abdominal adiposity. Further analysis should be conducted to determine the appropriate amount and intensity for a clinically significant effect.

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Sample Characteristics: CHARMS

	Men (n = 57)			Women (n = 69)			Total (n = 126)		
	Mean (n)	SD	95% C.I.	Mean (n)	SD	95% C.I.	Mean (N)	SD	95% C.I
Biological									
Age	49.82	9.55	47.28 - 52.36	52.6	7.3	50.85 - 54.36	51.34	8.48	49.85 - 52.84
Weight (kg)	93.7	12.14	90.42 - 96.98	82.77	10.94	80.12 - 85.42	87.66	12.68	85.40 - 89.92
BMI (kg/m^2)	31.6	3.5	30.66 - 32.55	33.1	3.76	32.18 - 34.00	32.42	3.7	31.76 - 33.09
Girth (in)	108.04	8.94	105.58 - 110.50	101.69	8.04	99.74 - 103.64	104.48	8.98	102.86 - 106.09
Average Systolic BP (mm/hg)	127.14	15.23	123.02 - 131.26	123.34	17.93	119.00 - 127.68	125.04	16.82	122.04 - 128.04
Average Diastolic BP (mm/hg)	80.27	9.44	77.72 - 82.82	78.16	9.66	75.82 - 80.50	79.1	9.58	77.4 - 80.82
Observed Max VO2 (ml/kg/min)	18.72	3.4	1774 - 19.71	14.21	2.8	13.47 - 14.96	16.28	3.81	15.54 - 17.01
Triglycerides (mg/dL)	171.34	77.86	177.40 - 210.91	200.04	93.84	117.33 - 222.76	208.16	95.07	191.32 - 224.99
Log-transformed Triglycerides	5.29	0.44	5.18 - 5.40	5.21	0.41	5.11 - 5.31	5.24	0.42	5.17 - 5.32
HDL-C (mg/dL)	34.61	6.23	32.96 - 36.26	42.9	9.06	40.70 - 45.08	39.12	8.88	37.54 - 40.69
LDL-C (mg/dL)	120.04	34.16	110.98 - 129.11	128.96	32.66	120.98 - 136.92	124.86	33.52	118.90 - 130.82
Total Cholesterol	198.18	32.46	189.59 - 206.79	211.08	36.84	202.16 - 220.00	205.2	35.37	198.94 - 211.46
Fasting Glucose (mg/dL)	91.11	8.9	88.66 - 93.56	89.22	10.13	86.72 - 91.74	90.07	9.6	88.32 - 91.82
Fasting Insulin	16.12	9.68	13.52 - 18.72	16.76	13.37	13.50 - 20.02	16.47	11.79	14.36 - 18.58
HOMA-IR	3.74	2.50	3.04 - 4.43	3.63	3.44	2.76 - 4.49	3.68	3.04	3.12 - 4.24
Log HOMA-IR	1.14	0.58	0.98-1.30	1.06	0.62	0.90 - 1.22	1.10	0.60	0.99 - 1.21
C- Reactive Protein (mg/L)	3.5	3.18	2.66 - 4.34	5.66	3.88	4.72 - 6.61	4.67	3.72	4.01 - 5.33
Log-transformed CRP	0.87	0.9	.63 - 1.12	1.5	0.7	1.34 - 1.68	1.22	0.86	1.06 - 1.37
Behavioral									
Steps per Week	4940	3330	3830 - 6050	3896	2737	3083 - 4708	4361	3042	3697 - 5026
Psychological									
BDI Total Score	8.24	7.88	6.16 - 10.34	12.51	10.11	10.06 - 14.96	10.56	9.37	8.90 - 12.22

Table 1a. displays biological, behavioral, and psychological characteristics of CHARMS participants included in the study by gender.

Sample Characteristics: CALM-D

	Men (n = 34)			Women (n = 82)			Total (n = 116)		
	Mean (n)	SD	95% C.I.	Mean (n)	SD	95% C.I.	Mean (N)	SD	95% C.I
Biological									
Age	53.26	7.8	50.54 - 55.98	55.47	7.1	53.91 - 57.04	54.82	7.35	53.48 - 56.18
Weight (kg)	94.6	13.86	89.76 - 99.44	81.29	12.75	78.47 - 84.11	85.22	14.38	82.56 - 87.88
BMI (kg/m^2)	32.22	3.82	30.89 - 33.56	32.76	5.1	31.63 - 33.88	32.6	4.74	31.72 - 33.48
Girth (in)	110.89	10.78	107.00 – 114.78	102.65	10.32	100.35 - 104.94	105.00	11.06	102.93 – 107.08
Average Systolic BP (mm/hg)	129	13.78	124.18 - 133.81	128.14	19.94	123.72 - 132.54	128.39	18.28	125.01 - 138.76
Average Diastolic BP (mm/hg)	80.62	8.36	76.82 - 82.35	77.3	10.81	74.90 - 79.68	78.28	10.22	76.38 - 80.16
Observed Max VO2 (ml/kg/min)	16.07	4.56	77.70 - 83.53	13.67	3.48	12.87 - 14.47	14.36	3.74	13.62 - 15.08
Triglycerides (mg/dL)	201.09	134.39	153.44 - 248.74	163.38	79.4	145.24 - 181.52	174.8	100.16	155.78 - 193.81
Log-transformed Triglycerides	5.14	0.55	4.94 - 5.34	4.99	0.45	4.88 - 5.10	5.04	0.49	4.94 - 5.13
HDL-C (mg/dL)	36.88	8.45	33.88 - 39.88	44.39	8.72	42.4 - 46.38	42.12	9.28	40.36 - 43.88
LDL-C (mg/dL)	106.66	38.91	92.86 - 120.46	104.76	33.48	97.12 - 112.42	105.34	35.04	98.68 - 111.99
Total Cholesterol	183.76	42.5	168.68 - 198.82	181.82	40.54	172.56 - 191.09	182.41	40.95	174.64 - 190.18
Fasting Glucose (mg/dL)	130.22	33.36	118.39 - 142.06	129.72	36.72	121.26 - 138.16	129.87	35.58	123.08 - 136.66
Fasting Insulin (mg/dL)	25.14	22.28	17.36 - 32.92	16.82	9.6	14.64 - 19.02	19.4	15.12	16.54 - 22.56
HOMA-IR	8.06	6.38	5.79 - 10.32	5.62	4.48	4.58 - 6.66	6.37	5.23	5.36 - 7.37
Log HOMA-IR	1.80	0.80	1.51 - 2.08	1.50	0.66	1.35 - 1.66	1.60	0.72	1.46 - 1.74
C- Reactive Protein (mg/L)	3.36	2.28	2.55 - 4.16	5.34	4.27	4.36 - 6.32	4.74	3.87	4.00 - 5.48
Log-transformed CRP	0.97	0.74	.71 - 1.24	1.3	0.96	1.08 - 1.52	1.2	0.91	1.02 - 1.37
Behavioral									
Steps per Week	3705	2600	2696 - 4713	4306	3038	3514 - 5097	4112	2903	3494 - 4731
Psychological									
BDI Total Score	17.24	7.46	14.62 - 19.84	21.22	6.48	19.79 - 22.66	20.04	7	18.75 - 21.34

Table 1b. displays biological, behavioral, and psychological characteristics of CALM-D participants included in the study by gender.

CHARMS Demographic Characteristics

	Men (n = 57)		Women (n = 69)		Total (n = 126)	
	n	%	n	%	n	%
Ethnicity						
Asian	0	0	0	0.93	1	0.55
Black	4	7.14	8	11.59	12	9.60
Caucasian	1	1.79	5	7.25	6	4.80
Hispanic	51	91.07	56	81.16	107	85.60
Missing	1		0		1	
Language[*m]						
English Only	5	8.77	12	17.39	17	13.49
Spanish Only	40	70.18	53	76.81	93	73.81
Bilingual	12	21.05	4	5.80	16	12.70
Marital Status						
Single	11	19.30	15	21.74	26	20.63
Widowed	1	1.75	9	13.04	10	7.94
Married/Partner	30	52.63	24	34.78	54	42.86
Divorced	9	15.79	17	24.64	26	20.63
Separated	6	10.53	4	5.80	10	7.94
Highest Education						
Elementary School	5	8.77	10	14.49	15	11.90
High School	24	42.11	32	46.38	56	44.44
College	20	35.09	24	34.78	44	34.92
Graduate School	8	14.04	3	4.35	11	8.73
Employment Status [m]						
Employed	28	51.85	28	40.58	76	42.7
Disabled	0	0	4	10.26	4	6.15
Retired	1	3.85	2	5.13	3	4.62
Unemployed	24	92.31	31	79.49	55	84.62
Homemaker	0	0	1	2.56	1	1.54
Other	1	3.85	1	2.56	2	3.08
Missing	3		2		5	
Total Income						
0-15,000	6	11.32	5	8.77	11	10.00
15,001-30,000	30	56.60	37	64.91	67	60.91
30,001-45,000	15	28.30	15	26.32	30	27.27
45,001 +	2	3.77	0	0	2	1.82
Missing	4		12		16	

Table 2b. displays demographic characteristics of CHARMS participants included in the sample. *= significant differences by gender // m/w = significant differences by study.

CALM-D Demographic Characteristics

	Men (n = 34)		Women (n = 82)		Total (n = 116)	
	n	%	n	%	n	%
Ethnicity						
Black	3	8.82	9	10.98	12	10.34
Caucasian	0	0	5	6.10	5	4.31
Hispanic	31	91.18	68	82.93	99	85.34
Language [m]						
English Only	3	8.82	11	13.41	14	12.07
Spanish Only	29	85.29	61	74.39	90	77.59
Bilingual	2	5.88	9	10.98	11	9.48
Missing	0		0		0	
Marital Status[*]						
Single	7	20.59	12	14.81	19	16.52
Widowed	0	0	8	9.88	8	6.96
Married/Partner	16	47.06	25	30.86	41	35.65
Divorced	6	17.65	28	34.57	34	29.57
Separated	5	14.71	8	9.88	13	11.30
Missing	0		1		1	
Highest Education[*]						
Elementary School	1	2.94	14	17.28	15	13.04
High School	17	50.00	33	40.74	50	43.48
College	11	32.35	30	37.04	41	35.65
Graduate School	5	14.71	4	4.94	9	7.83
Missing	0		1		1	
Employment Status [m]						
Employed	8	24.24	28	35.00	36	31.86
Disabled	3	13.04	4	7.69	7	9.33
Retired	1	4.35	7	13.46	8	10.67
Unemployed	19	82.61	34	65.38	53	70.67
Homemaker	0	0	4	7.69	4	5.33
Other	0	0	3	5.77	3	4.00
Missing	3		2		5	
Total Income						
0-15,000	8	25.00	12	18.18	20	20.41
15,001-30,000	13	40.63	38	57.58	51	52.04
30,001-45,000	8	25.00	15	22.73	23	23.47
45,001 +	3	9.38	1	1.52	4	4.08
Missing	2		16		18	

Table 2a. displays demographic characteristics of CALM-D participants included in the sample . *= significant differences by gender // m/w = significant differences by study.

Bivariate Correlations (n=37)

	Sedentary Time	Walking Time	Aerobic Time	Steps per Day	VO_{2max}	Girth	Log CRP	Log HOMA-IR
Sedentary Time	1.000							
Walking Time	-.002	1.000						
Aerobic Time	.230	.352**	1.000					
Steps per Day	.005	.298*	.616***	1.000				
VO_{2max}	.015	.038	.240	.038	1.000			
Girth	.172	-.136	-.159	-.135	-.318*	1.000		
Log CRP	.286*	.173	.172	.125	-.144	-.006	1.000	
Log HOMA-IR	-.157	.001	-.180	-.129	.250	.286	-.010	1.000

Table 3. displays bivariate correlations among variables included in measurement and structural models.

*p< 0.10

**p < 0.05

***p< 0.001

Parameter Statistics

	B	SE	*p*-value
Activity			
Aerobic time	1.000	.000	999.000
Steps per day	.808	.313	.010
Self-reported walking	.523	.227	.021
VO_{2max}			
Age	-.096	.031	.002
Sex	-3.222	.550	<.001
Activity	.885	.338	.009
Girth			
Sex	-10.306	1.410	<.001
VO_{2max}	-.786	.187	<.001
Log CRP			
Sex	.698	.116	<.001
Girth	.025	.006	<.001
Log HOMA-IR			
Girth			
CALMD	.017	.004	<.001
CHARMS	.013	.004	.003

Table 4. displays parameter statistics for factor loadings and paths included in the final model for CALMD and CHARMS.

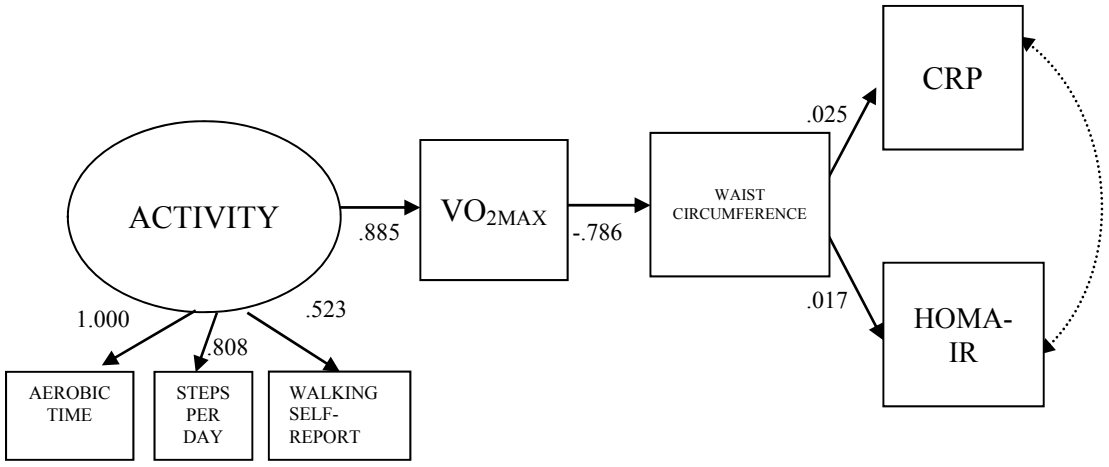

Figure 1a. displays the final model for CALMD participants. Unstandardized path coefficients are displayed for significant associations. Insignificant associations are represented by dashed lines. * $\alpha = p < .05$.

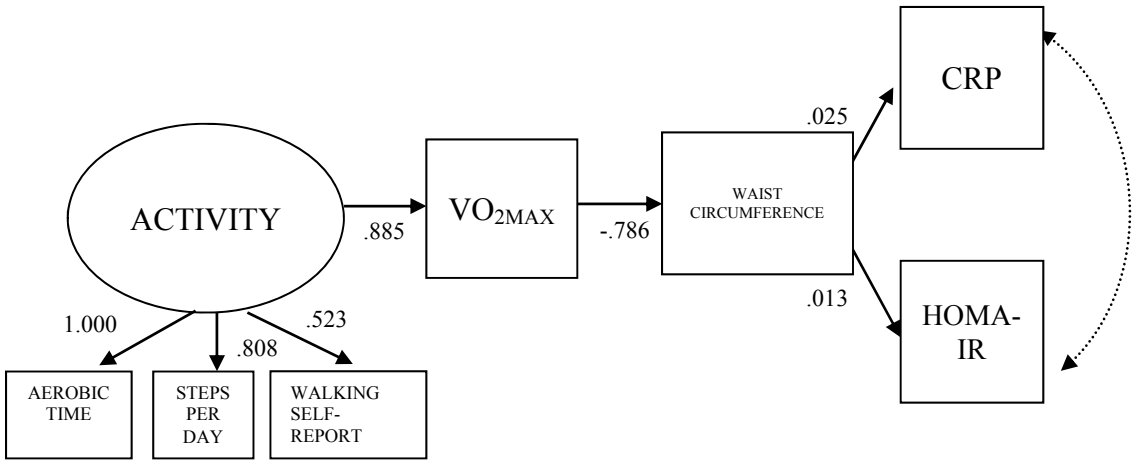

Figure 1b. displays the final model using CHARMS participants. Unstandardized path coefficients are displayed for significant associations. Insignificant associations are represented by dashed lines. * $\alpha = p < .05$.